US 20070111008A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0111008 A1**

Pacetti (43) **Pub. Date: May 17, 2007**

(54) **RATE-REDUCING MEMBRANE FOR RELEASE OF AN AGENT**

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(21) Appl. No.: **11/637,301**

(22) Filed: **Dec. 11, 2006**

Related U.S. Application Data

(63) Continuation of application No. 11/330,926, filed on Jan. 11, 2006, which is a continuation of application No. 10/760,132, filed on Jan. 15, 2004, now Pat. No. 7,014,913, which is a continuation of application No. 09/966,787, filed on Sep. 27, 2001, now Pat. No. 6,753,071.

Publication Classification

(51) **Int. Cl.**

B32B 27/00	(2006.01)
A61L 33/00	(2006.01)
B05D 3/00	(2006.01)
B05D 3/02	(2006.01)

(52) **U.S. Cl.** **428/411.1**; 427/2.1; 427/372.2

(57) **ABSTRACT**

A membrane that reduces the rate at which a therapeutic substance is released from an implantable medical device, such as a stent, is disclosed.

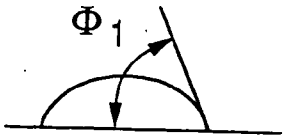


Figure 1A

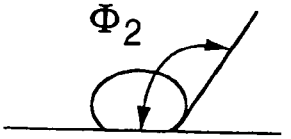


Figure 1B

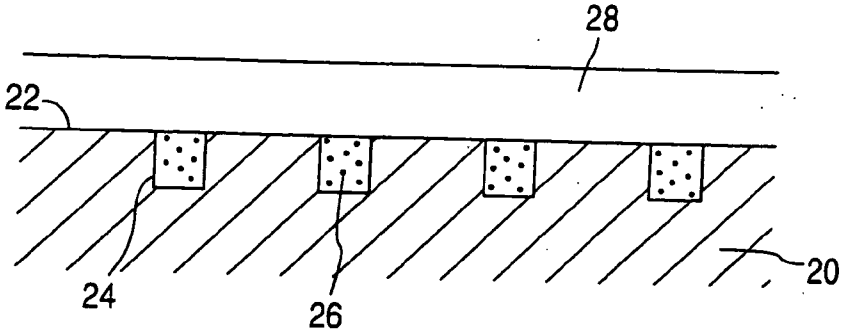


Figure 2A

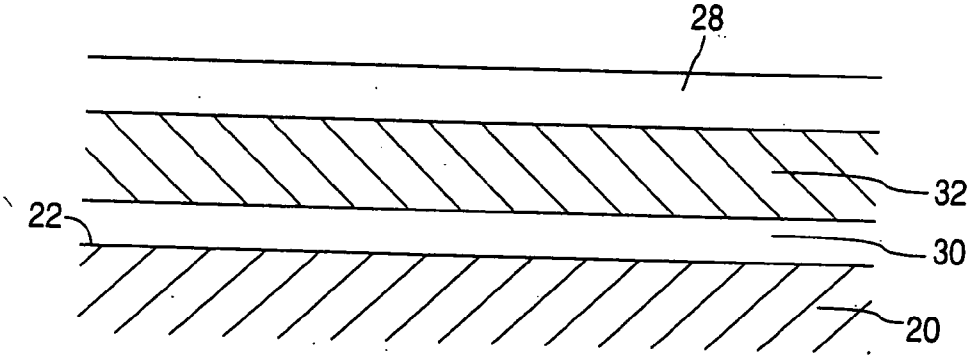


Figure 2B

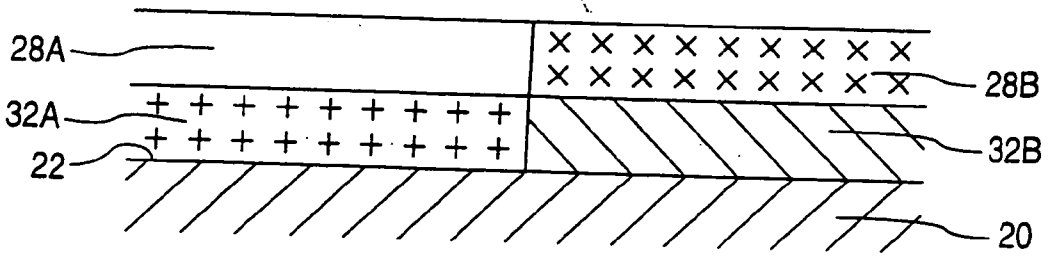


Figure 2C

RATE-REDUCING MEMBRANE FOR RELEASE OF AN AGENT

CROSS REFERENCE

[0001] This is a continuation of application Ser. No. 11/330,926, filed on Jan. 11, 2006, which is a continuation of Ser. No. 10/760,132 filed on Jan. 15, 2004, which is a continuation of application Ser. No. 09/966,787 filed on Sep. 27, 2001 (U.S. Pat. No. 6,753,071).

