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(54) COATING FOR IMPLANTABLE DEVICES AND A METHOD OF FORMING THE SAME
BESCHICHTUNG FÜR IMPLANTIERBARE VORRICHTUNGEN UND VERFAHREN ZU IHRER HERSTELLUNG
REVETEMENT POUR DISPOSITIFS IMPLANTABLES ET LEUR PROCEDE DE FORMATION

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BACKGROUND

Field of the Invention

[0001] The invention relates to coatings and methods of forming the coatings on stents.

Description of the Background

[0002] Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially press against the atherosclerotic plaque of the lesion for remodeling of the vessel wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

[0003] A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Vasospasms and recoil of the vessel wall also threaten vessel closure. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining, and to reduce the chance of the development of thrombosis and restenosis, an expandable, intraluminal prosthesis, one example of which includes a stent, is implanted in the lumen to maintain the vascular patency.

[0004] Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, 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 cavities via catheters, and then expanded to a larger diameter once they are at the desired location. Mechanical intervention via stents has reduced the rate of restenosis as compared to balloon angioplasty; but restenosis is still a significant clinical problem with rates ranging from 20-40%. When restenosis does occur in the stented segment, its treatment can be challenging, as clinical options are more limited as compared to lesions that were treated solely with a balloon.

[0005] Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. The embodiments of the present invention provide stent coatings for local delivery of drugs.

SUMMARY

[0006] In accordance with one aspect of the present invention, a method of forming a coating for a stent is provided. The method comprises forming a primer layer, which primer layer comprises a polymer and is substantially free of active ingredients, on at least a portion of a surface of the stent, wherein the primer layer has a weight measurement of $X$, or a thickness $X$; and forming a reservoir layer comprising a polymer and an active ingredient on at least a selected portion of the primer layer, wherein the reservoir layer has a weight measurement of $Y$, or a thickness $Y$; wherein (a) $X/Y$ is equal to or greater than 0.25, or (b) $X$ is from 0.5 to 3 micrometres and $Y$ is from 1 to 10 micrometres provided that $X/Y$ is equal to or greater than 0.25; and wherein (i) said polymer of the primer layer is poly(butyl methacrylate) and said polymer of the reservoir layer is an ethylene vinyl alcohol copolymer; or (ii) said polymer of the primer layer is poly(butyl methacrylate) and said polymer of the reservoir layer is poly(butyl methacrylate); or (iii) said polymer of the primer layer is an ethylene vinyl alcohol copolymer and said polymer of the reservoir layer is poly(butyl methacrylate). In one embodiment, the coating has a drug loading equal to or greater than 30%. In another embodiment, the method further comprises forming asperities on a surface of the primer layer preceding the formation of the reservoir layer. In yet another embodiment, the primer layer includes at least a region having a degree of porosity.

[0007] In yet another aspect of the present invention, stent is provided comprising a coating for delivery of an active ingredient. The coating comprises a primer region, which primer region comprises a polymer and is substantially free of active ingredients, on at least a portion of a surface of the stent, wherein the primer region has a thickness $X'$, or a weight measurement $X$; a reservoir region comprising a polymer and the active ingredient on at least a selected portion of the primer region, wherein the reservoir region has a thickness $Y'$, or a weight measurement $Y$; and wherein: (a) the thickness $X'$ is measured from the outer surface of the primer region to the surface of the stent prior to the migration of
the active ingredient from the reservoir region to the primer region, and wherein \( X' \) is from 0.5 to 3 micrometres and \( Y' \)
is from 1 to 10 micrometres, provided that \( X/Y' \) is equal to or greater than 0.25; or (b) \( X/Y \) is equal to or greater than
0.25; and wherein: (i) said polymer of the primer region is poly(butyl methacrylate) and said polymer of the reservoir
region is an ethylene vinyl alcohol copolymer; or (ii) said polymer of the primer region is poly(butyl methacrylate) and
said polymer of the reservoir region is poly(butyl methacrylate); or (iii) said polymer of the primer region is an ethylene
vinyl alcohol copolymer and said polymer of the reservoir region is poly(butyl methacrylate).

[0008] In one embodiment, the coating further includes a barrier region located on at least a selected portion of the
reservoir region for reducing the rate at which the active ingredient is released from the coating after insertion of the
device into a body of a patient. In another embodiment, the primer region includes a porous matrix extending from the
interface of the primer region and the reservoir region into the primer.

[0009] In another aspect, a stent comprising a coating for delivery of an active ingredient is provided, wherein the
coating comprises a primer region comprising a polymer and a reservoir region comprising a polymer and an active
ingredient, and wherein the thickness or the weight of the primer region is sufficiently high so as to allow drug loading
of 30% in the reservoir region without causing the coating to crack when the stent is expanded; and wherein: (i) said
polymer of the primer region is poly(butyl methacrylate) and said polymer of the reservoir region is an ethylene vinyl
alcohol copolymer; or (ii) said polymer of the primer region is poly(butyl methacrylate) and said polymer of the reservoir
region is poly(butyl methacrylate); or (iii) said polymer of the primer region is an ethylene vinyl alcohol copolymer and
said polymer of the reservoir region is poly(butyl methacrylate).

BRIEF DESCRIPTION OF THE FIGURES

[0010] Figures 1A-1E illustrate coatings in accordance with some of the embodiments of the present invention;
Figures 2A and 2B illustrate coatings having different layers;
Figure 3A illustrates a fluid on a solid substrate having a contact angle \( \Phi_1 \);
Figure 3B illustrates a fluid on a solid substrate having a contact angle \( \Phi_2 \);
Figure 4 graphically illustrates elution profiles for stents with a coating of ethylene vinyl alcohol copolymer impregnated
with vinblastine as made according to Reference Example 4;
Figure 5 graphically illustrates in vitro experimental data, in accordance with Reference Example 15, showing effects
of actinomycin D, mitomycin, and docetaxel on smooth muscle cell proliferation;
Figure 6A is a picture of a histology slide of a coronary vessel from the control group in accordance with Reference
Example 16;
Figure 6B is a picture of a histology slide of a coronary vessel from the actinomycin D group in accordance with
Reference Example 16;
Figure 7A is a picture of a histology slide of a coronary vessel from the control group in accordance with Reference
Example 26;
Figure 7B is a picture of a histology slide of a coronary vessel from the actinomycin D group in accordance with
Reference Example 26;
Figure 8A is a Scanning Electron Microscope photograph of a stent coating having a primer layer with ethylene vinyl
alcohol copolymer applied in accordance with Example 39;
Figure 8B is a Scanning Electron Microscope photograph of a stent coating having a primer layer with ethylene vinyl
alcohol copolymer applied in accordance with Example 39;
Figure 9A is a Scanning Electron Microscope photograph of a stent coating having a primer layer with poly(butyl
methacrylate) applied in accordance with Example 39; and
Figure 9B is a Scanning Electron Microscope photograph of a stent coating having a primer layer with poly(butyl
methacrylate) applied in accordance with Example 39.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0011] For ease of discussion, the methods and apparatus detailed herein will be described with reference to a coating
for a stent. The stent coated in accordance with embodiments of the present invention may be for example a self-
expandable stent or a balloon-expandable stent. The underlying structure of the stent can be of virtually any design.
The stent can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY),
stainless steel (316L), "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% molyb-
denum. Spents made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

Coating

[0012] Referring to Figure 1A, a body of a stent 20 is illustrated having a surface 22, e.g., a metallic surface such as stainless steel. A coating 24 is disposed on surface 22. Coating 24 includes a reservoir region 26 containing an active ingredient. A primer region 28 that is substantially free of any active ingredients is disposed underneath at least a portion of reservoir region 26. As illustrated in Figure 1B, coating 24 can also include a barrier region 30 that is substantially free of any active ingredients. The Figures have not been drawn to scale, and the depth and thickness of the various regions and layers have been over or under emphasized for illustrative purposes.

[0013] In one embodiment of the present the invention, the interface between the primer region and the reservoir region is modified to increase the permeability of the primer layer to the active ingredient. The interface can be modified using one of several methods. These methods include, for example, partially blending of the polymers of the primer region with the polymers of the reservoir region, modifying the surface of the primer layer by forming areas of roughness, or forming a porous matrix on the surface of the primer layer, as more fully described below.

[0014] The interface between the primer region and the reservoir region can be modified by partially blending the polymers of the primer region with the polymers of the reservoir region during the coating process through the use of a common solvent. For example, primer region 28 can be formed on stent 20 by applying a primer coating composition having a polymer dissolved in a solvent. Stent 20 can then be baked to essentially remove the solvent in the composition to form the coating. Subsequently, another composition is applied having a polymer, a solvent and an active ingredient dispersed therein. If the solvent in the active ingredient composition is capable of dissolving the polymer in the primer layer, then the polymers of the primer region and the reservoir region will intermix or blend. This blending can allow the active ingredient to be absorbed or flux into primer layer 28.

[0015] In another embodiment, asperities, or areas of roughness, are formed on the surface of the primer layer to increase the permeability of the primer layer. The asperities enable the primer region to physically entrap the reservoir region. In addition, the asperities can promote the migration of the active ingredient from the reservoir region to the primer region through capillary action. Because the active ingredient migrates into the deeper portions of the coating, the diffusion rate of the active ingredient from the coating is decreased when the coated device is inserted into a body of a patient. As a result, the asperities can promote an increased residence time of the active ingredient and thereby prevent the "burst effect" of the active ingredient from the coating. "Burst effect" refers to the quick release of an active ingredient from a polymeric coating when the device is inserted into a biological lumen.

[0016] The primer region can include a porous matrix extending from the interface of the primer region and the reservoir region into the primer region. The porous matrix can extend partially into the primer region, or all the way up to the surface of the implantable device. The active ingredient can migrate from the reservoir region by capillary action into the primer region.

[0017] In another embodiment of the present invention, the thickness of the primer region is increased relative to the thickness of the reservoir region. The thicker primer region can decrease the diffusion rate of the active ingredient from the coating. Additionally, by increasing the thickness of the primer region, the primer region can act as a more effective tie layer between the surface of the device and the reservoir region. For example, the thicker primer region can reduce or prevent the formation of cracks in the stent coating as the stent is expanded as shown in Examples 37-39. Typically the presence of an active ingredient in a polymeric matrix interferes with the ability of the matrix to adhere effectively to the surface of the device. An increase in the quantity of the active ingredient reduces the effectiveness of the adhesion. High drug loadings of, for example, 10-40% by weight in the coating significantly hinder the retention of the coating on the surface of the device. "Drug loading" means the percentage ratio of active ingredient to polymer by weight. By increasing the thickness of primer region 28 relative to reservoir region 26, primer region 28 can allow for the quantity of the active ingredient in reservoir region 26 to be increased without compromising the ability of reservoir region 26 to be effectively contained on the device during delivery and, if applicable, expansion of the device. The coating of the present invention has superior results when the drug loading is relatively high. In particular, the mechanical integrity of the coating of the present invention can withstand expansion of the stent (i.e., the coating does not significantly peel or crack) even when the drug loading in the coating is relatively high. In one embodiment of the present invention, drug loadings equal to or greater than 30% can be achieved.

[0018] Referring to Figure 1B, by way of example, reservoir region 26 for coating 24 can have a thickness T₁ of about 0.5 microns to about 10 microns. Primer region 28 can have a thickness T₂, examples of which can be in the range of about 0.1 to about 10 microns, more narrowly about 0.5 to about 5 microns. The thickness of the reservoir region T₁ is measured from the outer surface of the reservoir region to the primer region prior to the migration of the active ingredient from the reservoir region to the primer region. Similarly, the thickness of the primer region T₂ is measured from the outer surface of the primer region to the surface of the stent prior to the migration of the active ingredient from the reservoir region.
region to the primer region. In an embodiment of the present invention, \( T_2/T_1 \) is greater than or equal to 0.25. In another embodiment, \( T_2/T_1 \) is greater than or equal to 0.33. The particular thicknesses \( T_1 \) and \( T_2 \) are based in part on the type of procedure for which stent 20 is employed and the amount of the active ingredient that is desired to be delivered.

**[0019]** Referring to Figure 1B, diffusion barrier region 30 can have any suitable thickness \( T_3 \), as the thickness \( T_3 \) is dependent on parameters such as, but not limited to, the desired rate or duration of release and the procedure for which stent 20 will be used. Diffusion barrier region 30 can have a thickness \( T_3 \) of about 0.1 to about 10 microns, more narrowly dependent on parameters such as, but not limited to, the desired rate or duration of release and the procedure for which stent 20 is employed and the amount of the active ingredient that is desired to be delivered.

**[0020]** Each of the layers of the polymeric coating can have different sections with different properties in order to provide a coating with variable active ingredient release parameters. As illustrated in Figure 1D, for example, reservoir region 26 can include first and second reservoir sections 26A and 26B, each containing a different active ingredient, e.g., actinomycin D and taxol, respectively. Accordingly, coating 24 can carry a combination of at least two different active ingredients for sustained delivery. First and second sections 26A and 26B can be deposited by, for example, masking the area of primer region 28 over second section 26B and applying a first composition containing a first active ingredient to form first section 26A. First section 26A can then be masked and a second composition containing a second active ingredient can be applied to form second section 26B. This procedure can be followed to form any suitable number of sections containing a different active ingredient.

**[0021]** Barrier region 30 can be formed on reservoir sections 26A and 26B, as illustrated in Figure 1D. Referring to Figure 1E, barrier region 30 can also include a first barrier section 30A disposed over first reservoir section 26A containing a first active ingredient, e.g., actinomycin D. A second barrier section 30B can be formed over second reservoir section 26B containing a second active ingredient, e.g., taxol. First barrier section 30A is particle free and second barrier section 30B contains particles 32. As a result, coating 24 harbors two different release parameters for each of the active ingredients contained in reservoir sections 26A and 26B.

**[0022]** Different polymeric materials having interfacial compatibilities can be used to form individual, distinct layers for the primer, reservoir, and diffusion barrier components of the coating. Referring to Figure 2A, a coating 34 is provided having a primer region 36, made from a first polymeric material, formed on surface 22 of stent 20. A reservoir region 38 made from a second polymeric material is deposited on a selected area of primer region 36. A barrier region 40, made from a third polymeric material can be deposited on reservoir region 38. Examples of different polymeric materials having interfacial compatibilities include, for example, a poly(n-butyl methacrylate) primer with an EVAL reservoir layer. Other combinations can be derived by one of ordinary skill in the art.

**[0023]** One of ordinary skill in the art can appreciate that a variety of coating combinations can be provided. For example, as illustrated in Figure 2B, coating 34 contains primer region 36 made from a first polymeric material. Reservoir region 38, made from a second polymeric material, is formed on primer region 36. Reservoir region 38 contains first and second sections, illustrated as 38A and 38B. First and second sections 38A and 38B each contain a different active ingredient. Barrier region 40, made from a third polymeric material, can be deposited on reservoir region 38. Barrier region 40 includes a first section 40A deposited over first section 38A of reservoir region 38. Barrier region 40 additionally includes a second section 40B deposited over second section 38B of reservoir region 38. Second section 40B can include particles 32 and/or be made out of a fourth polymeric material to create a variety of different release parameters.

**Composition for The Primer Layer**

**[0024]** The embodiments of the composition for a primer layer are prepared by conventional methods wherein all components are combined, then blended. More particularly, a predetermined amount of a polymer or a prepolymer is added to a predetermined amount of a solvent or a combination of solvents. The mixture can be prepared in ambient pressure and under anhydrous atmosphere. If necessary, a free radical or UV initiator can be added to the composition for initiating the curing or cross-linking of the prepolymer. Heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent.

**[0025]** "Polymer," "poly," and "polymeric" are defined as compounds that are the product of a polymerization reaction and are inclusive of homopolymers, copolymers, terpolymers etc., including random, alternating, block, and graft vari-
The polymers should have a high capacity of adherence to the surface of an implantable device, such as a metallic surface of a stent. Stainless steel, such as 316L, is a commonly used material for the manufacturing of a stent. Stainless steel includes a chromium oxide surface layer which makes the stent corrosion resistant and confers, in large part, biocompatibility properties to the stent. The chromium oxide layer presents oxide, anionic groups, and hydroxyl moieties, which are polar. Consequently, polymeric materials with polar substituents and cationic groups can adhere to the surface.

[0026] The polymer for the primer layer is poly(butyl methacrylate) (PBMA), or ethylene vinyl alcohol copolymer. Ethylene vinyl alcohol copolymer, commonly known by the generic name EVOH or by the trade name EVAL, refers to copolymers comprising residues of both ethylene and vinyl alcohol monomers. One of ordinary skill in the art understands that ethylene vinyl alcohol copolymer may also be a terpolymer so as to include small amounts of additional monomers, for example less than about five (5) mole percentage of styrenes, propylene, or other suitable monomers. In a useful embodiment, the copolymer comprises a mole percent of ethylene of from about 27% to about 47%. Typically, 44 mole percent ethylene is suitable. Ethylene vinyl alcohol copolymers are available commercially from companies such as Aldrich Chemical Company, Milwaukee, Wis., or EVOH Company of America, Lisle, IL, or can be prepared by conventional polymerization procedures that are well known to one of ordinary skill in the art. The copolymer possesses good adhesive qualities to the surface of a stent, particularly stainless steel surfaces, and has illustrated the ability to expand with a stent without any significant detachment of the copolymer from the surface of the stent.

[0027] The solvent should be mutually compatible with the polymer and should be capable of placing the polymer into solution at the concentration desired in the solution. Useful solvents should also be able to expand the chains of the polymer for maximum interaction with the surface of the device, such as a metallic surface of a stent. Examples of solvent can include, but are not limited to, dimethylsulfoxide (DMSO), chloroform, water (buffered saline), xylene, acetone, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanol, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate, methylethylketone, propylene glycol monomethylether, isopropanol, N-methyl pyrrolidinone, toluene and mixtures thereof.

[0028] By way of example, and not limitation, the polymer can comprise from about 0.1% to about 35%, more narrowly about 2% to about 20% by weight of the total weight of the composition, and the solvent can comprise from about 65% to about 99.9%, more narrowly about 80% to about 98% by weight of the total weight of the composition. A specific weight ratio is dependent on factors such as the material from which the implantable device is made and the geometrical structure of the device.

[0029] A fluid can also be added to the composition to enhance the wetting of the composition for a more uniform coating application. To enhance the wetting of the composition, a suitable fluid typically has a high capillary permeation. Capillary permeation or wetting is the movement of a fluid on a solid substrate driven by interfacial energetics. Capillary permeation is quantitated by a contact angle, defined as an angle at the tangent of a droplet in a fluid phase that has taken an equilibrium shape on a solid surface. A low contact angle means a higher wetting liquid. A suitably high capillary permeation is quantitated by a contact angle, defined as an angle at the tangent of a droplet in a fluid phase that has taken an equilibrium shape on a solid surface. A low contact angle means a higher wetting liquid. A suitably high capillary permeation corresponds to a contact angle less than about 90°. Figure 3A illustrates a fluid droplet 10A on a solid substrate 12, for example a stainless steel surface. Fluid droplet 10A has a high capillary permeation that corresponds to a contact angle Φ₁, which is less than about 90°. In contrast, Figure 3B illustrates a fluid droplet 10B on solid substrate 12, having a low capillary permeation that corresponds to a contact angle Φ₂, which is greater than about 90°. The wetting fluid, typically, should have a viscosity not greater than about 50 centipoise at room temperature, narrowly about 0.3 to about 5 centipoise, more narrowly about 0.4 to about 2.5 centipoise. The wetting fluid, accordingly, when added to the composition, reduces the viscosity of composition.

[0030] The wetting fluid should be mutually compatible with the polymer and the solvent and should not precipitate the polymer. The wetting fluid can also act as the solvent. Useful examples of the wetting fluid include, but are not limited to, tetrahydrofuran (THF), dimethylformamide (DMF), 1-butanol, n-butyl acetate, dimethyl acetamide (DMAC), and mixtures and combinations thereof. By way of example and not limitation, the polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition; the solvent can comprise from about 19.9% to about 98.9%, more narrowly from about 58% to about 84% by weight of the total weight of the composition; the wetting fluid can comprise from about 1% to about 80%, more narrowly from about 5% to about 40% by weight of the total weight of the composition. The specific weight ratio of the wetting fluid depends on the type of wetting fluid employed and type of and the weight ratio of the polymer and the solvent. More particularly, tetrahydrofuran used as the wetting fluid can comprise, for example, from about 1% to about 44%, more narrowly about 21% by weight of the total weight of the solution. Dimethylformamide used as the wetting fluid can comprise, for example, from about 1% to about 80%, more narrowly about 8% by weight of the total weight of the solution. 1-butanol used as the wetting fluid can comprise, for example, from about 1% to about 33%, more narrowly about 9% by weight of the total weight of the solution. N-butyl acetate used as the wetting fluid can comprise, for example, from about 1% to about 34%, more narrowly about 14% by weight of the total weight of the solution. Dimethyl acetamide used as the wetting fluid can comprise, for example, from about 1% to about 40%, more narrowly about 20% by weight of the total weight of the solution.

[0031] Table 1 illustrates some examples of suitable combinations for the primer composition:
The embodiments of the composition for an active ingredient-containing or reservoir layer are prepared by conventional methods wherein all components are combined, then blended. More particularly, a predetermined amount of a polymeric compound is added to a predetermined amount of a mutually compatible solvent or combination of solvents. The polymeric compound can be added at ambient pressure and under anhydrous atmosphere. If necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example 12 hours in a water bath at about 60°C.

The polymer chosen must be a polymer that is biocompatible and minimizes irritation to the vessel wall when the device is implanted.

Ethylene vinyl alcohol is functionally a very suitable choice of polymer. The copolymer allows for good control capabilities over the release rate of the active ingredient. As a general rule, an increase in the amount of the ethylene comonomer content decreases the rate that the active ingredient is released from the copolymer matrix. The release rate of the active ingredient typically decreases as the hydrophilicity of the copolymer decreases. An increase in the amount of the ethylene comonomer content increases the overall hydrophobicity of the copolymer, especially as the content of vinyl alcohol is concomitantly reduced. It is also known that the release rate and the cumulative amount of the active ingredient that is released is directly proportional to the total initial content of the ingredient in the copolymer matrix. Accordingly, a wide spectrum of release rates can be achieved by modifying the ethylene comonomer content and the initial amount of the active ingredient.

The choice of polymer for the reservoir layer can be the same as or different from the selected polymer for the primer layer. The use of the same polymer significantly reduces or eliminates any interfacial incompatibilities, such as lack of an adhesive tie or bond, which may exist with the employment of two different polymeric layers.

The solvent should be capable of placing the polymer into solution at the concentration desired in the solution. Examples of solvent can include, but are not limited to, DMSO, chloroform, water (buffered saline), xylene, acetone, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanol, dimethylformamide, dimethyacetamide, cyclohexanone, and N-methyl pyrrolidinone. With the use of low ethylene content, e.g., 29 mol%, ethylene vinyl alcohol copolymer, a suitable choice of solvent is iso-propylalcohol (IPA) admixed with water.

Sufficient amounts of an active ingredient are dispersed in the blended composition of the polymer and the solvent. The active ingredient should be in true solution or saturated in the blended composition. If the active ingredient is not completely soluble in the composition, operations including mixing, stirring, and/or agitation can be employed to effect homogeneity of the residues. The active ingredient may be added so that the dispersion is in fine particles. The mixing of the active ingredient can be conducted in an anhydrous atmosphere, at ambient pressure, and at room temperature such that supersaturating the active ingredient is not desired.

The active ingredient should inhibit the activity of vascular smooth muscle cells. More specifically, the active ingredient is aimed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells.

"Smooth muscle cells" include those cells derived from the medial and adventitial layers of the vessel which proliferate in intimal hyperplastic vascular sites following vascular trauma or injury. Under light microscopic examination, characteristics of smooth muscle cells include a histological morphology of a spindle shape with an oblong nucleus located centrally in the cell with nucleoli present and myofibrils in the sarcoplasm. Under electron microscopic examination, smooth muscle cells have long slender mitochondria in the juxtanuclear sarcoplasm, a few tubular elements of granular endoplasmic reticulum, and numerous clusters of free ribosomes. A small Golgi complex may also be located near one pole of the nucleus.

"Migration" of smooth muscle cells means movement of these cells in vivo from the medial layers of a vessel into the intima, such as may also be studied in vitro by following the motion of a cell from one location to another, e.g., using time-lapse cinematography or a video recorder and manual counting of smooth muscle cell migration out of a defined area in the tissue culture over time.

"Proliferation" of smooth muscle cells means increase in cell number.

"Abnormal" or "inappropriate" proliferation means division, growth or migration of cells occurring more rapidly or to a significantly greater extent than typically occurs in a normally functioning cell of the same type, i.e., hyper-proliferation.
"Inhibiting" cellular activity means reducing, delaying or eliminating smooth muscle cell hyperplasia, restenosis, and vascular occlusions, particularly following biologically or mechanically mediated vascular injury or trauma or under conditions that would predispose a mammal to suffer such a vascular injury or trauma. As used herein, the term "reducing" means decreasing the intimal thickening that results from stimulation of smooth muscle cell proliferation. "Delaying" means retarding the progression of the hyper-proliferative vascular disease or delaying the time until onset of visible intimal hyperplasia, as observed, for example, by histological or angiographic examination. "Elimination" of restenosis following vascular trauma or injury means completely "reducing" and/or completely "delaying" intimal hyperplasia in a patient to an extent which makes it no longer necessary to surgically intervene, i.e., to reestablish a suitable blood flow through the vessel by, for example, repeat angioplasty, atherectomy, or coronary artery bypass surgery. The effects of reducing, delaying, or eliminating restenosis may be determined by methods known to one of ordinary skill in the art, including, but not limited to, angiography, intravascular ultrasound, fluoroscopic imaging, fiber optic visualization, optical coherence tomography, intravascular MRI, or biopsy and histology. Biologically mediated vascular injury includes, but is not limited to, injury caused by or attributed to autoimmune disorders, alloimmune related disorders, infectious disorders including endotoxins and herpes viruses such as cytomegalovirus, metabolic disorders such as atherosclerosis, and vascular injury resulting from hypothermia and irradiation. Mechanically mediated vascular injury includes, but is not limited to, vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous transluminal coronary angioplasty, vascular surgery, stent placement, transplantation surgery, laser treatment, and other invasive procedures which disrupted the integrity of the vascular intima or endothelium. The active ingredient of the invention is not restricted in use for therapy following vascular injury or trauma; rather, the usefulness of the active ingredient will also be determined by the ingredient's ability to inhibit cellular activity of smooth muscle cells or inhibit the development of restenosis.

The active ingredient also includes any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention as well as having positive pharmacological effects on the expression of the extracellular matrix. The active ingredient can also be for enhancing wound healing in a vascular site and improving the structural and elastic properties of the vascular site. Examples of such active ingredients include antiproliferative substances as well as antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitic, antibiotic, antitoxoid, and combinations thereof. A suitable example of an antiproliferative substance includes actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, WI 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include daunomycin, actinomycin IV, actinomycin I, actinomycin X, and actinomycin C. Examples of suitable antineoplastics include paclitaxel and docetaxel. Examples of suitable antiplatelets, anticoagulants, antifibrins, and antithrombins include heparin, sodium heparin, low molecular weight heparin, heparin sulfate, heparin having a hydrophobic counterion, hirudin, argatroban, forskolin, vapid, prostanoids, and prostacyclin analogs, dexamethasone, and dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), diprydiamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B (an antiplatelet drug from Centocore).

Examples of suitable antimotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of suitable cytostatic or antiproliferative agents include angiopentin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL (available from Squibb), CILAZAPRIL (available from Hoffman-LaRoche), or LISINOPRIL (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonist, LOVASTATIN (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available form Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotolease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents which may be appropriate include mannose-6-phosphate, superoxide dismutase, retinoic acid, suramin, asiasodioside, hyaluronan, alpha-interferon, genetically engineered epithelial cells, dexamethasone and rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin. Exposure of the composition to the active ingredient is not permitted to adversely alter the active ingredient's composition or characteristic. Accordingly, the particular active ingredient is selected for mutual compatibility with the blended composition.

The dosage or concentration of the active ingredient required to produce a favorable therapeutic effect should be less than the level at which the active ingredient produces toxic effects and greater than the level at which nontherapeutic results are obtained. The dosage or concentration of the active ingredient required to inhibit the desired cellular activity of the vascular region can depend upon factors such as the particular circumstances of the patient; the nature of the trauma; the nature of the therapy desired; the time over which the ingredient administered resides at the vascular site; and if other bioactive substances are employed, the nature and type of the substance or combination of substances. Therapeutic effective dosages can be determined empirically, for example by infusing vessels from suitable animal model systems and using immunohistochemical, fluorescent or electron microscopy methods to detect the agent...
and its effects, or by conducting suitable in vitro studies. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art.

By way of example, the polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can comprise from about 59.9% to about 99.8%, more narrowly from about 79% to about 87% by weight of the total weight of the composition, and the active ingredient can comprise from about 0.1% to about 75%, more narrowly from about 20% to about 60% by weight of the total weight of the composition. Selection of a specific weight ratio of the polymer and solvent is dependent on factors such as, but not limited to, the material from which the device is made, the geometrical structure of the device, and the type and amount of the active ingredient employed. The particular weight percentage of the active ingredient mixed within the composition depends on factors such as duration of the release, cumulative amount of release, and release rate that is desired.

Optionally, a second fluid or solvent, such as tetrahydrofuran (THF) or dimethylformamide (DMF) can be used to improve the solubility of an active ingredient in the composition and/or to increase the wetting of the composition. Increasing the wetting of the composition has been discovered to lead to the application of a more uniformed coating. The second fluid or solvent can be added to the composition or the active ingredient can be added to the second solvent prior to admixture with the blend.

With use of a second fluid, by way of example, the polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can comprise from about 19.8% to about 98.8%, more narrowly from about 49% to about 79% by weight of the total weight of the composition, the second solvent can comprise from about 1% to about 80%, more narrowly from about 5% to about 40% by weight of the total weight of the composition, and the active ingredient can comprise from about 0.1% to about 40%, more narrowly from about 1% to about 9% by weight of the total weight of the composition. Selection of a specific weight ratio of the polymer, the solvent, and the second solvent is dependent on factors such as, but not limited to, the material from which the implantable device is made, the geometrical structure of the device, and the type and amount of the active ingredient employed. The particular weight percentage of the active ingredient mixed within the composition depends on factors such as duration of the release, cumulative amount of release, and release rate that is desired.

Table 2 is an exemplary list of suitable combinations:

<table>
<thead>
<tr>
<th>POLYMER</th>
<th>SOLVENT</th>
<th>SECOND SOLVENT</th>
<th>ACTIVE INGREDIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVAL (29 mol % ethylene content e.g., Soarnole®)</td>
<td>IPA/H₂O (11:1)</td>
<td>-</td>
<td>Actinomycin D</td>
</tr>
<tr>
<td>EVAL (44 mol % ethylene content)</td>
<td>DMSO</td>
<td>THP</td>
<td>Actinomycin D</td>
</tr>
<tr>
<td>EVAL</td>
<td>DMSO</td>
<td>THF</td>
<td>Actinomycin D</td>
</tr>
<tr>
<td>EVAL</td>
<td>DMSO</td>
<td>DMF</td>
<td>Paclitaxel</td>
</tr>
</tbody>
</table>

Composition for The Rate Reducing Membrane

The embodiments of the composition for a rate-reducing membrane or diffusion barrier layer are prepared by conventional methods wherein all components are combined. In the embodiment with the use of particles, dispersion techniques should also be employed to circumvent agglomeration or formation of particle flocs.