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The invention relates to a coating disposed on an implantable device, one example of which is a stent, for reducing the release rate of an agent carried by the device.

[0004] 2. Description of the Background

[0005] 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 remodel the vessel wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

[0006] 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 necessitate 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 is a stent, is implanted in the lumen to maintain the vascular patency.

[0007] Stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed so that they can be inserted through small lumens via catheters and then expanded to a larger diameter once they are at the desired location. Examples in the patent literature disclosing stents that have been applied in PTCA procedures include U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, and U.S. Pat. No. 4,886,062 issued to Wiktor. Mechanical intervention via stents has reduced the rate of restenosis as compared to balloon angioplasty. Yet, restenosis is still a significant clinical problem with rates ranging from 20-40%. When restenosis does occur in the stehted segment, its treatment can be challenging, as clinical options are more limited as compared to lesions that were treated solely with a balloon.

[0008] Stents are used not only for mechanical intervention but also as vehicles for providing biological therapy. Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or even 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.

[0009] One proposed method for medicating stents included use of a heparin-coated metallic stent, whereby a heparin coating was tonically or covalently bonded to the stent. Significant disadvantages associated with the aforementioned method include loss of the therapeutic substance from the body of the stent during delivery and expansion of the stent as well as lack of control of the release rate of the substance from the stent.

[0010] Another proposed method of medicating stents involved the use of a polymeric carrier coated onto the surface of the stent. A composition including a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent by immersing the stent in the composition or by spraying the composition onto the stent. The solvent is allowed to evaporate, leaving on the stent strut surfaces a coating of the polymer and the therapeutic substance impregnated in the polymer.

[0011] Depending on the physiological mechanism targeted, the therapeutic substance may be required to be released at an efficacious concentration for an extended duration of time. Increasing the quantity of the therapeutic substance in the polymeric coating can lead to poor coating mechanical properties, inadequate coating adhesion, and overly rapid rate of release. Increasing the quantity of the polymeric compound by producing a thicker coating can perturb the geometrical and mechanical functionality of the stent as well as limit the procedures for which the stent can be used.

[0012] It is desirable to increase the residence time of a substance at the site of implantation, at a therapeutically useful concentration, without needing to add a greater percentage of the therapeutic substance to the polymeric coating and without needing to apply a significantly thicker coating.

SUMMARY OF THE INVENTION

[0013] In accordance with one embodiment of the present invention, a method of forming a coating for a medical device, such as a stent, carrying an agent is provided. The method includes applying a first composition including a polymer to at least a portion of a medical device to form a first polymeric coating. The polymer has a solubility parameter not greater than approximately 11.5 $(cal/cm^3)^{1/2}$. The first polymeric coating reduces the rate of release of the agent from the medical device. In some embodiments of the method, the polymer of the first coating additionally has an equilibrium water absorption factor of less than about 5% by weight under physiologic conditions.

[0014] Also provided is a composition for forming a coating on a medical device. The composition includes a solvent and a hydrophobic polymer dissolved in the solvent.

The hydrophobic polymer has an equilibrium water absorption factor of less than about 5% by weight under physiological conditions. In some embodiments, the hydrophobic polymer additionally has a solubility parameter not greater than approximately 11.5 $(cal/cm^3)^{1/2}$.

[0015] An implantable medical device for carrying a therapeutic agent is also provided. The device includes a first coating including a polymeric material. The polymeric material has a solubility parameter not greater than approximately 11.5 $(cal/cm^3)^{1/2}$. The first coating reduces the rate of release of the agent. In some embodiments, the polymeric material additionally has an equilibrium water absorption factor of less than about 5% by weight under physiologic conditions.