More particularly, the composition for the barrier layer can be applied on a selected portion of the reservoir layer. The barrier layer can reduce the rate of release or delay the time at which the active ingredient is released from the reservoir region. In one embodiment, for maximum blood compatibility, polyethylene glycol or polyethylene oxide can also be added to the blend. Ethylene vinyl alcohol is functionally a very suitable choice of polymer. The copolymer allows for good control capabilities over the release rate of the active ingredient. As a general rule, an increase in the amount of the ethylene comonomer content decreases the rate that the active ingredient is released from the copolymer matrix. The release rate of the active ingredient decreases as the hydrophilicity of the polymer decreases. An increase in the amount of the ethylene comonomer content increases the overall hydrophobicity of the copolymer, especially as the content of vinyl alcohol is concomitantly reduced.

Usefully, the choice of polymer for the barrier layer can be the same as the selected polymer for the reservoir. The use of the same polymer can significantly reduce or eliminate interfacial incompatibilities, such as lack of adhesion, which may exist in the employment of two different polymeric layers.

Particles of inorganic or organic type can be added to the blend. The particles can be made from any suitable material having barrier-type properties, such as, but not limited to tortuosity, excluded volume, and adsorptivity. **Tor-
of carbon atoms and halogen substituted olefins, i.e., halogenated polyolefins. By way of example, and not limitation, low
density polyethylenes are generally understood to have densities of about 0.92 g cm\(^{-3}\) to about 0.96 g cm\(^{-3}\), however, no bright line can be drawn for density classifications and the density can vary according to the
supplier.

**[0054]** The particles should be dispersed in the blend. “Dispersed” is defined as the particles being present as individual
particles, not agglomerates or flocs. In certain polymer-solvent blends, certain particles will disperse with ordinary mixing.
Otherwise the particles can be dispersed in the composition by high shear processes such as ball mill, disc mill, sand
mill, attritor, rotor stator mixer, ultrasonication -- all such high shear dispersion techniques being well known to one of
ordinary skill in the art. Optionally, one of the aforementioned wetting fluids can also be added to the blend. The wetting
fluid can be added prior to, contemporaneously with, or subsequent to the agitation. Biocompatible dispersing agents
in the form of surfactants, emulsifiers, or stabilizers may also be added to the blend to assist in particle dispersion.

**[0055]** The particles can be made from a metal oxide, such as rutile titanium oxide, anatase titanium dioxide, niobium
oxide, tantalum oxide, zirconium oxide, titanium oxide, or tungsten oxide. In another embodiment, the particles can be
made from a main group oxide such as silica (silicon oxide) or alumina (aluminum oxide). Metallic particles such as gold,
hafnium, platinum, iridium, palladium, tungsten, tantalum, niobium, zirconium, titanium, aluminum, or chromium can also
be employed. In another embodiment, carbonaceous particles made from, for example, lamp black, furnace black, carbon
black, fumed carbon black, gas black, channel black, activated charcoal, diamond, diamond like carbon, or CVD diamond
can be employed. In yet another embodiment, the particles can be made from nitrides such as titanium nitride, chromium
nitride, and zirconium nitride. In yet another embodiment, carbides such as tungsten carbide, silicon carbide, or titanium
carbide, and calcium salts such as hydroxyapatite, dahlique, brushite, tricalcium phosphate, calcium sulphate, and calcium
carbonate can be used. Other inorganic particles can include particles made from silicides, barium titanate, and strontium
titanate.

**[0056]** The particles can also be made from a suitable polymer including polymers of polyolefins, polyurethanes,
cellulosics (i.e., polymers having mer units derived from cellulose), polyesters, polyamides, poly(hexamethylene isoph-
thalamide/terephthalamide) (commercially available as SELAR PA™), poly(ethylene terephthalate-co-p-oxybenzoate)
(PET/PHB, e.g., copolymer having about 60-80 mole percent PHB), poly(hydroxy amide ethers), polyacrylates, poly-
acrylonitrile, acrylonitrile/styrene copolymer (commercially available as LOPAC), rubber-modified acrylonitrile/acrylate
copolymer (commercially available as BAREX), poly(methyl methacrylate), liquid crystal polymers (LCP) (e.g., VECTRA
available from Hoechst-Celanese, ZENITE available from DuPont, and XYDAR available from Amoco Performance
Chemicals), poly(phenylene sulfide), polystyrenes, polycarbonates, poly(vinyl alcohols), poly(ethylene-vinyl alcohol)
(EVAL, e.g., having about 27 to about 47 mole percent of ethylene content), epoxies composed of bisphenol A based
diepoxides with amine cure, aliphatic polyketones (e.g., CARILON available from Shell, and KETONEX available from
British Petroleum), polysulfones, poly(ester-sulfone), poly(carbonate-sulfone), poly(3-hydroxy-
thalamide/terephthalamide) (commercially available as SELAR PA™), poly(ethylene terephthalate-co-p-oxybenzoate)
cellulosics (i.e., polymers having mer units derived from cellulose), polyesters, polyamides, poly(hexamethylene isoph-
thalamide/terephthalamide) (commercially available as SELAR PA™), poly(ethylene terephthalate-co-p-oxybenzoate)
(PET/PHB, e.g., copolymer having about 60-80 mole percent PHB), poly(hydroxy amide ethers), polyacrylates, poly-
acrylonitrile, acrylonitrile/styrene copolymer (commercially available as LOPAC), rubber-modified acrylonitrile/acrylate
copolymer (commercially available as BAREX), poly(methyl methacrylate), liquid crystal polymers (LCP) (e.g., VECTRA
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Chemicals), poly(phenylene sulfide), polystyrenes, polycarbonates, poly(vinyl alcohols), poly(ethylene-vinyl alcohol)
(EVAL, e.g., having about 27 to about 47 mole percent of ethylene content), epoxies composed of bisphenol A based
diepoxides with amine cure, aliphatic polyketones (e.g., CARILON available from Shell, and KETONEX available from
British Petroleum), polysulfones, poly(ester-sulfone), poly(carbonate-sulfone), poly(3-hydroxy-
xotane), poly(ether ketones), gelatin, amylose, parylene-C, parylene-D, parylene-N.

**[0057]** Representatives polyolefins include those based upon alpha-monoolefin monomers having from about 2 to 6
carbon atoms and halogen substituted olefins, i.e., halogenated polyolefins. By way of example, and not limitation, low
to high density polyethylenes, essentially unplasticized poly (vinyl chloride), poly (vinylidene chloride), poly (vinylfluoride),
poly (vinylidene fluoride), poly (tetrafluoroethylene) (Teflon), poly (chlorotrifluoroethylene) (KEL-F), and mixtures thereof
are suitable. Low to high density polyethylenes are generally understood to have densities of about 0.92 g cm\(^{-3}\) to about
0.96 g cm\(^{-3}\); however, no bright line can be drawn for density classifications and the density can vary according to the
supplier.

**[0058]** Representative polyurethanes include polyurethanes having a glass transition temperature above a storage
or ambient temperature, for example having a glass transition temperature of at least 40°C to 60°C, or having a non-
polar soft segment which includes a hydrocarbon, silicone, fluorosilicone, or mixtures thereof. For example, ELAST-
EON, manufactured by Elastomedic/CSIRO Molecular Science, is a polyurethane with a non-polar soft segment which
is made from 1,4-butanediol, 4,4’-methylenebisphenyl diisocyanate, and a soft segment composed of a blend poly(hex-
amethylene oxide) (PHMO) and bis(hydroxyethoxypropyl)polydimethylsiloxane (PDMS). A useful example has a blend
of 20% by weight PHMO and 80% by weight PDMS.

**[0059]** Representative examples of cellulosics include, but are not limited to, cellulose acetate having a degree of
substitution (DS) greater than about 0.8 or less than about 0.6, ethyl cellulose, cellulose nitrate, cellulose acetate butyrate,
methyl cellulose, and mixtures thereof.

**[0060]** Representative polyesters include saturated or unsaturated polyesters such as, but not limited to, poly (butylene
terephthalate), poly(ethylene 2,6-naphthalene dicarboxylate) (PEN), and poly (ethylene terephthalate).

**[0061]** Representative polyamides include crystalline or amorphous polyamides such as, but not limited to, nylon-6,
nylon-6,6, nylon-6,9, nylon-6,10, aromatic nylon MXD6 (manufactured by Mitsubishi Gas Chemical America, Inc.), and
mixtures thereof.
Methods For Applying the Compositions to the Stent

Before applying the primer layer, the surface of the stent is should be clean and free from contaminants that may be introduced during manufacturing. However, the surface of the stent requires no particular surface treatment to retain the applied coating. Metallic surfaces of stents can be, for example, cleaned by argon plasma process as is well known to one of ordinary skill in the art. Application of the composition can be by any conventional method, such as by spraying the composition onto the prosthesis or immersing the stent is in the composition. Operations such as wiping, centrifugation, blowing, or other web clearing acts can also be performed to achieve a more uniform coating. Briefly, wiping refers to physical removal of excess coating from the surface of the stent; centrifugation refers to rapid rotation of the stent about an axis of rotation; and blowing refers to application of air at a selected pressure to the deposited coating. The excess coating can also be vacuumed off the surface of the stent. The addition of a wetting fluid leads to a consistent application of the composition, which also causes the coating to be uniformly deposited on the surface of the stent.

With the use of the thermoplastic polymer EVAL, the deposited primer composition can 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. Unexpected 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 a stent. The device should be exposed to the heat treatment for any suitable duration of time, which would allow for the formation of the primer coating on the surface of the stent and allows for the evaporation of the solvent or combination of solvent and wetting fluid. It is understood that essentially all of the solvent and the wetting fluid will be removed from the composition but traces or residues can remain blended with the polymer.

Table 3 lists the \(T_g\) and \(T_m\) for a polymer used in embodiments of the present invention. \(T_g\) and \(T_m\) of polymers are attainable by one of ordinary skill in the art. The cited exemplary temperature and time for exposure is provided by way of illustration and it is not meant to be limiting.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>(T_g) (°C)</th>
<th>(T_m) (°C)</th>
<th>Exemplary Temperature (°C)</th>
<th>Exemplary Duration of Time For Heating</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVAL</td>
<td>55</td>
<td>165</td>
<td>140</td>
<td>4 hours</td>
</tr>
</tbody>
</table>

As the primer layer is being applied or after the primer coating has been formed, the surface of the primer can be modified in order to increase the surface area of the primer. For instance, in one embodiment, asperities, or areas of roughness, are created on the surface of the primer layer. A variety of methods can be used to create the asperities on the primer layer covering the outer surface of the stent. In one method, a pressurized stream of grit material is directed upon the polymeric primer coating after the primer layer has been dried. Examples of such processes include bead blasting and sand blasting. Bead blasting refers to the use of pressurized gas to project beads of a relatively uniform diameter at an object at a high velocity. The beads may be made of materials such as, but not limited to, aluminum oxide, silicon oxide, or latex. In sand blasting, the grit projected does not have as uniform diameter as in bead blasting. Both bead blasting and sand blasting are techniques that are well known to those of ordinary skill in the art. The roughness achieved using a pressurized grit source can be controlled by the size of the grit, e.g., the diameter of the beads, the pressure used, the distance between the grit source and the primer surface and the length of time the grit is blasted at the primer surface. By way of example and not limitation, the grit can be beads having a diameter of between 3 to 10 cm from the stent.

Laser etching can also be used to create asperities or pores on the primer coating after the primer layer has been dried. Laser lithographic methods are known to those of ordinary skill in the art. A laser is directed onto the primer coating for a predetermined period of time, which depends on the etch rate and the depth of etch desired. A patterned mask that has openings may be applied over the primer coating before the laser is utilized. The laser is then allowed to etch the primer through the openings of the mask. The use of patterned masks with laser etchings is known to those of ordinary skill in the art.

In addition, the manner in which the primer is deposited onto the outer surface of the stent can create the
Method of Use

In accordance with the above-described method, the active ingredient can be applied to a stent, retained on the stent during delivery and expansion of the stent, and released at a desired control rate and for a predetermined duration of time at the site of implantation. A stent having the above-described coating layers is useful for a variety of medical procedures, including, by way of example, treatment of obstructions caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating layers is particularly useful for treating occluded regions of blood vessels caused abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries and veins. Representative examples of sites include the iliac, renal, and coronary arteries. The application of the present invention should not, however, be limited to stents such that the embodiments of the coating can be used with a variety
of medical substrates.

Briefly, an angiogram is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by injecting a radiopaque contrast agent through a catheter inserted into an artery or vein as an x-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above described coating regions may then be expanded at the desired area of treatment. A post insertion angiogram may also be utilized to confirm appropriate positioning.

EXAMPLES

The embodiments of the 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 be construed to unduly limit the scope of the embodiments of the invention.

Example 1 (Reference Example)

Multi-Link™ stents (available from Guidant Corporation) were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVAL solution was made with 1 gram of EVAL and 7 grams of DMSO, making an EVAL:DMSO ratio of 1:7. The mixture was placed in a warm water shaker bath at 60°C for 24 hours. The solution was cooled and vortexed. The cleaned Multi-Link™ stents were dipped in the EVAL solution and then passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60°C. The coated stents were heated for 6 hours in an air box and then placed in an oven at 60°C, under vacuum condition, and for 24 hours. The coated stents were expanded on a 4.0 mm angioplasty balloon. The coatings remained intact on the stents. The coatings were transparent giving the Multi-Link™ stents a glossy-like shine.

Example 2 (Reference Example)

Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVAL solution was made with 1 gram of EVAL and 4 grams of DMSO, making an EVAL:DMSO ratio of 1:4. Dexamethasone was added to the 1:4 EVAL:DMSO solution. Dexamethasone constituted 9% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60°C. The coated stents were cured for 6 hours in an air box and then placed in a vacuum oven at 60°C for 24 hours. The above-recited step was repeated twice. The average weight of the coating was 0.0003 gram, having an estimated dexamethasone content of 75 ug per stent. The coated stents were expanded on a 4.0 mm angioplasty balloon. The coatings remained intact on the stents. Verification of coverage and physical properties of the coatings were visualized using a scanning electron microscope. The coatings were transparent, giving the Multi-Link™ stents a glossy-like shine.

Example 3 (Reference Example)

Multi-Link Duet™ stents are cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents are dried and plasma cleaned in a plasma chamber. The EVAL solution is made with 1 gram of EVAL and 4 grams of DMSO, making an EVAL:DMSO ratio of 1:4. Dexamethasone is added to the 1:4 EVAL:DMSO solution. Dexamethasone constitutes 9% by weight of the total weight of the solution. The solution is vortexed and placed in a tube. The cleaned Multi-Link™ stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60°C. The coated stents are cured for 6 hours in an air box then placed in a vacuum oven at 60°C for 24 hours. The single layered dexamethasone/EVAL coated stents are dipped into the 1:4 ratio EVAL:DMSO solution, free from dexamethasone. The stents are passed over the hot plate, cured, and placed in the oven as previously described. The top coating will provide a barrier layer for controlling the release of dexamethasone from the drug coated layer. The coated stents can be expanded on a 4.0 mm angioplasty balloon. It is predicted that the coatings will remain intact on the stents. The coatings will be transparent, giving the Multi-Link™ stents a glossy-like shine.
Example 4 (Reference Example)

[0081] Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVAL solution was made with 1 gram of EVAL and 7 grams of DMSO, making an EVAL:DMSO ratio of 1:7. Vinblastine was added to the 1:7 EVAL:DMSO solution. Vinblastine constituted 2.5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60°C. The coated stents were cured for 6 hours in an air box then placed in a vacuum oven at 60°C for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00005 gram, with an estimated vinblastine concentration of 12 microgram per stent. Some of the stents were sterilized by electron beam radiation. The sterilized and unsterilized vinblastine coated stents were tested for a 24 hour elution period by placing one sterilized and one unsterilized stent in 5 ml of phosphated saline solution (pH 7.4) at room temperature with rotational motion. The amount of vinblastine eluted was evaluated by High Performance Liquid Chromatography (HPLC) analysis. The results of this test are given below and plotted in Figure 4. The data indicates that electron beam radiation procedure does not interfere in the release of vinblastine from EVAL.

### Release Profile For Vinblastine - Unsterilized

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Microgram Released</th>
<th>Total Microgram Released</th>
<th>Microgram Release Per Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>2.12</td>
<td>2.12</td>
<td>4.24</td>
</tr>
<tr>
<td>3</td>
<td>1.91</td>
<td>4.03</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>0.27</td>
<td>4.30</td>
<td>0.27</td>
</tr>
<tr>
<td>6</td>
<td>0.38</td>
<td>4.68</td>
<td>0.19</td>
</tr>
<tr>
<td>24</td>
<td>1.7</td>
<td>6.38</td>
<td>0.09</td>
</tr>
</tbody>
</table>

### Release Profile For Vinblastine - Sterilized

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Microgram Released</th>
<th>Total Microgram Released</th>
<th>Microgram Released Per Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>2.14</td>
<td>2.14</td>
<td>4.28</td>
</tr>
<tr>
<td>3</td>
<td>1.7</td>
<td>3.84</td>
<td>0.68</td>
</tr>
<tr>
<td>4</td>
<td>0.28</td>
<td>4.12</td>
<td>0.28</td>
</tr>
<tr>
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Example 5 (Reference Example)

[0084] Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVAL solution was made with 1 gram of EVAL and 7 grams of DMSO, making an EVAL:DMSO ratio of 1:7. Cephalotaxin was added to the 1:7 EVAL:DMSO solution. Cephalotaxin constituted 5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60°C. The coated stents were cured for 6 hours in an air box then placed in a vacuum oven at 60°C for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00013 gram, with an estimated cephalotaxin concentration of 33 ug. The stents were sterilized by electron beam radiation. Cephalotaxin/EVAL coated stents and EVAL-coated control stents were implanted in the coronary arteries of 4 pigs, generally in accordance to the procedure set forth in "Restenosis After Balloon Angioplasty-A Practical Proliferative Model in Porcine Coronary Arteries" by Robert
Examples 6 (Reference Example)

[0085] Multi-Link Duet™ stents (available from Guidant Corporation) were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 20 minutes, then air dried. An EVAL stock solution was made with 1 gram of EVAL and 7 grams of DMSO, making an EVAL:DMSO ratio of 1:7. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. A co-solvent was added to the EVAL solution to promote wetting of the struts of the Multi-Link Duet™ stents. One gram of tetrahydrofuran (THF) was mixed with 1.2 grams of the EVAL:DMSO solution. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were then heated in a laboratory oven at 90°C for 4 hours. The thin EVAL coating adhered to stainless steel without peeling or cracking. EVAL forms a superior primer base coat for other polymers that do not adhere well to stainless steel.

Example 7 (Reference Example)

[0086] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL solution was made with 1 gram of EVAL and 5 grams of DMSO, making an EVAL:DMSO ratio of 1:5. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. The dissolved EVAL:DMSO solution was mixed with 24.6 grams of THF and 19.56 grams of DMSO. The solution was mixed then placed in the reservoir of an air pressured atomizing sprayer. Multi-Link Duet™ stents were sprayed while the stents rotated between 30 to 120 rpm. The spray time was dependent upon the flow rate of the sprayer. A flow rate between 1 to 20 mg/second required a stent to be sprayed between 1 to 30 seconds. The polymer coated Multi-Link Duet™ stents were heated in a forced air convection oven for 12 hours. The coatings were transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 8 (Reference Example)

[0087] Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution was made having an EVAL:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. Various co-solvents were examined to determine which co-solvent would promote a thicker coating. These co-solvents were THF, DMF, 1-butanol, and n-butyl acetate. The formulation for the co-solvents was as follows. Three grams of dissolved EVAL:DMSO solution was mixed with 0.9 gram of THF; three grams of dissolved EVAL:DMSO solution was mixed with 0.39 gram of DMF; three grams of dissolved EVAL:DMSO solution was mixed with 0.5 gram of 1-butanol; and three grams of dissolved EVAL:DMSO solution was mixed with 0.68 gram of n-butyl acetate. The cleaned Multi-Link Duet™ stents, attached to mandrel wires, were dipped into the solutions. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were heated in a forced air convection oven for 24 hours. A second layer of coating was applied to coated Multi-Link Duet™ stents and the stents were heated in the same manner as above. No difference was seen between the stents coated with the various co-solvents (e.g., greater weight of coating or physical appearance). All coated stents were transparent, giving the Multi-Link Duet™ stents a glossy-like shine. No webbing or bridging of the coating was seen between the struts of the coated Multi-Link Duet™ stents. The weight of the coatings was between 0.2 to 0.27 mg/stent.

Example 9 (Reference Example)

[0088] Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution is made having an EVAL:DMSO ratio of 1:4. The mixture is placed in a warm water shaker bath at 60°C for 12 hours. The solution is mixed, then cooled to room temperature. A 9% by weight Dexamethasone solution is formulated as follows: 2.96 grams of the EVAL:DMSO solution is mixed with 0.29 gram of Dexamethasone, then 0.9 gram of THF is added. The cleaned Multi-Link Duet™ stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner. It is predicted that the coatings will be transparent, giving the Multi-Link Duet™ stents a glossy-like
Example 10 (Reference Example)

Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution is made having an EVAL:DMSO ratio of 1:4. The mixture is placed in a warm water shaker bath at 60°C for 12 hours. The solution is mixed, then cooled to room temperature. A 9% by weight Dexamethasone solution is formulated as follows: 2.96 grams of the EVAL:DMSO solution is mixed with 0.29 gram of Dexamethasone, then 0.9 gram of THF is added. The cleaned Multi-Link Duet™ stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner. It is predicted that the coatings will be transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 11 (Reference Example)

Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution was made having an EVAL:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. A 4.75% by weight actinomycin D solution was formulated as follows: 600 milligrams of the EVAL:DMSO solution was mixed with 40 milligrams of actinomycin D, then 200 milligrams of THF was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 12 (Reference Example)

Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution was made having an EVAL:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. A 3.60% by weight actinomycin D solution was formulated as follows: 600 milligrams of the EVAL:DMSO solution was mixed with 40 milligrams of actinomycin D, then 480 milligrams of DMF was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 13 (Reference Example)

Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution was made having an EVAL:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. A 6.45% by weight actinomycin D solution was formulated as follows: 680 milligrams of the EVAL:DMSO solution was mixed with 80 milligrams of actinomycin D, then 480 milligrams of DMF was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 14 (Reference Example)

Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution is made having an EVAL:DMSO ratio of 1:40. The mixture is placed in a warm water shaker bath at 60°C for 12 hours. The solution is mixed, then cooled to room temperature. A 0.60% by weight actinomycin D solution can be formulated as follows: 4920 milligrams of the EVAL:DMSO solution is mixed with 40 milligrams of Actinomycin D, then 2000 milligrams of THF is added. The cleaned Multi-Link Duet™ stents can be sprayed upon by the above formulation. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner.
Examples 15 (Reference Example)

Inhibition of SMC proliferation with Actinomycin D

[0094] Medial smooth muscle cells (SMC) were isolated from rat aorta and cultured according to explant methods known to one of ordinary skill in the art. Cells were harvested via trypsinization and subcultivated Cells were identified as vascular SMC through their characteristic hill-and-valley growth pattern as well as indirect immunofluorescence with monoclonal anti SMC α-actin. Studies were performed with cells at passage 3-4. SMC monolayers were established on 24 well culture dishes, scrape wounded and treated with actinomycin D, mytomycin and docetaxel. The cells were exposed to the drug solution of different concentrations for 2 hours and then washed with buttered saline solution. The proliferation of the cells was quantified by standard technique of thymidine incorporation. The results from the study are tabulated in Figure 5.

[0095] The IC50 (concentration at which 50% of the cells stop proliferating) of actinomycin D was 10^-9M as compared to 5 x 10^-5M for mitomycin and 10^-6M for docetaxel. Actinomycin D was the most potent agent to prevent SMC proliferation as compared to other pharmaceutical agents.

Example 16 (Reference Example)

Reduction in Restenosis in the Porcine Coronary Artery Model

[0096] Porcine coronary models were used to assess the degree of the inhibition of neointimal formation in the coronary arteries of a porcine stent injury model by Actinomycin D, delivered with a microporous balloon catheter (1x10^6 pores/mm^2 with sizes ranging from 0.2-0.8 micron).

[0097] The preclinical animal testing was performed in accordance with the NIH Guide for Care and Use of Laboratory Animals. Domestic swine were utilized to evaluate effect of the drug on the inhibition of the neointimal formation. Each testing procedure, excluding the angiographic analysis at the follow-up endpoints, was conducted using sterile techniques. During the study procedure, the activated clotting time (ACT) was monitored regularly to ensure appropriate anticoagulation. Base line blood samples were collected for each animal before initiation of the procedure. Quantitative coronary angiographic analysis (QCA) and intravascular ultrasound (IVUS) analysis was used for vessel size assessment.

[0098] The vessels at the sites of the delivery were denuded by inflation of the PTCA balloons to 1:1 balloon to artery ratio and moving the balloons back and forth 5 times. The drug was delivered to the denuded sites at 3.5 atm (3.61 Kg/sq cm) for 2 minutes using the microporous balloon catheters before stent deployment The average volume of delivery was about 3.3 +/- 1.2 ml. Following drug delivery, stents were deployed at the delivery site such that final stent to artery ratio was 1:1:1.

[0099] QCA and IVUS analyses were used for stent deployment guidance. Pre-stenting IVUS measurements of the lumen size at the targeted vessel sites were performed for determination of the balloon (size) inflation pressure. Quantitative analysis of the stented coronary arteries to compare pre-stenting, post-stenting, follow-up minimal luminal diameters, stent recoil, and balloon/stent to artery ratio were performed. Following stent implantation and final angiogram, all devices were withdrawn and the wounds closed; the animals were allowed to recover from anesthesia as managed by the attending veterinarian or animal care professionals at the research center.

[0100] Upon return to the research laboratory at the 28-day endpoint, angiographic assessments were performed. Coronary artery blood flow was assessed and the stented vessels were evaluated to determine minimal lumen diameter. The animals were euthanized following this procedure at the endpoint. Following euthanasia, the hearts were pressure perfusion fixed with formalin and prepared for histological analysis, encompassing light microscopy, and morphometry. Morphometric analysis of the stented arteries included assessment of the position of the stent struts and determination of vessel/lumen areas, percent (%) stenosis, injury scores, intimal and medial areas and intima/media ratios. Percent stenosis is quantitated by the following equation:

\[
\text{Percent Stenosis} = \frac{\text{IEL area} - \text{lumen area}}{\text{IEL area}}
\]

where IEL is the internal elastic lamia.

[0101] The control group of animals received delivery of water instead of the drug. The test group of animals received actinomycin D in two different concentration of 10^-5M and 10^-4M. The results of the study are tabulated in Table 4. The percent stenosis in the treated groups (32.3 +/-11.7) was significantly decreased as compared to the control groups (48.8 +/- 9.8). Figures 6A and 6B illustrate sample pictures of the histology slides of the coronary vessels from the control and the Dose 1 group, respectively.
The results of the in vitro and in vivo standard test procedures demonstrate that actinomycin D is useful for the treatment of hyper-proliferative vascular disease. Specifically, actinomycin D is useful for the inhibition of smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly occlusions following a mechanically mediated vascular trauma or injury.

Example 17 (Reference Example)

Multi-Link Duet™ stents (13 mm in length) were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution was made having an EVAL:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. A 5.06% by weight actinomycin D solution was formulated as follows: 40 milligrams of actinomycin D was dissolved in 150 milligrams of THF, then 600 milligrams of the EVAL:DMSO was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were cured in a forced air convection oven at 60°C for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60°C for 4 hours. An average coating weight of about 260 micrograms and an average actinomycin D loading of about 64 micrograms was achieved.

Example 18 (Reference Example)

Multi-Link Duet™ stents (13 mm in length) were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution was made having an EVAL:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. A 3.75% by weight actinomycin D solution was formulated as follows: 60 milligrams of actinomycin D was dissolved in 310 milligrams of DMF, then 1.22 grams of EVAL:DMSO solution was added. The cleaned Multi-Link Duet™ stents were attached to...
mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were cured in a forced air convection oven at 60°C for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60°C for 4 hours. An average coating weight of about 270 micrograms with an average actinomycin D content of about 51 micrograms was achieved.

Example 19 (Reference Example)

Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution was made having an EVAL:DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60°C for 12 hours. The solution was mixed, then cooled to room temperature. A 6.1% by weight actinomycin D solution was formulated as follows: 100 milligrams of actinomycin D was dissolved in 310 milligrams of DMF, then 1.22 grams of EVAL:DMSO was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60°C. The coated stents were cured in a forced air convection oven at 60°C for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60°C for 4 hours. An average coating weight of about 250 micrograms and an average actinomycin D loading of about 75 micrograms was achieved.

Example 20 (Reference Example)

Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVAL stock solution is made having an EVAL: DMSO ratio of 1:40. The mixture is placed in a warm water shaker bath at 60°C for 12 hours. The solution is mixed, then cooled to room temperature. A 0.60% by weight actinomycin D solution can be formulated as follows: 4920 milligrams of the EVAL: DMSO solution is mixed with 40 milligrams of Actinomycin D, then 2000 milligrams of THF is added. The cleaned Multi-Link Duet™ stents can be sprayed upon by the above formulation. The coated stents are cured in a forced air convection oven 60°C for 15 minutes. Additional layers of the coating are applied and cured in the above manner. The final curing step for the coated stents is conducted for about 4 hours.

Example 21 (Reference Example)

A stainless steel stent can be spray coated with a formulation of EVAL and a drug, as previously described in any of the above examples. A diffusion barrier composition can be formulated with 2 grams of EVAL blended with 20 grams of dimethylsulfoxide. 2.2 grams of fumed silica can be added and dispersed with a high shear process. With constant agitation, 50 grams of tetrahydrofuran and 30 grams of dimethylformamide are admixed with the blend. The stent, having the EVAL coating, can be immersed in the diffusion barrier composition to form a layer.

Example 22 (Reference Example)

A stainless steel stent can be spray coated with a formulation of EVAL and a drug, as previously described in any of the above examples. A diffusion barrier formulation can be made by dissolving 8 grams of EVAL into 32 grams of dimethylsulfoxide. 10.5 grams of solution precipitated hydroxyapatite can be added to the blend. The particles can be dispersed using a ball mill. The final solution is diluted with 39 grams of tetrahydrofuran, added slowly with constant agitation. It is predicted that the diffusion barrier will reduce the rate at which the drug is released from the stent.

Example 23 (Reference Example)

A stainless steel stent can be coated with a formulation of EVAL and a drug, as previously described in any of the above examples. A diffusion barrier formulation can be made by dissolving 8 grams of EVAL in 32 grams of dimethylsulfoxide. 10.5 grams of solution precipitated hydroxyapatite can be added to the blend. The particles can be dispersed using a ball mill. With constant agitation, 30 grams of tetrahydrofuran can be added. The stent can be coated by immersion followed by centrifugation.