[0016] Polymeric material suitable for use in the first coating of the present invention include hydrophobic and non-polar polymers such as, but not limited to, polytetrafluoroethylene, perfluoro elastomers, amorphous fluoropolymer, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropylene, low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, atactic polypropylene, polyisobutene, polybutylenes, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-anhydride copolymers, ethylene vinyl acetate copolymers, ethylene-acrylic acid copolymers, ethylene methacrylic acid copolymers, polyurethanes with a polydimethylsiloxane soft segment, and cross-linked silicone elastomers.

[0017] The medical device can be, for example, a balloon-expandable stent, a self-expandable stent, a graft, a stent graft. The medical device can include cavities containing an active ingredient for the release of the active ingredient when the device is implanted. Alternatively, the device can include a reservoir coating carrying an active ingredient.

BRIEF DESCRIPTION OF THE FIGURES

[0018] FIG. 1A illustrates a fluid on a solid substrate having a contact angle Φ_1;

[0019] FIG. 1B illustrates a fluid on a solid substrate having a contact angle Φ_2;

[0020] FIG. 2A illustrates a first coating deposited over an implantable medical substrate in accordance with one embodiment of the present invention;

[0021] FIG. 2B illustrates a first coating deposited over an implantable medical substrate in accordance with another embodiment of the present invention; and

[0022] FIG. 2C illustrates a pair of coatings deposited over an implantable medical substrate in accordance with yet another embodiment of the present invention.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Composition for Forming an Optional Primer Layer

[0023] The presence of an active ingredient in a polymeric matrix can interfere with the ability of the matrix to adhere effectively to the surface of the device. Increasing 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 can hinder the retention of the coating on the surface of the device. A primer layer can serve as a functionally useful intermediary layer between the surface of the device and an active ingredient-containing or reservoir coating. The primer layer provides an adhesive tie between the reservoir coating and the device—which, in effect, would also allow for the quantity of the active ingredient in the reservoir coating to be increased without compromising the ability of the reservoir coating to be effectively contained on the device during delivery and, if applicable, expansion of the device.

[0024] The embodiments of the composition for an optional primer layer are prepared by conventional methods wherein all components are combined, then blended. More particularly, in accordance with one embodiment, 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 at ambient pressure and under anhydrous atmosphere. 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 variations thereof. The polymers should have a high capacity of adherence to the surface of an implantable device, such as a metallic surface of a stent.

[0026] Representative examples of suitable polymeric materials include, but are not limited to, polyisocyanates, such as triisocyanurate and polyisocyanate polyether polyurethanes based on diphenylmethane diisocyanate; acrylates, such as copolymers of ethyl acrylate and methacrylic acid; titanates, such as tetra-iso-propyl titanate and tetra-n-butyl titanate; zirconates, such as n-propyl zirconate and n-butyl zirconate; silane coupling agents, such as 3-aminopropyltriethoxysilane and (3-glydidoxypropyl) methyldimethoxysilane; high amine content polymers, such as polyethyleneamine, polyallylamine, and polylysine; polymers with a high content of hydrogen bonding groups, such as polyethylene-co-polyvinyl alcohol, ethylene vinyl acetate, and melamine formaldehydes; and unsaturated polymers and prepolymers, such as polycaprolactone diacrylates, polyacrylates with at least two acrylate groups, and polyacrylated polyurethanes. With the use of unsaturated prepolymers, a free radical or UV initiator can be added to the composition for the thermal or UV curing or cross-linking process, as is understood by one of ordinary skill in the art.

[0027] Biocompatible polymers can also be used for the primer material. The polymer can be bioabsorbable or biostable. Bioabsorbable polymers that could be used include poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and

biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. In addition, biostable polymers such as polyurethanes, silicones, and polyesters could be used. Other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins; polyurethanes; rayon, rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

[0028] Ethylene vinyl alcohol is a very suitable choice of polymer for the primer layer. 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. 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 48%. Ethylene vinyl-alcohol copolymers are available commercially from companies such as Aldrich Chemical Company, Milwaukee, Wis., or EVAL Company of America, Lisle, Ill., or can be prepared by conventional polymerization procedures that are well known to one of ordinary skill in the art.