Example 24 (Reference Example)

A stent can be coated with a formulation of EVAL and a drug, as previously described in any of the above examples. 8 grams of EVAL can be added 50 grams of dimethylsulfoxide and the polymer can be dissolved by agitation
and heat. Four grams of lamp black can be added and dispersed in a ball mill. 60 grams of dimethyl sulfoxide and 110 grams of tetrahydrofuran are slowly added while stirring. The stent can be spray coated.

**Example 25** (Reference Example)

[0111] A stent can be coated with a formulation of EVAL and a drug, as previously described in any of the above examples. Colloidal gold can be prepared by reduction of tetrachloroauric acid with sodium citrate in aqueous solution. The solution can be exchanged by rinsing with tetrahydrofuran. Eight grams of EVAL can be dissolved in 32 grams of dimethylsulfoxide. To this is added a solution of 77 grams of colloidal gold in 32 grams of tetrahydrofuran. The stent can be coated by a dip coating process.

**Example 26** (Reference Example)

[0112] In vivo data is provided illustrated positive remodeling caused by the application of actinomycin D. Stents coated with EVAL impregnated with actinomycin D and a control group of stents coated with EVAL free from actinomycin D were implanted in porcine coronary arteries. The animals were sacrificed at the end of 28 days. The EEL area of the actinomycin D-loaded vessels was statistically significantly greater than the EEL area of the control vessels.

[0113] The index of remodeling was 1.076 (8.54/7.94).

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<th>Std. Dev.</th>
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### EEL Area (mm²)

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<td></td>
<td></td>
<td></td>
<td>8.5425</td>
</tr>
<tr>
<td>SD</td>
<td>0.8046</td>
<td></td>
<td></td>
<td></td>
<td>0.7349</td>
</tr>
</tbody>
</table>

### ActD vs EVAL

<table>
<thead>
<tr>
<th></th>
<th>P= 0.014709</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVG % EEL growth</td>
<td>7.486304</td>
</tr>
</tbody>
</table>

### IEL Area (mm²)

<table>
<thead>
<tr>
<th>ill #</th>
<th>Control IEL</th>
<th>ID #</th>
<th>Actinomycin D IEL</th>
<th>ID#</th>
<th>EVAL IEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 LCX d</td>
<td>5.2178</td>
<td>63 LCX d</td>
<td>6.3785</td>
<td>63 LAD d</td>
<td>6.9687</td>
</tr>
<tr>
<td>48 LCX m</td>
<td>6.2108</td>
<td>63 LCX m</td>
<td>7.5206</td>
<td>63 LAD m</td>
<td>7.3908</td>
</tr>
<tr>
<td>48 LCX p</td>
<td>6.1125</td>
<td>63 LCX p</td>
<td>6.9992</td>
<td>63 LAD p</td>
<td>7.3563</td>
</tr>
<tr>
<td>49 LAD d</td>
<td>7.2848</td>
<td>63 RCA d</td>
<td>6.9632</td>
<td>64 LCX d</td>
<td>6.4420</td>
</tr>
<tr>
<td>49 LAD m</td>
<td>7.4117</td>
<td>63 RCA m</td>
<td>6.0418</td>
<td>64 LCX m</td>
<td>6.0064</td>
</tr>
<tr>
<td>49 LAD p</td>
<td>5.9918</td>
<td>63 RCA p</td>
<td>7.4794</td>
<td>64 LCX p</td>
<td>5.9970</td>
</tr>
<tr>
<td>58 LAD d</td>
<td>7.2049</td>
<td>65 LAD d</td>
<td>6.2324</td>
<td>64 RCA d</td>
<td>6.8001</td>
</tr>
<tr>
<td>58 LAD m</td>
<td>6.9334</td>
<td>65 LAD m</td>
<td>8.3785</td>
<td>64 RCA m</td>
<td>6.8561</td>
</tr>
<tr>
<td>58 LAD p</td>
<td>6.9454</td>
<td>65 LAD p</td>
<td>8.5819</td>
<td>64 RCA p</td>
<td>7.0172</td>
</tr>
</tbody>
</table>
Figures 7A and 7B illustrate sample pictures of the histology slides of the coronary vessels from the control group 64 RCA (Right Coronary Group) and the actinomycin D loaded stent group 68 LAD (Left Anterior Descending), respectively. The stent used was an Advanced Cardiovascular Systems Multi-Link Duet™ (stainless steel). As is illustrated by Figure 7B, the positive remodeling of EEL 50, caused by the application of actinomycin D, creates a gap between stent struts 52 and EEL 50. Thrombus deposits, illustrated by reference number 54, are formed in the gap over time. The use of a self-expandable stent eliminates the formation of the gap as the stent self-expands in response to the positive remodeling of IEL. Thrombus deposits can be, accordingly, eliminated.

Actinomycin D induces the positive remodeling of the vessel walls, more particularly positive remodeling of the external elastic lamina (EEL) of a blood vessel wall. Positive remodeling is generally defined as the ability of the vessel walls to structurally adapt, by increasing in lumen size, to chronic stimuli. A positively remodeled lumen wall has a greater diameter or size as compared to a lumen wall which has not been subjected to the remodeling effect. Accordingly, the flow of blood through the remodeled site is increased - flow which would have otherwise been reduced because of, for example, the presence of plaque build-up or migration and proliferation of cells. The index of remodeling is defined by the ratio of the area circumscribed by the EEL of the lesion site to the area circumscribed by the EEL of a reference site. As a result of the positive remodeling of the EEL, the internal elastic lamina (IEL), in response, can also increases in area or diameter. Actinomycin D, or analogs or derivative thereof, not only can inhibit abnormal or inappropriate migration and/or proliferation of smooth muscle cells, which can lead to restenosis, but can also induce positive remodeling of the blood vessel walls. Thus the widening of the diseased region becomes more pronounced.

<table>
<thead>
<tr>
<th>ill #</th>
<th>Control</th>
<th>ID #</th>
<th>Actinomycin D</th>
<th>ID#</th>
<th>EVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>59 LCA d</td>
<td>7.2640</td>
<td>68 LAD d</td>
<td>8.0964</td>
<td>65 LCX d</td>
<td>5.2485</td>
</tr>
<tr>
<td>59 LCX m</td>
<td>6.2014</td>
<td>68 LAD m</td>
<td>8.6879</td>
<td>65 LCX m</td>
<td>6.1135</td>
</tr>
<tr>
<td>59 LCX p</td>
<td>6.7283</td>
<td>68 LAD p</td>
<td>8.0914</td>
<td>65 RCA d</td>
<td>7.1525</td>
</tr>
<tr>
<td>59 RCA d</td>
<td>6.0519</td>
<td>69 LCX d</td>
<td>8.7181</td>
<td>65 RCA m</td>
<td>6.4815</td>
</tr>
<tr>
<td>59 RCA m</td>
<td>5.9992</td>
<td>69 LCX m</td>
<td>8.0273</td>
<td>65 RCA p</td>
<td>7.1775</td>
</tr>
<tr>
<td>59 RCA p</td>
<td>5.9032</td>
<td>69 LCX p</td>
<td>8.5222</td>
<td>68 LCX d</td>
<td>6.9571</td>
</tr>
<tr>
<td>62 LCX d</td>
<td>6.5329</td>
<td>69 RCA d</td>
<td>8.3796</td>
<td>68 LCX m</td>
<td>6.5724</td>
</tr>
<tr>
<td>62 LCX m</td>
<td>6.2804</td>
<td>69 RCA m</td>
<td>6.4219</td>
<td>68 LCX p</td>
<td>6.7740</td>
</tr>
<tr>
<td>62 LCX p</td>
<td>4.9303</td>
<td>69 RCA p</td>
<td>7.7757</td>
<td>68 RCA d</td>
<td>7.2425</td>
</tr>
<tr>
<td>62 RCA d</td>
<td>7.0977</td>
<td>70 LCX d</td>
<td>7.5392</td>
<td>68 RCA p</td>
<td>7.5554</td>
</tr>
<tr>
<td>62 RCA m</td>
<td>6.7466</td>
<td>70 LCX m</td>
<td>7.6573</td>
<td>69 LAD d</td>
<td>5.5505</td>
</tr>
<tr>
<td>62 RCA p</td>
<td>7.1747</td>
<td>70 LCX p</td>
<td>6.9749</td>
<td>69 LAD m</td>
<td>5.5571</td>
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<tr>
<td>67 LAD d</td>
<td>8.0264</td>
<td>70 RCA d</td>
<td>6.2815</td>
<td>69 LAD p</td>
<td>6.2697</td>
</tr>
<tr>
<td>67 LAD m</td>
<td>8.1144</td>
<td>70 RCA m</td>
<td>5.9760</td>
<td>70 LAD d</td>
<td>6.3212</td>
</tr>
<tr>
<td>67 LAD p</td>
<td>7.2091</td>
<td>70 RCA p</td>
<td>7.6195</td>
<td>70 LAD m</td>
<td>6.6518</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70 LAD p</td>
<td>6.9032</td>
</tr>
<tr>
<td>AVG</td>
<td>6.6489</td>
<td></td>
<td>7.4727</td>
<td></td>
<td>6.6025</td>
</tr>
<tr>
<td>SD</td>
<td>0.7883</td>
<td></td>
<td>0.8972</td>
<td></td>
<td>0.6130</td>
</tr>
</tbody>
</table>

ActD vs EVAL

| p= | 0.000283 |
| AVG % IEL growth | 13.17981 |
Example 27 (Reference Example)

[0116]  2 grams of an acrylate terminated urethane (Henkel 12892) can be added to 18 grams of ethyl acetate with 0.08 grams of benzophenone and 0.08 grams of 1-hydroxycyclohexyl phenyl ketone. After application, the stent can be cured for 5 minutes under medium pressure mercury lamp.

Example 28 (Reference Example)

[0117]  For a thermoset system, 1.67 grams of Epon 828 (Shell) resin can be added to 98 grams of propylene glycol monomethyl ether and 0.33 grams of Jeffamine T-430 (Huntsman). After application, the stent can be baked for 2 hours at 80°C and 2 hours at 160°C.

Example 29 (Reference Example)

[0118]  A 0.25% (w/w) solution of tetra-n-butyl titanate can be made in anhydrous ethyl acetate. The solution can be applied by spraying to a surface of a stainless steel stent. The stent can be heated at 100°C for two hours.

Example 30 (Reference Example)

Objective

[0119]  Coated stents tested through simulated delivery to a target lesion for testing the mechanical integrity of the coating.

<table>
<thead>
<tr>
<th>Group</th>
<th>Quantity</th>
<th>Coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>Control: 2% EVAL in 1:1 THF:DMSO, 3:1 EVAL: Act-d; no primer</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>2% EVAL in 5:3:2 THF:DMF:DMSO, 3:1 EVAL: Act-d; no primer</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>EVAL primer layer baked at 120 C/60C for 2/10 hrs + 2% EVAL in 1:1 THF:DMSO, 3:1 EVAL: Act-d; primer</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>EVAL primer layer baked at 140 C/60 C for 2/2 hrs + 2% EVAL in 1:1 THP:DMSO, 3:1 EVAL: Act-d; primer</td>
</tr>
</tbody>
</table>

Background

[0120]  In this experiment four different treatment groups were tested through a simulated delivery and use. Number of peel defects at rings 3, 5, and 7, with a peel defect defined as a location on the stent where coating has been removed to expose bare stent or an underlying layer of coating, were observed.

Materials and Equipment

[0121]

1. 8, 13 mm Solo stents (Available from Guidant Corporation);
2. 8, 3.0 x 30 mm Duet catheters;
3. 100% IPA;
4. Tominator Stent Crimper S/N 400;
5. 7F JL4 guiding catheter;
6. 0.014" Balance Middle Weight guide wire;
7. Rotating Hemostatic Valve; and
8. SVS tortuosity tree (2.5 mm lumen tapering to 1.5 mm lumen).

Preparation

[0122]  Crimped the stents onto the catheters using the Tominator crimper and the following conditions: 3 crimps, 65 psi, rotation between crimps.
Test Procedure

1. Performed simulation using heart model having a tortuosity and contained in a tub filled with water.
   a. Inserted the stents through the following set-up: RHF, 7F JL4 guiding catheter, SVS tortuosity tree (2.5 mm lumen at entrance, 1.5 mm lumen at exit).
   b. Once the stent passed through the distal opening of tortuosity, the balloon was cut from the catheter just distal to proximal marker.

2. Examined the stents under 100x magnification using Leica MZFLIII microscope in the clean environment room (CER).
3. Recorded number of peel defects at stent rings 3, 5, and 7. Only the outer diameter ("OD") was examined for peel defects.
4. All test samples were handled with personal protective equipment (PPE) appropriate for drug containing stents.

Data Summary and Results

<table>
<thead>
<tr>
<th>Group</th>
<th># Peel Defects/Ring</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (THP)</td>
<td>2.0</td>
<td>-</td>
</tr>
<tr>
<td>B (DMF)</td>
<td>5.3</td>
<td>Began with poor coating finish.</td>
</tr>
<tr>
<td>C (140°C)</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>D (120°C)</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Discussion

The test was performed to observe the coating integrity after a simulated delivery to a tortuosity without a lesion. The primer layer improved coating adhesion to the stents that resulted in fewer defects after a simulated use. Group B had a number defects. Although the coating surface for Group B was poor to begin with, and the defects were not too severe.

Example 31 (Reference Example)

Objective

The adhesion of 0.67% Actinomycin-D (in 5% EVAL 1:1 THF:DMSO solution) coating on stents with two different surface treatments was compared to control samples. The specific surface treatments consisted of (1) Argon plasma treatment; and (2) Argon plasma treatment with a primer layer of 5% EVAL in 1:1 DMSO:DMF solution applied with the dip-spin process, i.e., centrifugation process, and followed by heat treatments at 120°C for two hours and 60°C for 10 hours. The test method used to test adhesion of coatings on stents was a wet flow test, expanding the stents in a Tecoflex tubing at 37°C of water or saline. Water or saline is then flushed through the stents for 18 hours to simulate blood flow through the stents. The stents were then removed from the Tecoflex with a "stent catcher" and observed under optical microscope for defects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>B</td>
<td>Argon plasma</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>C</td>
<td>Argon plasma + 5% EVAL in 1:1 DMSO:DMF heated at 120°C for two hours and 60°C for 10 hours</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>D</td>
<td>None</td>
<td>100 mL/min</td>
</tr>
</tbody>
</table>
Materials and Equipment

[0127]

1. 30, 13 mm coated Solo stents, cleaned ultrasonically in IPA for 15 minutes;
2. 30, balloon catheters or subassemblies to expand the stents (3.0 x 20 mm RX Rocket);
3. 0.67% Actinomycin-D in 5% EVAL with 1:1 THF:DMSO solution;
4. 5% EVAL in 1:1 DMF:DMSO;
5. 3.0 mm, thin walled Tecoflex tubing;
6. Saline;
7. Lint Free Wipes SU 00126 or equivalent;
8. 100% IPA;
9. Oven;
10. Timer;
11. Centrifuge;
12. Plasma Machine (available from Advanced Plasma System);
13. Ultrasonic cleaner;
14. Mettler balance with 0.1 micrograms resolution; and
15. Spray Coater with Fan Air Cap and EFD dispenser (EFD Inc. East Providence, RI).

Preparation

[0128]

1. Sonicated the stents in IPA for 15 minutes;
2. Weighed each stent to the nearest microgram;
3. Prepared 5 stent samples:

   A. Groups A and D:

   i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no
      blowing.
   ii. Weighed each sample at the end of the last pass to the nearest microgram.
   iii. Baked the samples for 4 hrs at 60°C.
   iv. Placed the stents into the Tecoflex tubing with a balloon catheter--submerged in 37°C saline.

   B. Groups B and E:

   i. Placed the samples on a sample holder. Performed argon plasma treatment using plasma machine.
   ii. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no
      blow.
   iii. Weighed each sample at the end of the last pass to the nearest microgram.
   iv. Baked the samples for 4 hrs at 60°C.
   v. Placed the stents into the Tecoflex tubing with the balloon catheter--submerged in 37°C saline.

   C. Groups C and F:

---

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Argon plasma</td>
<td>100 mL/min</td>
</tr>
<tr>
<td>F</td>
<td>Argon plasma + 5% EVAL in 1:1 DMF:DMSO heated at 120°C for two hours and 60°C for 10 hours</td>
<td>100 mL/min</td>
</tr>
</tbody>
</table>
i. Placed samples flat on a sample holder. Performed argon plasma treatment.
ii. Used dip-spin process to apply 2% EVAL primer layer, 1:1 DMSO:DMF.
iii. Baked the stents at 120°C for two hours.
iv. Baked the stents at 60°C for ten hours.
v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
vi. Weighed each sample at the end of the last pass to the nearest microgram.
vii. Baked the samples for 4 hrs at 60°C.
viii. Placed the stents into the Tecoflex tubing with a balloon catheter--submerged in 37°C water.

Test Procedure

[T0129]  Tested three samples from each group. Wet Flow Testing:

1. Expanded the stents into the 3.0 mm Tecoflex tubing in 37°C saline.
2. Performed wet flow testing for 18 hrs.
3. Removed the stents from the Tecoflex tubing with a stent catcher.
4. Count defects, based on the following categories: Defect type; defect size; defect location; and peel defects on rings 3, 5, and 7.
5. Stent weight could not be a measurable because of the loss of the drug and uptake of water.
6. All test samples were handled with PPE appropriate for drug containing stents.

Data Summary

[T0130]

<table>
<thead>
<tr>
<th>Group</th>
<th>Average # of Peel Defects/Stent (3 rings) After Flow Test</th>
<th>Average # Peel Defects/Ring After Flow Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>18.0</td>
<td>6.0</td>
</tr>
<tr>
<td>B</td>
<td>15.3</td>
<td>5.1</td>
</tr>
<tr>
<td>C</td>
<td>14.3</td>
<td>4.9</td>
</tr>
<tr>
<td>D</td>
<td>14.0</td>
<td>4.8</td>
</tr>
<tr>
<td>E</td>
<td>14.0</td>
<td>4.7</td>
</tr>
<tr>
<td>F</td>
<td>0.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Discussion

[T0131]  Peel defects are defined as areas where the coating separated from the stent. The number of peel defects were counted on the stents' OD/sidewall on rings 3, 5, and 7. The flow field was on the inner diameter ("ID") of the stents' surface. Some of the damage to the OD surface could have been aggravated by the Tecoflex tubing. The number of peel defects observed on groups C and F (EVAL primer) was clearly lower than the other two test groups, regardless of flow rate.

[T0132]  The increased flow rate did not induce more peel defects.

Example 32 (Reference Example)

Objective

[T0133]  The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer. The coated stents were tested in a wet flow test condition of saline heated to 37°C. The number of "peel defects" on a select number of stent rings was observed. A "peel defect" is defined as a location on the stent surface devoid of coating, i.e., bare metal or underlying coating layer that is visible under optical magnification of less than 100x.
Materials and Equipment

1. 10, 13 mm Solo stents, cleaned ultrasonically in IPA for 15 minutes;
2. 10, balloon catheters or subassemblies to expand the stents;
3. 15% EVAL in 1:1 DMF:DMSO solution;
4. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL:Act-D;
5. Tecoflex tubing
6. Saline
7. Lint Free Wipes SU 00126 or equivalent
8. 100% IPA
9. Oven
10. Timer
11. Plasma Machine (Advanced Plasma System);
12. Ultrasonic cleaner; and
13. Mettler balance with 0.1 micrograms resolution.

Preparation

1. Sonicated the stents in IPA for 15 minutes.
2. Weighed each stent to the nearest microgram.
3. Prepared 5 stent samples for each group:
   A. Group A (Control):
      i. Placed the samples flat on a sample holder. Performed argon plasma treatment.
      ii. Used dip-spin process, i.e., centrifugation at 6000 rpm for one minute, to apply the EVAL primer layer, 1:1 DMSO:DMF.
      iii. Baked the stents at 140°C for two hours in the convection oven.
      iv. Took weight measurements of each stent to the nearest microgram.
      v. Baked the stents at 60°C for two hours in vacuum oven.
      vi. Took weight measurements of each stent to the nearest microgram.
      vii. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
      viii. Weighed each sample at the end of the last pass to the nearest microgram.
      ix. Baked samples for 4 hrs at 60°C.
      x. Took weight measurements of each stent to the nearest microgram.
      xi. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.
   B. Groups B:
      i. Placed samples flat on sample holder. Performed argon plasma treatment.
      ii. Used dip-spin process at 6000 rpm for one minute to apply EVAL primer layer, 1:1 DMSO:DMF.
      iii. Baked the stents at 120°C for two hours in the convection oven.
iv. Took weight measurements on each stent to the nearest microgram.

v. Baked the stents at 60°C for ten hours in vacuum oven.

vi. Took weight measurements for each stent to the nearest microgram.

vii. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.

viii. Weighed each sample at the end of the last pass to the nearest microgram.

ix. Baked the samples for 4 hrs at 60°C.

x. Took weight measurements of each stent to the nearest microgram.

xi. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

Test Procedure

[0136]

1. Performed wet flow testing overnight for about 18 hrs.

2. Removed the stents from the Tecoflex tubing with a stent catcher.

3. Counted the defects based on the number of peel defects at rings 3, 5, and 7 on the stents’ OD. Count the defects on the ID of the same rings.

4. The weight could not be measured because of the loss of the drug and uptake of water.

5. All test samples were handled with PPE appropriate for drug containing stents.

Data Summary and Results

[0137]

<table>
<thead>
<tr>
<th>Group</th>
<th># Peel Defects (OD)</th>
<th>Average # of Peel Defects/Ring (OD, rings 3, 5, 7)</th>
<th># Peel Defects (ID)</th>
<th>Average # of Peel Defects/Ring (ID, rings 3, 5, 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>1*</td>
<td>0.3</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Defect occurred at a location of a defect in the stent surface.

Example 33 (Reference Example)

Objective

[0138] The objective of this study was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer. The coated stents were tested under wet flow conditions of saline heated to 37°C. The number of “peel defects” on a select number of stent rings was observed. A “peel defect” is defined as a location on the stent surface devoid of coating, i.e., bare metal or an underlying coating layer that is visible under
optical magnification of no more than 100x.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Control</td>
<td>None</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>B</td>
<td>Argon plasma treatment + EVAL primer layer by dip-spin (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 4 hours</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>C</td>
<td>EVAL primer layer by dip-spin (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 4 hours</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>D</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 4 hours</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>E</td>
<td>EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 4 hours</td>
<td>50 mL/min</td>
</tr>
</tbody>
</table>

Materials and Equipment

[0139]

1. 25,13 mm Solo stents, cleaned ultrasonically in IPA for 15 minutes;
2. 25, balloon catheters or subassemblies to expand the stents;
3. 2% EVAL in 1:1 DMF:DMSO solution;
4. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL:Act D;
5. 3.0 mm Tecoflex tubing;
6. Saline;
7. Lint Free Wipes SU 00126 or equivalent;
8. 100% IPA;
9. Convection Oven
10. Timer,
11. Plasma Machine;
12. Ultrasonic cleaner; and
13. Mettler balance with 0.1 micrograms resolution.

Preparation

[0140]

1. Sonicated the stents in IPA for 15 minutes.
2. Weighed each stent to the nearest microgram.
3. Prepared 5 stent samples for each group.

A. Group A (Control):
   i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
   ii. Weighed each sample at the end of the last pass to the nearest microgram.
   iii. Baked the samples for 4 hrs at 60°C.
   iv. Took the weight measurements of each stent to the nearest microgram.
   v. Placed the stents into the Tecoflex tubing with the balloon catheter-submerged in 37°C water.

B. Group B:
   i. Placed samples flat on sample holder. Perform argon plasma treatment.
   ii. Used dip-spin process to apply EVAL primer layer, 1:1 DMSO:DMF (6000 rpm for one minute).
   iii. Baked the stents at 140°C for 4 hours in convection oven.
   iv. Took weight measurements on each stent to the nearest microgram.
   v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.
   vi. Weighed each sample at the end of the last pass to the nearest microgram.
   vii. Baked the samples for 4 hrs at 60°C.
viii. Took the weight measurements of each stent to the nearest microgram.
ix. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

C. Group C:
   i. Used dip-spin process to apply EVAL primer layer, 1:1 DMSO:DMF (6000 rpm for one minute).
   ii. Baked the stents at 140°C for four hours in convection oven.
   iii. Took weight measurements on each stent to the nearest microgram.
   iv. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
   v. Weighed each sample at the end of the last pass to the nearest microgram.
   vi. Baked the samples for 4 hrs at 60°C.
   vii. Took weight measurements of each stent to the nearest microgram.
   viii. Placed stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

D. Group D:
   i. Placed the samples flat on a sample holder. Perform argon plasma treatment.
   ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
   iii. Baked the stents at 140°C for 4 hours in the convection oven.
   iv. Took weight measurements on each stent to the nearest microgram.
   v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.
   vi. Weighed each sample at the end of the last pass to the nearest microgram.
   vii. Baked samples for 4 hrs at 60°C.
   viii. Took weight measurements of each stent to the nearest microgram.
   ix. Placed stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

E. Group E:
   i. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
   ii. Baked the stents at 140°C for four hours in convection oven.
   iii. Took weight measurements on each stent to the nearest microgram.
   iv. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.
   v. Weighed each sample at the end of the last pass to the nearest microgram.
   vi. Baked the samples for 4 hrs at 60°C.
   vii. Took weight measurements of each stent to the nearest microgram.
   viii. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

Test Procedure
[0141]
1. Performed wet flow testing overnight for about 18 hrs.
2. Removed stents from the Tecoflex tubing with a stent catcher.
3. Counted the defects based on the number of peel defects at rings 1, 3, 5, and 7 on the stents’ OD. Count the defects on the ID of the same rings.
4. Stent weight could not be a measurable because of the loss of the drug and uptake of water.
5. All test samples were handled with PPE appropriate for drug containing stents.

Data Summary and Results
[0142]

<table>
<thead>
<tr>
<th>Group</th>
<th>Defects/Ring (OD)</th>
<th>Defects/Ring (ID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.67</td>
<td>3.00</td>
</tr>
</tbody>
</table>
Discussion

Peel Defects of Primer Coated Stents vs. Untreated Controls

[0143] An improved adhesion, based on the number of peel defects, of the drug containing coating to the Tri-Star stent when an EVAL primer layer was applied is illustrated. All four treatment groups displayed significantly fewer peel defects per stent than the untreated control stents. Use of a spray-coated, 2% EVAL solution in 1:1 DMF:DMSO as a primer significantly improved adhesion of Actinomycin-D containing coating to the Tri-Star stents vs. the controls. The spray-coated primer produced slightly higher peel defect counts compared to the dip-spin deposited primer.

Example 34 (Reference Example)

Objective

[0144] The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating to stainless steel stents having an EVAL primer layer. More specifically, this experiment attempted to illustrate the effect of different bake times on the final result. The coated stents were tested under wet flow conditions of saline heated to 37°C. The number of "peel defects" on a select number of stent rings was observed.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Control</td>
<td>None</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>B</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 15 minutes</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>C</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 30 minutes</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>D</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 60 minutes</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>E</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL, 1:1 DMF:DMSO) baked at 140°C for 120 minutes</td>
<td>50 mL/min</td>
</tr>
</tbody>
</table>

Materials and Equipment

[0145]

1. 25, 13 mm Solo stents, cleaned ultrasonically in IPA for 15 minutes;
2. 25, balloon catheters or subassemblies to expand the stents;
3. 2% EVAL in 1:1 DMF:DMSO solution;
4. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL:Act-D;
5. 3.0 mm Tecoflex tubing;
6. Saline;
7. Lint Free Wipes SU 00126 or equivalent;
8. 100% IPA;
9. Convection Oven;
10. Timer;
11. Plasma Machine;
Preparation

12. Ultrasonic cleaner; and
13. Mettler balance with 0.1 micrograms resolution.

[0146]

1. Sonicated stents in IPA for 15 minutes.
2. Weighed each stent to the nearest microgram.
3. Prepared 5 stent samples for each group.

A. Group A (Control):
   i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
   ii. Weighed each sample at the end of the last pass to the nearest microgram.
   iii. Baked the samples for 240 minutes at 50°C.
   iv. Took weight measurements of each stent to the nearest microgram.
   v. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

B. Group B:
   i. Placed samples flat on sample holder. Perform argon plasma treatment.
   ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
   iii. Baked the stents at 140°C for 15 minutes in the convection oven.
   iv. Took weight measurements on each stent to the nearest microgram.
   v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
   vi. Weighed each sample at the end of the last pass to the nearest microgram.
   vii. Baked the samples for 240 minutes at 50°C.
   viii. Took weight measurements of each stent to the nearest microgram.
   ix. Placed stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

C. Group C:
   i. Placed the samples flat on sample holder. Perform argon plasma treatment.
   ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
   iii. Baked the stents at 140°C for 30 minutes in the convection oven.
   iv. Took weight measurements on each stent to the nearest microgram.
   v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
   vi. Weighed each sample at the end of the last pass to the nearest microgram.
   vii. Baked the samples for 240 minutes at 50°C.
   viii. Took weight measurements of each stent to the nearest microgram.
   ix. Placed stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

D. Group D:
   i. Placed samples flat on sample holder. Perform argon plasma treatment.
   ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes
to achieve 10-40 micrograms of coating.
iii. Baked the stents at 140°C for 60 minutes in the convection oven.
iv. Took weight measurements on each stent to the nearest microgram.
v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
vi. Weighed each sample at the end of the last pass to the nearest microgram.
vii. Took weight measurements of each stent to the nearest microgram.
ix. Placed stents into the Tecoflex tubing with a balloon catheter--submerged in 37°C water.

E. Group E:

i. Placed samples flat on sample holder. Perform argon plasma treatment.
ii. Spray coated primer layer (2% EVAL, 1:1 DMF:DMSO) onto stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
iii. Baked the stents at 140°C for 120 minutes in the convection oven.
iv. Took weight measurements on each stent to the nearest microgram.
v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.
vi. Weighed each sample at the end of the last pass to the nearest microgram.
vii. Baked samples for 240 minutes at 50°C.
viii. Took weight measurements of each stent to the nearest microgram.
ix. Placed stent into the Tecoflex tube with balloon catheter--submerged in 37°C water.

Test Procedure

[0147]

1. Performed wet flow testing overnight for about 18 hrs.
2. Removed the stents from the Tecoflex tubing with a stent catcher.
3. Counted the defects based on the number of peel defects at rings 3, 5, and 7 on the stents’ OD. Count the defects on the ID of the same rings.
4. Stent weight could not be a measurable because of the loss of the drug and uptake of water.
5. All test samples were handled with PPE appropriate for drug containing stents.