[0029] The solvent should be compatible with the polymer and should be capable of placing the polymer into solution at the concentration desired. Particularly 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 suitable solvents include, but are not limited to, dimethylsulfoxide (DMSO), chloroform, acetone, water (buffered saline), xylene, acetone, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate, methylethylketone, propylene glycol monomethylether, isopropanol, N-methyl pyrrolidinone, toluene and mixtures thereof.

[0030] 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, and the solvent can comprise from about 65% to about 99.9%, more narrowly from 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, the geometrical structure of the device, the choice of polymer-solvent combination, and the method of application.

[0031] In accordance with another embodiment, a fluid can be added to the composition to enhance the wetting of the primer 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 indicates a higher wetting liquid. A suitably high capillary permeation corresponds to a contact angle less than about 90°. FIG. **1**A illustrates a fluid droplet **10**A on a solid substrate **12**, for example a stainless steel surface. Fluid droplet **10**A has a high capillary permeation that corresponds to a contact angle Φ_1, which is less than about 90°. In contrast, FIG. **1**B illustrates a fluid droplet **10**B on solid substrate **12**, having a low capillary permeation that corresponds to a contact angle Φ_2, which is greater than about 90°. The wetting fluid, typically, should have a viscosity not greater than about 50 centipoise, 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.

[0032] The wetting fluid should be 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; and 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 polymer, solvent and wetting fluid employed as wells as the weight ratio of the polymer and the solvent.

Composition for Forming an Active Ingredient-Containing Coating

[0033] The embodiments of the composition for an active ingredient-containing or reservoir coating are prepared by conventional methods wherein all components are combined, then blended. More particularly, in accordance with one embodiment, a predetermined amount of a polymeric compound is added to a predetermined amount of a compatible solvent. The polymeric compound can be added to the solvent 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.

[0034] Sufficient amounts of an active ingredient are dispersed in the blended composition of the polymer and the

solvent. 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 89% 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. More than 9% by weight of the active ingredient could adversely affect characteristics that are desirable in the polymeric coating, such as adhesion of the coating to the device. With the use of the optional primer layer, weight ratios of more than 9% for the active ingredient are achievable without compromising the effectiveness of the adhesion. 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.

[0035] Optionally, a second solvent, such as tetrahydrofuran (THF) or dimethylformamide (DMF), can be used to improve the solubility of an active ingredient in the composition. The second solvent can be added to the composition or the active ingredient can be added to the second solvent prior to admixture with the blend. In this embodiment, 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.

[0036] 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 can also be first added to the second solvent prior to admixing with the composition. 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 achieved.

[0037] The active ingredient may be any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. Examples of such active ingredients include antiproliferative, antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, and antioxidant substances as well as combinations thereof. A suitable example of an antiproliferative substance is actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, Wis. 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. Examples of suitable antineoplastics include paclitaxel and docetaxel. Examples of suitable antiplatelets, anticoagulants, antifibrins, and antithrombins include sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of suitable cytostatic or antiproliferative agents include angiopeptin (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, 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, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents that may be appropriate include alpha-interferon; genetically engineered epithelial cells; dexamethasone; rapamycin; estradiol; clobetasol propionate; cisplatin; and carboplatin. Exposure of the composition to the active ingredient should not adversely alter the active ingredient's composition or characteristic. Accordingly, the particular active ingredient is selected for compatibility with the blended composition.

[0038] The dosage or concentration of the active ingredient required to produce a therapeutic effect should be less than the level at which the active ingredient produces toxic effects and greater than the level at which non-therapeutic results are obtained. The dosage or concentration of the active ingredient required to inhibit the desired cellular activity of the vascular region, for example, 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. Therapeutically 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.

[0039] The polymer chosen should be biocompatible so as not to cause any adverse response. The solvent chosen should be capable of placing the polymer into solution at the concentration desired. Representative examples of biocom-

patible polymers as well as of suitable solvents include those provided above with reference to the primer composition. With the use of a low ethylene content, e.g., 29 mol %, ethylene vinyl alcohol, for example, a suitable solvent is iso-propylalcohol (IPA) admixed with water e.g., from about 40% to about 60% by weight IPA. If an optional primer layer is used, the choice of polymer for the reservoir coating can be the same as that selected for the primer so as to eliminate any interfacial incompatibilities.