Data Summary and Results

[0148]

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Defects per Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.33</td>
</tr>
<tr>
<td>15 min bake</td>
<td>1.00</td>
</tr>
<tr>
<td>30 min bake</td>
<td>3.00</td>
</tr>
<tr>
<td>60 min bake</td>
<td>1.67</td>
</tr>
<tr>
<td>120 min bake</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Discussion

[0149] The control group with no primer layer had significantly more peel defects as compared to the treatment groups with a primer layer. The groups with shorter baking times (15 and 30 minutes) had higher defect counts than the groups with longer baking times.
Example 35 (Reference Example)

Objective

[0150] The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer. More specifically, different solvent systems (e.g., THF and DMF) were evaluated. The coated stents were tested under wet flow conditions of saline heated to 37°C. The number of "peel defects" on a select number of stent rings was observed.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Control</td>
<td>None</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>B</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL,1:1 DMF:DMSO) baked at 140°C for 15 minutes</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>C</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL,1:1 DMF:DMSO) baked at 140°C for 60 minutes</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>D</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL,1:1 DMF:DMSO) baked at 140°C for 240 minutes</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>E</td>
<td>Argon plasma treatment + EVAL primer layer by spray (2% EVAL,1:1 THF:DMSO) baked at 140°C for 60 minutes</td>
<td>50 mL/min</td>
</tr>
</tbody>
</table>

Materials and Equipment

[0151]

1. 25, 13 mm Solo stents, cleaned ultrasonically in IPA for 15 minutes;
2. 25, balloon catheters or subassemblies to expand the stents;
3. 2% EVAL in 1:1 DMF:DMSO solution;
4. 2% EVAL in 1:1 THF:DMSO solution;
5. Actinomycin-D solution, 1:1 THF:DMSO with 3:1 EVAL:Act-D, 2% EVAL;
6. 3.0 mm Tecoflex tubing;
7. Saline;
8. Lint Free Wipes SU 00126 or equivalent;
9. 100% IPA;
10. Convection Oven;
11. Timer;
12. Plasma Machine;
13. Ultrasonic cleaner; and
14. Mettler balance with 0.1 micrograms resolution.

Preparation

[0152]

1. Sonicated stents in IPA for 15 minutes.
2. Weighed each stent to the nearest microgram.
3. Prepared 5 stent samples for each group.

A. Group A (Control):
   i. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
   ii. Weighed each sample at the end of the last pass to the nearest microgram.
   iii. Baked samples for 240 minutes at 50°C.
   iv. Took weight measurements of each stent to the nearest microgram.
   v. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.
B. Group B:

i. Placed samples flat on a sample holder. Performed argon plasma treatment.
ii. Spray coated the primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
iii. Baked the stents at 140°C for 15 minutes in the convection oven.
iv. Took weight measurements of each stent to the nearest microgram.
v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
vi. Weighed each sample at the end of the last pass to the nearest microgram.
vii. Baked the samples for 240 minutes at 50°C.
viii. Took weight measurements of each stent to the nearest microgram.
ix. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

C. Group C:

i. Placed samples flat on a sample holder. Performed argon plasma treatment.
ii. Spray coated the primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
iii. Baked the stents at 140°C for 60 minutes in the convection oven.
iv. Took weight measurements of each stent to the nearest microgram.
v. Performed spray-coating process in CER under the following conditions: 3 passes, 3-second spray, no blow.
vi. Weighed each sample at the end of the last pass to the nearest microgram.
vii. Baked the samples for 240 minutes at 50°C.
viii. Took weight measurements of each stent to the nearest microgram.
ix. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

D. Group D:

i. Placed samples flat on a sample holder. Performed argon plasma treatment.
ii. Spray coated the primer layer (2% EVAL, 1:1 DMF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
iii. Baked the stents at 140°C for 240 minutes in the convection oven.
iv. Took weight measurements of each stent to the nearest microgram.
v. Performed spray-coating process in CER at the following conditions: 3 passes, 3-second spray, no blow.
vi. Weighed each sample at the end of the last pass to the nearest microgram.
vii. Baked the samples for 240 minutes at 50°C.
viii. Took weight measurements of each stent to the nearest microgram.
ix. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

E. Group E:

i. Placed samples flat on a sample holder. Perform argon plasma treatment.
ii. Spray coated the primer layer (2% EVAL, 1:1 THF:DMSO) onto the stents. Used 1.5 sec. spray time, 1-2 passes to achieve 10-40 micrograms of coating.
iii. Baked the stents at 140°C for 60 minutes in the convection oven.
iv. Took weight measurements of each stent to the nearest microgram.
v. Performed spray-coating process in CER under the following conditions: 3 passes, 3 second spray, no blow.
vi. Weighed each sample at the end of the last pass to the nearest microgram.
vii. Baked the samples for 240 minutes at 50°C.
viii. Took weight measurements of each stent to the nearest microgram.
ix. Placed the stents into the Tecoflex tubing with a balloon catheter-submerged in 37°C water.

Test Procedure

[0153]
1. Performed wet flow testing overnight for about 18 hrs.
2. Removed the stents from the Tecoflex tubing with a stent catcher.
3. Counted the defects, based on the number of peel defects at rings 3, 5, and 7 on the stents’ OD. Counted defects on the ID of the same rings.
4. The weight of the stents could not be a measurable because of the loss of the drug and uptake of water.
5. All test samples were handled with PPE appropriate for drug containing stents.

**Data Summary and Results**

![Table]

**Example 36** (Reference Example)

**Objective**

The objective of this experiment was to test the adhesive properties of an Actinomycin-D containing coating on stainless steel stents having an EVAL primer layer made from a DMSO:THF solution applied to the stents. The coated stents were tested under wet flow conditions of saline heated to 37°C. The number of “peel defects” on a select number of stent rings was observed.

**Materials and Equipment**

1. 10, 13 mm SOLO stents, cleaned ultrasonically in IPA for 15 minutes;
2. 2% EVAL in 1:1 THF:DMSO solution;
3. 10 Balloon catheters or subassemblies to expand the stents;
4. Actinomycin-D solution, 1:1 THF:DMSO with 1:3 Act-D:EVAL, 2% EVAL;
5. 4.0 mm Tecoflex tubing;
6. Saline;
7. Lint Free Wipes SU 00126 or equivalent;
8. 100% IPA;
9. Convection Oven;
10. Timer;
11. Plasma Machine;
12. Ultrasonic cleaner;
13. Mettler balance with 0.1 microgram resolution;
14. Spray/bake mandrels and tips;
EP 1 575 631 B1

15. Flow Meter, N1429;
16. Microscope, minimum magnification 50x;
17. EFD controller with spray apparatus without translational stage; and
18. EFD controller with spray apparatus with translational stage.

Preparation

[0157]

1. Sonicated the stents in IPA for 15 minutes.
2. Weighed each stent to the nearest microgram.
3. Prepare the stent samples for each group.

A. Primer Coat

i. Placed samples on sample holder. Performed argon plasma treatment.
ii. Sprayed the primer layer (2% EVAL, 1:1 THF:DMSO) onto the stents with translational spray coater. Used 1.5 sec. for the spray time and speed 7 to achieve 10-40 μg of coating.
iii. Baked the stents at 140°C for the specified time in the convection oven.
iv. Weighed the stents and recorded measurements to the nearest microgram.

B. Drug Coat

i. Sprayed the stents with a 3:1, EVAL:Act-D, 2% EVAL, 1:1 DMSO:THF solution for three seconds per pass for three passes. After each spray pass, dried the stents in the convection oven for 15 minutes at 50°C.
ii. Weighed the stents and recorded measurements. If the drug coat weight matched the target weight, the stents were returned to the oven for 240 minutes. If weight gain did not match, the stents were returned to the glove box for additional spray coat application. Spray time on subsequent passes was adjusted to achieve target weight.

4. Wet Flow Test Sample Preparation

A. Crimped the stents onto the balloon catheters.
B. Inflated the stents to 4.0 mm in the Tecoflex tubing with the balloon catheters-submerged in 37°C water.
C. Disposed Act-D contaminated water as hazardous waste.

Test Method / Procedure

[0158]

1. Set flow rate at 50ml/min.
2. Performed wet flow testing overnight for about 18 hrs.
3. Removed the stents from the Tecoflex tubing with a stent catcher.
4. Counted defects, based on the number of peel defects at rings 1, 3, 5, 7, and 10 on the stents’ OD. Counted defects on the ID of the same rings.
5. All test samples were handled with PPE appropriate for drug containing stents.

Data Summary and Results

[0159]

<table>
<thead>
<tr>
<th>Drying Time (min.)</th>
<th>Total Defects per Stent</th>
<th>Total Defects per Stent (end rings)</th>
<th>Total Defects per Stent (middle rings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>30</td>
<td>2.0</td>
<td>2.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Example 37 (Reference Example)

[0160] Multi-Link Tetra™ stents (available from Guidant Corporation) were provided. A 2% EVAL solution in dimethyl acetamide (DMAC) was prepared. The stents were sprayed with the 2% EVAL solution. The stents were then heated in an oven for about 1 hour at about 140°C to essentially remove the DMAC solvent from the layer to form a primer coating. The weight of EVAL on the primer coating was determined to be about 160 µg. Another solution was prepared containing a mixture of EVAL and the active ingredient Clobetasol in a DMAC solvent. The EVAL-Clobetasol solution was then sprayed onto the primer coating. The stents were then heated in an oven for about 2 hours at about 50°C to essentially remove the DMAC solvent to form a drug reservoir region. The weight of the reservoir region was determined to be about 500 µg. Next, the stents were sprayed with the 2% EVAL solution. The stents were then heated in an oven for about 2 hours at about 50°C to essentially remove the DMAC solvent to form a barrier region. The weight of the barrier region was determined to be about 300 µg.

[0161] After final drying, the coatings were transparent giving the stents a glossy-like shine. The stents were exposed to simulation tests by being expanded to about 3 mm. No peeling was detected. Also, it was calculated that as applied, the coating in total contained 2% EVAL, 2% Clobetasol and 96% DMAC by weight.

Example 38

[0162] 18 mm Vision-D stents (cobalt-chromium alloy stents prepared for Guidant Corporation) were provided. The stents were separated into different test groups to investigate two variables: (1) the thickness of the primer layer and (2) the drug:polymer ratio.

[0163] A primer solution was prepared by mixing poly (butyl methacrylate) (PBMA) with a solvent containing 60% acetone and 40% xylene to produce a 2% PBMA solution. Stents from selected test groups were sprayed with the 2% PBMA solution with multiple spray cycles. After each spray repetition, warm air was directed onto the stents to facilitate evaporation. The stents were then heated in an oven for about 1/2 hour at about 80°C to essentially remove the solvent from the layer to form a primer coating. Then, the weight of PBMA on the primer coatings was determined.

[0164] The following table summarizes the spray process parameters for each of the layers, including the primer layer:

<table>
<thead>
<tr>
<th>Drying Time (min.)</th>
<th>Total Defects per Stent</th>
<th>Total Defects per Stent (end rings)</th>
<th>Total Defects per Stent (middle rings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1.0</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>90</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>120</td>
<td>0.5</td>
<td>0.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Another solution was prepared by mixing PBMA and the active ingredient 40-O-(2-hydroxy)ethyl-rapamycin (EVEROLIMUS) in a solvent containing 60% acetone and 40% xylene. The polymer-drug solution was then sprayed onto the primer coating with the same spray process parameters as for the application of the primer coating. The amount of drug solution sprayed onto the individual stents depended on the test group. Each test group contained 3 stents. The stents were then heated in an oven for 1/2 hour at 80°C to essentially remove the solvent to form a drug reservoir layer. The weight of the reservoir region was then determined.

A barrier layer solution was prepared by mixing PBMA with a solvent containing 15% acetone, 40% xylene and 45% hydrofluoroether (HFE) (Novec™ Engineered Fluid HFE-7100, available from 3M Specialty Materials, St. Paul, MN) to produce a 2% PBMA solution. The PBMA solution was then sprayed onto the reservoir coating with the same spray process parameters as for the application of the primer coating. The stents were then heated in an oven for about 1/2 hour at about 80°C to essentially remove the solvent to form a barrier layer.

After final drying, the coatings were expanded to test the mechanical integrity of the coating. In particular, the stents from each test group were expanded to an inner diameter of about 3.5 mm at about 37°C in water. The coatings were then studied using a Scanning Electron Microscope (SEM) to determine if there were visible cracks as a result of the expansion of the stents. As the results demonstrate in the following table, the stents with a thicker primer layer have greater mechanical integrity:

<table>
<thead>
<tr>
<th>Drug to Polymer Ratio</th>
<th>Primer Layer (μg)</th>
<th>Reservoir Layer (μg)</th>
<th>Total Drug Content (μg)</th>
<th>Cracks Visible in Coating?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: 1.25</td>
<td>0</td>
<td>360</td>
<td>160</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>360</td>
<td>160</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>360</td>
<td>160</td>
<td>No</td>
</tr>
<tr>
<td>1: 1.35</td>
<td>0</td>
<td>376</td>
<td>160</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>376</td>
<td>160</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>376</td>
<td>160</td>
<td>No</td>
</tr>
</tbody>
</table>
Example 39 (Reference Example)

18 mm Vision-D stents were provided. The stents were separated into different test groups to investigate three variables: (1) the thickness of the primer layer, (2) the drug:polymer ratio and (3) the type of polymer used for primer layer.

A first primer solution was prepared by mixing PBMA with a solvent containing 60% acetone and 40% xylene to produce a 2% PBMA solution. A second primer solution was prepared by mixing EVAL with a solvent containing 80% dimethyl acetamide (DMAC) and 20% pentane to produce a 4% EVAL solution. Stents from selected test groups were sprayed with either the 2% PBMA solution or the 4% EVAL solution with multiple spray cycles. After each spray repetition, warm air was directed onto the stents to facilitate evaporation. The stents were then heated in an oven for about 2 hours at about 80°C to essentially remove the solvent from the layer to form a primer coating. Then, the weight of PBMA or EVAL on the primer coatings was determined.

The following table summarizes the spray process parameters for each layer, including the primer layer:

<table>
<thead>
<tr>
<th>Drug to Polymer Ratio</th>
<th>Primer Layer (µg)</th>
<th>Reservoir Layer (µg)</th>
<th>Total Drug Content (µg)</th>
<th>Cracks Visible in Coating?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: 1.50</td>
<td>0</td>
<td>400</td>
<td>160</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>400</td>
<td>160</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>400</td>
<td>160</td>
<td>No</td>
</tr>
</tbody>
</table>

(continued)
Another solution was prepared by mixing EVAL and the active ingredient Everolimus in a solvent containing 80% DMAC and 20% pentane. The polymer-drug solution was then sprayed onto the primer coating. The amount of drug solution sprayed onto the individual stents depended on the test group. Each test group contained 5 stents. The stents were then heated in an oven for 2 hours at 80°C to essentially remove the solvent to form a drug reservoir layer. The weight of the reservoir region was then determined.

A barrier layer solution was prepared by mixing EVAL with a solvent containing 80% DMAC and 20% pentane to produce a 4% EVAL solution. The EVAL solution was then sprayed onto the reservoir coating. The stents were then heated in an oven for 2 hours at 80°C to essentially remove the solvent to form a barrier layer. The following table summarizes the parameters for the test groups:
After final drying, the coatings were expanded to test the mechanical integrity of the coating. In particular, the stents from each test group were hydrated in about 37°C water for about 5 minutes. The stents were then expanded to have an inner diameter of about 3.5mm with the use of a balloon catheter. The stents were then dried at about 37°C and studied using a SEM to determine if there were visible cracks as a result of the expansion of the stents.

The SEM photos of the stents with an EVAL primer layer showed that the number and severity of cracks were reduced with an increase in the thickness of the primer coating. The results also suggest that as the drug to polymer ratio increases, the thickness of the primer layer should be increased in order to prevent or reduce cracking. The least number of cracks was observed in the group B2 (Figure 8A) which had significantly fewer cracks than group C1 which had a relatively thin primer layer (Figure 8B). Group B2 had 160 μg of EVAL primer and the drug to polymer ratio was 1:2.3 (i.e., about 30% drug loading).