Composition for Forming the Rate-Reducing Membrane

[0040] If it is desired to increase the rate at which an active ingredient diffuses through a membrane, the membrane should be made of a polymer in which the active ingredient readily dissolves. By contrast, if it is desired to decrease the rate at which an active ingredient diffuses through a membrane, the membrane should be made of a polymer in which the active ingredient is less soluble. The purpose of the rate-reducing membrane of the present invention is to decrease the rate of release of an underlying active ingredient. Accordingly, the polymer for forming the rate-reducing membrane should be selected such that the active ingredient may not readily dissolve therein.

[0041] Polar substances are substances that have a dipole moment μ greater than 0 Debye. As a general rule, polar substances dissolve well in other polar substances, such as water. Accordingly, polar substances can be broadly categorized as "hydrophilic." Polar substances typically dissolve less readily in non-polar substances, which can be broadly categorized as "hydrophobic." The syllogism follows that a polar active ingredient will not readily dissolve in a hydrophobic polymer. Accordingly, a polymeric membrane that is hydrophobic may be employed to reduce the rate at which a polar active ingredient is released from an implantable device, such as a stent.

[0042] One method of defining the hydrophobicity of a polymer is by the solubility parameter of the polymer. The solubility parameter is represented by Equation 1:

$$\delta=(\Delta E/V)^{1/2} \quad \text{(Equation 1)}$$

[0043] where δ=solubility parameter $((cal/cm^3)^{1/2})$

[0044] ΔE=energy of vaporization (cal)

[0045] V=molar volume (cm^3)

("Polymer Handbook", 2nd Ed., Brandrup J. and E H Immergut, ed., Wiley-Interscience, John Wiley & Sons, N.Y. (1975)). Because polymers are typically non-volatile and thus cannot be vaporized without decomposition, the solubility parameter is measured indirectly. Briefly, solvents in which a polymer dissolves without a change in heat or volume are identified. The solubility parameter of the polymer is then defined to be the same as the solubility parameters of the identified solvents.

[0046] As a general rule, the value of the solubility parameter δ is inversely proportional to the degree of hydrophobicity of a polymer. Polymers that are very hydrophobic may have a low solubility parameter value. This general proposition is particularly applicable for polymers having a glass transition temperature below physiological temperature. A polymer that is sufficiently hydrophobic for use in the rate-limiting membrane of the present invention can have a solubility parameter not more than about 11.5 $(cal/cm^3)^{1/2}$, more narrowly not more than about 10 $(cal/cm^3)^{1/2}$, even more narrowly not more than 8.5 $(cal/cm^3)^{1/2}$.

[0047] Table 1 illustrates the solubility parameters of various polymers.

TABLE 1

Polymer	Solubility Parameter $(cal/cm^3)^{1/2}$
polytetrafluoroethylene	6.2
polydimethylsiloxane	7.3–7.62
polyethylene	7.7–8.79
polybutylmethacrylate	8.3–8.8
polypropylene	9.2–9.4
ethyl cellulose	10.3
polyvinyl acetate	9.4–11.0

[0048] Another method of defining the hydrophobicity of a polymer is by the equilibrium moisture absorption factor. The equilibrium moisture absorption factor is represented by Equation 2:

$$MAF=(W_w/W_p+W_w)\times 100 \quad \text{(Equation 2)}$$

[0049] where MAF=equilibrium moisture absorption factor (%)

[0050] W_w=weight of water taken up by the polymer when immersed in water or exposed to physiologic conditions

[0051] W_p=weight of the polymer

[0052] Generally, the less water absorbed by a polymer, and thus the lower the equilibrium moisture absorption factor, the better the polymer functions as a diffusion barrier for a polar active ingredient. Upon absorption of water, a polymer can swell and the spaces between polymer chains can enlarge, allowing an active ingredient to diffuse more easily through the polymer. In addition, absorbed water provides an otherwise non-polar polymer with polar water groups. These polar regions more readily dissolve a polar active ingredient via hydrogen bonding interactions, thereby allowing the active ingredient to diffuse through the otherwise non-polar polymer more quickly. Thus, a polymer that is sufficiently hydrophobic for use in the rate-limiting membrane of the present invention should have an equilibrium moisture absorption factor of less than about 5% by weight, more narrowly less than about 2%. Repreresitative examples of such polymers include polytetrafluoroethylene, perfluoro elastomers, fluoropolymers such as polyvinylidene fluoride, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropylene, low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, atactic polypropylene, polyisobutene, polybutylenes, polybutenes, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-anhydride copolymers, ethylene vinyl acetate copolymers, polybutylmethacrylate, ethylene-acrylic acid copolymers of low acrylic acid content, ethylene methacrylic acid copolymers of low methacrylic acid content, ethylene vinyl alcohol copolymers with an ethylene content greater than 48 mole percent, and cross-linked silicone elastomers.

[0053] In addition to having a solubility parameter not more than about 11.5 $(cal/cm^3)^{1/2}$ and/or an equilibrium moisture absorption factor of less than about 5% by weight, the selected polymer should be biocompatible. The polymer should also be capable of being placed into solution at a desired concentration by a selected solvent, such as a non-polar solvent so as to prevent dissolution of the polar active ingredient with the non-polar solvent. Prevention of dissolution of the active ingredient during the coating process of the rate-limiting layer significantly reduces or eliminates the migration or leaching of the active component out from the underlying reservoir layer or device. Accordingly, the quantity of active ingredient will not be reduced during the application of the rate-limiting layer.

[0054] Fluoropolymers are a suitable choice for the barrier layer composition. For example, the solubility parameter of polytetrafluoroethylene is about 6.2 $(cal/cm^3)^{1/2}$, and the equilibrium moisture absorption factor is about 0.01%. Solution processing of fluoropolymers is possible, particularly the low crystallinity varieties such as CYTOP available from Asahi Glass and TEFLON AF available from DuPont. Solutions of up to about 15% (wt/wt) are possible in perfluoro solvents, such as FC-75 (available from 3M under the brand name FLUORINERT), which are non-polar, low boiling solvents. Such volatility allows the solvent to be easily and quickly evaporated following the application of the polymer-solvent solution to the medical device.

[0055] Another particularly suitable choice of polymer for the barrier layer composition is styrene-ethylene/butylene-styrene block copolymer. The solubility parameter of this material lies in the range of from about 7.7 $(cal/cm^3)^{1/2}$ to about 10.3 $(cal/cm^3)^{1/2}$, and the equilibrium moisture absorption factor is less than about 1%. Styrene-ethylene/butylene-styrene block copolymer, e.g., Kraton G-series, can be dissolved in non-polar solvents such as, but not limited to, toluene, xylene, and decalin.

[0056] Still other suitable choices of polymers for the rate-limiting membrane include, but are not limited to, ethylene-anhydride copolymers; ethylene vinyl acetate copolymers having, for example, a mol % of vinyl acetate of from about 9% to about 25%; and ethylene-acrylic acid copolymers having, for example, a mol % of acrylic acid of from about 2% to about 25%. The ethylene-anhydride copolymer available from Bynel adheres well to EVAL and thus would function well as a topcoat over a reservoir layer made from EVAL. The copolymer can be dissolved in organic solvents, such as dimethylsulfdxide and dimethylacetamide. Ethylene vinyl acetate polymers can be dissolved in organic solvents, such as toluene and n-butyl acetate. Ethylene-acrylic acid copolymers can be dissolved in organic solvents, such as methanol, isopropyl alcohol, and dimethylsulfoxide.

[0057] Yet another suitable choice of polymer for the rate-limiting membrane composition is a cross-linked silicone elastomer. Such substances have a solubility parameter in the range of about 7.3 $(cal/cm^3)^{1/2}$ to about 7.6 $(cal/cm^3)^{1/2}$, and an equilibrium moisture absorption factor of less than about 0.5%. Loose silicone and silicone with very low cross-linking are thought to cause an inflammatory biological response. However, it is believed that a thoroughly cross-linked silicone elastomer, having low levels of leachable silicone polymer and oligomer, is an essentially non-inflammatory substance. Silicone elastomers, such as Nusil MED-4750, MED-4755, or MED2-6640, having high tensile strengths, for example between 1200 psi and 1500 psi, will likely have the best durability during crimping, delivery, and expansion of a stent as well as good adhesion to a reservoir layer, e.g., EVAL or the surface of a medical device.

[0058] The embodiments of the composition for a rate-reducing membrane or diffusion barrier layer are prepared by methods wherein all components are combined, then blended. More particularly, in accordance with one embodiment, a predetermined amount of a polymeric compound is added to a predetermined amount of a compatible solvent. The selected solvent should be capable of placing the polymer into solution at the concentration desired.