The SEM photos of the stents with a PBMA primer layer also showed that the number and severity of cracks were reduced with an increase in the thickness of the primer coating. For example, the group E2 with 160 μg of primer (Figure 9A) had significantly fewer cracks than Group F1 (Figure 9B).

Example 40

This Example describes the formation of a porous matrix for a primer layer. A 4% (w/w) PBMA solution is prepared by gently mixing the PBMA with a solvent solution containing 60% acetone, 20% xylene and 20% ethylene glycol. The ethylene glycol is a less compatible solvent for PBMA than acetone and xylene. The polymer solution is applied to a 18 mm Vision-D stent. The stent is then heated in an oven for 1/2 hour at 80°C to essentially remove the solvent to form a primer layer. A porous matrix forms in the primer layer during the evaporation step because of the presence of the ethylene glycol in the composition.

Example 41

This Example describes the formation of a porous matrix for a primer layer. EVAL pellets are provided. An EVAL powder is formed by cryogenically grinding the pellets. After grinding, the powder has an average particle size of about 1 micron to about 10 microns. The powder is applied to the outer surface of a 18 mm Vision-D stent. The adhesion of the powder to the stent surface can be improved by first mixing the polymeric powder with a small portion of a non-solvent to give the powder a paste-like consistency. Pressure is then applied to the powder on the stent so that the particles are pressed together. Then, the stent is placed in an oven and heated at about 150°C to about 170°C for about 15 minutes to about 1 hour. After this sintering process, space remains between the lattice of the EVAL particles to form porous cavities.

Example 42

This Example describes the formation of a porous matrix for a primer layer. A 2% (w/w) EVAL solution in 80%...
DMAC and 20% pentane is prepared. The polymer solution is applied to a 18 mm Vision-D stent. A solution of 100% pentane is then applied to the stent surface to precipitate the polymer to form a porous matrix. The stent is then heated in an oven for 2 hours at 80°C to essentially remove the solvent to form a primer layer.

[0179] 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 this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

Claims

1. A method of forming a coating for a stent, comprising:

   forming a primer layer, which primer layer comprises a polymer and is substantially free of active ingredients, on at least a portion of a surface of the stent, wherein the primer layer has a weight measurement of X, or a thickness X'; and

   forming a reservoir layer comprising a polymer and an active ingredient on at least a selected portion of the primer layer, wherein the reservoir layer has a weight measurement of Y, or a thickness Y'; wherein

   (a) X/Y is equal to or greater than 0.25, or

   (b) X' is from 0.5 to 3 micrometres and Y' is from 1 to 10 micrometres provided that X'/Y' is equal to or greater than 0.25;

   and wherein:

   (i) said polymer of the primer layer is poly(butyl methacrylate) and said polymer of the reservoir layer is an ethylene vinyl alcohol copolymer; or

   (ii) said polymer of the primer layer is poly(butyl methacrylate) and said polymer of the reservoir layer is poly(butyl methacrylate); or

   (iii) said polymer of the primer layer is an ethylene vinyl alcohol copolymer and said polymer of the reservoir layer is poly(butyl methacrylate).

2. The method of Claim 1, wherein the coating has a drug loading equal to or greater than 30%.

3. The method of Claim 1, wherein the primer layer has a weight measurement of X and the reservoir layer has a weight measurement of Y, and X/Y is equal to or greater than 0.33.

4. The method of Claim 1, further comprising forming a barrier layer on at least a selected portion of the reservoir layer to reduce the rate at which the active ingredient is released from the reservoir layer after insertion of the stent into the body of a patient.

5. The method of Claim 1, further comprising forming asperities on a surface of the primer layer preceding the formation of the reservoir layer.

6. The method of Claim 1, wherein the primer layer comprises at least a region having a degree of porosity.

7. A stent comprising a coating for delivery of an active ingredient, wherein the coating comprises:

   a primer region, which primer region comprises a polymer and is substantially free of active ingredients, on at least a portion of a surface of the stent, wherein the primer region has a thickness X', or a weight measurement X; a reservoir region comprising a polymer and the active ingredient on at least a selected portion of the primer region, wherein the reservoir region has a thickness Y', or a weight measurement Y; and wherein:

   (a) the thickness X' is measured from the outer surface of the primer region to the surface of the stent prior to the migration of the active ingredient from the reservoir region to the primer region, and wherein X' is from 0.5 to 3 micrometres and Y' is from 1 to 10 micrometres, provided that X'/Y' is equal to or greater than 0.25; or

   (b) X/Y is equal to or greater than 0.25;
8. The stent of Claim 7, wherein the stent is selected from a group of balloon-expandable stents and self-expandable stents.

9. The stent of Claim 7, wherein the active ingredient is selected from the group of heparin, heparin sulfate, heparin having a hydrophobic counterion, mannose-6-phosphate, superoxide dismutase, clobetasol, retinoic acid, rapamycin, rapamycin analogs and derivatives, suramin, asiaticoside, hyaluronan and combinations thereof.

10. The stent of Claim 7, further comprising a barrier region located on at least a selected portion of the reservoir region for reducing the rate at which the active ingredient is released from the coating after insertion of the stent into the body of a patient.

11. The stent of Claim 7, wherein the primer region comprises a porous matrix extending from the interface of the primer region and the reservoir region into the primer.

12. A stent comprising a coating for delivery of an active ingredient, wherein the coating comprises a primer region comprising a polymer and a reservoir region comprising a polymer and an active ingredient, and wherein the thickness or the weight of the primer region is sufficiently high so as to allow drug loading of 30% in the reservoir region without causing the coating to crack when the stent is expanded; and wherein:

(i) said polymer of the primer region is poly(butyl methacrylate) and said polymer of the reservoir region is an ethylene vinyl alcohol copolymer; or
(ii) said polymer of the primer region is poly(butyl methacrylate) and said polymer of the reservoir region is poly(butyl methacrylate); or
(iii) said polymer of the primer region is an ethylene vinyl alcohol copolymer and said polymer of the reservoir region is poly(butyl methacrylate).
(iii) das Polymer der Grundschicht ein Ethylenvinylalkoholcopolymer ist und das Polymer der Speicherschicht Poly(butylmethacrylat) ist.

2. Verfahren nach Anspruch 1, wobei die Beschichtung eine Wirkstoffbeladung von gleich oder größer als 30% aufweist.

3. Verfahren nach Anspruch 1, wobei die Grundschicht eine Gewichtsmessung von X und die Speicherschicht eine Gewichtsmessung von Y aufweist, und X/Y gleich oder größer als 0,33 ist.

4. Verfahren nach Anspruch 1, ferner umfassend Bilden einer Barrierekomponente auf mindestens einem ausgewählten Teil der Speicherschicht, um die Rate, mit der der aktive Inhaltsstoff aus der Speicherschicht nach dem Einsetzen des Stents in den Körper eines Patienten abgegeben wird, reduziert wird.

5. Verfahren nach Anspruch 1, ferner umfassend Bilden von Oberflächenunebenheiten auf einer Oberfläche der Grundschicht vor dem Bilden der Speicherschicht.

6. Verfahren nach Anspruch 1, wobei die Grundschicht mindestens einen Bereich umfasst, der einen Porositätsgrad aufweist.

7. Stent, umfassend eine Beschichtung zum Abgeben eines aktiven Inhaltsstoffes, wobei die Beschichtung umfasst:

   einen Grundbereich, der Grundbereich umfasst ein Polymer und ist im Wesentlichen frei von aktiven Inhaltsstoffen, auf mindestens einem Teil einer Oberfläche des Stents, wobei der Grundbereich eine Dicke X', oder eine Gewichtsmessung X aufweist;

   einen Speicherbereich umfassend ein Polymer und den aktiven Inhaltsstoff auf mindestens einem ausgewählten Teil des Grundbereichs, wobei der Speicherbereich eine Dicke Y', oder eine Gewichtsmessung Y aufweist; und wobei

   (a) die Dicke X' gemessen ist von der äußeren Oberfläche des Grundbereichs bis zu der Oberfläche des Stents vor der Migration des aktiven Inhaltsstoffes in den Speicherbereich in den Grundbereich, und wobei X' von 0,5 bis 3 Mikrometer und Y' von 1 bis 10 Mikrometer ist, vorausgesetzt dass X'/Y' gleich oder größer als 0,25 ist; oder

   (b) X/Y gleich oder größer als 0,25 ist;

    und wobei:

   (i) das Polymer der Grundschicht Poly(butylmethacrylat) ist und das Polymer der Speicherschicht ein Ethylenvinylalkoholcopolymer ist; oder

   (ii) das Polymer der Grundschicht Poly(butylmethacrylat) ist und das Polymer der Speicherschicht Poly(butylmethacrylat) ist; oder

   (iii) das Polymer der Grundschicht ein Ethylenvinylalkoholcopolymer ist und das Polymer der Speicherschicht Poly(butylmethacrylat) ist.


10. Stent nach Anspruch 7, ferner umfassend einen Barrierebereich lokalisiert auf mindestens einem ausgewählten Teil des Speicherbereichs zum Reduzieren der Rate, mit der der aktive Inhaltsstoff von der Beschichtung nach Einsetzen des Stents in den Körper eines Patienten abgegeben wird.

11. Stent nach Anspruch 7, wobei der Grundbereich eine poröse Matrix umfasst, die sich von der Schnittstelle der Grundregion und der Speicherregion in die Grundierung ausbreitet.

12. Stent, umfassend eine Beschichtung zum Abgeben eines aktiven Inhaltsstoffes, wobei die Beschichtung einen Grundbereich, der ein Polymer umfasst, und einen Speicherbereich, der ein Polymer und einen aktiven Inhaltsstoff
Revendications

1. Procédé de formation d’un revêtement de stent, comprenant les étapes suivantes :

- former, sur au moins une partie d’une surface du stent, une couche de revêtement primaire, laquelle couche de primaire comprend un polymère et ne contient pratiquement pas d’ingrédients actifs, et laquelle couche de primaire présente un poids mesuré X ou une épaisseur X’;
- et former, sur au moins une partie sélectionnée de la couche de primaire, une couche réservoir comprenant un polymère et un ingrédient actif, laquelle couche réservoir présente un poids mesuré Y ou une épaisseur Y’;

étant entendu que :

a) le rapport X/Y est supérieur ou égal à 0,25,
b) ou X’ vaut de 0,5 à 3 μm et Y’ vaut de 1 à 10 μm, sous réserve que le rapport X’/Y’ soit supérieur ou égal à 0,25 ;

dans lequel procédé :

i) ledit polymère de la couche de primaire est du poly(méthacrylate de butyle) et ledit polymère de la couche réservoir est un copolymère d’éthylène et d’alcool vinylique ;
ii) ou ledit polymère de la couche de primaire est du poly(méthacrylate de butyle) et ledit polymère de la couche réservoir est du poly(méthacrylate de butyle) ;
iii) ou ledit polymère de la couche de primaire est un copolymère d’éthylène et d’alcool vinylique et ledit polymère de la couche réservoir est du poly(méthacrylate de butyle).

2. Procédé conforme à la revendication 1, dans lequel le revêtement est chargé en médicament à un taux supérieur ou égal à 30 %.

3. Procédé conforme à la revendication 1, dans lequel la couche de primaire présente un poids mesuré X et la couche réservoir présente un poids mesuré Y, et le rapport X/Y est supérieur ou égal à 0,33.

4. Procédé conforme à la revendication 1, qui comporte en outre le fait de former une couche barrière sur au moins une partie sélectionnée de la couche réservoir, afin de réduire la vitesse à laquelle l’ingrédient actif est libéré à partir de la couche réservoir après l’insertion du stent dans le corps d’un patient.

5. Procédé conforme à la revendication 1, qui comporte en outre le fait de former desaspérités sur une surface de la couche de primaire, avant de former la couche réservoir.

6. Procédé conforme à la revendication 1, dans lequel la couche de primaire comporte au moins une région dotée d’un certain degré de porosité.

7. Stent comprenant un revêtement conçu pour délivrer un ingrédient actif, lequel revêtement comprend :

- sur au moins une partie d’une surface du stent, une région de revêtement primaire, laquelle région de primaire comprend un polymère et ne contient pratiquement pas d’ingrédients actifs, et laquelle région de primaire présente une épaisseur X’ ou un poids mesuré X’ ;
- et sur au moins une partie sélectionnée de la région de primaire, une région réservoir comprenant un polymère et l’ingrédient actif, laquelle région réservoir présente une épaisseur \( Y' \) ou un poids mesuré \( Y \);

étant entendu que :

a) l’épaisseur \( X' \) est mesurée de la surface externe de la région de primaire à la surface du stent avant la migration de l’ingrédient actif depuis la région de réservoir vers la région de primaire, et \( X' \) vaut de 0,5 à 3 \( \mu \text{m} \) et \( Y' \) vaut de 1 à 10 \( \mu \text{m} \), sous réserve que le rapport \( X'/Y' \) soit supérieur ou égal à 0,25,

b) ou le rapport \( X/Y \) est supérieur ou égal à 0,25 ;

et dans lequel stent :

i) ledit polymère de la région de primaire est du poly(méthacrylate de butyle) et ledit polymère de la région réservoir est un copolymère d’éthylène et d’alcool vinylique ;

ii) ou ledit polymère de la région de primaire est du poly(méthacrylate de butyle) et ledit polymère de la région réservoir est du poly(méthacrylate de butyle) ;

iii) ou ledit polymère de la région de primaire est un copolymère d’éthylène et d’alcool vinylique et ledit polymère de la région réservoir est du poly(méthacrylate de butyle).

8. Stent conforme à la revendication 7, lequel stent est choisi dans l’ensemble formé par les stents expansibles par ballonnet et les stents auto-expansibles.

9. Stent conforme à la revendication 7, pour lequel l’ingrédient actif est choisi dans l’ensemble formé par les héparine, héparine-sulfate, héparine à contre-ion hydrophobe, mannose-6-phosphate, superoxyde dismutase, clobétasol, acide rétinoïque, rapamycine, analogues et dérivés de rapamycine, suramine, asiaticoside, hyaluronane, et leurs combinaisons.

10. Stent conforme à la revendication 7, comportant en outre une région barrière située sur au moins une partie sélectionnée de la région réservoir et servant à réduire la vitesse à laquelle l’ingrédient actif est libéré à partir du revêtement après l’insertion du stent dans le corps d’un patient.

11. Stent conforme à la revendication 7, dans lequel la région de primaire comprend une matrice poreuse qui s’étend dans le primaire à partir de l’interface entre la région de primaire et la région réservoir.

12. Stent comprenant un revêtement conçu pour délivrer un ingrédient actif, lequel revêtement comprend une région de revêtement primaire comprenant un polymère et une région réservoir comprenant un polymère et un ingrédient actif, et dans lequel l’épaisseur ou le poids de la région de primaire est suffisamment élevé pour permettre à la région réservoir d’être chargée à 30 % en médicament sans que cela provoque l’apparition de fissures dans le revêtement quand le stent est déployé ;

et dans lequel stent :

i) ledit polymère de la région de primaire est du poly(méthacrylate de butyle) et ledit polymère de la région réservoir est un copolymère d’éthylène et d’alcool vinylique ;

ii) ou ledit polymère de la région de primaire est du poly(méthacrylate de butyle) et ledit polymère de la région réservoir est du poly(méthacrylate de butyle) ;

iii) ou ledit polymère de la région de primaire est un copolymère d’éthylène et d’alcool vinylique et ledit polymère de la région réservoir est du poly(méthacrylate de butyle).
FIG. 5
FIG. 8A

FIG. 8B
REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description