[0059] The polymeric compound can be added to the solvent 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 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, and the solvent can comprise from about 65% to about 99.9%, more narrowly from about 80% to about 98% 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 type of polymer and solvent employed, the type of underlying reservoir layer, and the method of application. Optionally, one of the aforementioned wetting fluids can also be added to the blend.

EXAMPLES OF THE DEVICE

[0060] The device or prosthesis used in conjunction with the above-described compositions may be any suitable medical substrate that can be implanted in a human or veterinary patient. Examples of such implantable devices include self-expandable stents, balloon-expandable stents, stent-grafts, grafts, artificial heart valves, cerebrospinal fluid shunts, and pacemaker electrodes. The underlying structure of the device can be virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), high nitrogen stainless steel, e.g., BIODUR 108, cobalt chrome alloy L-605, "MP35N,""MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

[0061] It should be noted that the rate-reducing membrane or diffusion barrier layer in accordance with various embodiments of the present invention can be used without the active ingredient-containing coating. In such embodiments, the device may include cavities or micro-pores for containing the active ingredient such that the diffusion barrier layer is disposed over the cavities. The device can be formed by

sintering the stent material from metallic particles, filaments, fibers or other materials. The device can be formed from a sintered wire that is coiled or otherwise formed into a device. The prosthesis can also be formed from a sintered cylindrical tube or sintered metal sheet which can be laser cut or chemical etched into an expandable stent structure. Formation of cavities via a sintering process is described in U.S. Pat. No. 5,843,172 to Yan. By way of another example, the surface of the device can be exposed to an etchant or a laser discharge to form cavities of selected dimensional specification.

Methods For Applying the Compositions to the Device

[0062] To form the optional primer layer and/or the active ingredient-containing coating on a surface of the device or prosthesis, the surface of the device should be clean and free from contaminants that may be introduced during manufacturing. However, the surface of the prosthesis requires no particular surface treatment to retain the applied coating. Application of the composition can be by any conventional method, such as by spraying the composition onto the prosthesis or by immersing the prosthesis 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. Any excess coating can also be vacuumed off the surface of the device. 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 prosthesis.

[0063] With the use of the thermoplastic polymers for the primer, such as ethylene vinyl alcohol copolymer, polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), etc., the deposited primer composition should be exposed to a heat treatment at a temperature range greater than about the glass transition temperature (T_g) and less than about the melting temperature (T_m) of the selected polymer. 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 that would allow for the formation of the primer coating on the surface of the device as well as 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 may remain blended with the polymer.

[0064] Table 2 lists the T_g and T_m for some of the polymers used in the 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 are provided by way of illustration and are not meant to be limiting.

TABLE 2

Polymer	T_g (° C.)	T_m (° C.)	Exemplary Temperature (° C.)	Exemplary Duration of Time For Heating
EVAL	55	165	140	4 hours
polycaprolactone	−60	60	50	2 hours
ethylene vinyl acetate (e.g., 33% vinyl acetate content)	36	63	45	2 hours
Polyvinyl alcohol	75–85*	200–220*	165	2 hours

*Exact temperature depends on the degree of hydrolysis which is also known as the amount of residual acetate.

[0065] With the use of one of the aforementioned thermoset primer polymers, the use of initiators may be required. By way of example, epoxy systems consisting of diglycidyl ether of bisphenol A resins can be cured with amine curatives, thermoset polyurethane prepolymers can cured with polyols, polyamines, or water (moisture), and acrylated urethane can be cured with UV light. If baked, the temperature can be above the T_g of the selected polymer.

[0066] With the use of the inorganic primer polymers, such as silanes, titanates, and zirconates, the solvent is allowed to evaporate.

[0067] The composition containing the active ingredient can be applied to a designated region of the primer coating or the surface of the device. The solvent(s) or the combination of solvent(s) and the wetting fluid is removed from the composition by allowing the solvent(s) or combination of the solvent(s) and the wetting fluid to evaporate. The evaporation can be induced by heating the device at a predetermined temperature for a predetermined period of time. For example, the device can be heated at a temperature of about 60° C. for about 12 hours to about 24 hours. The heating can be conducted in an anhydrous atmosphere and at ambient pressure and should not exceed the temperature which would adversely affect the active ingredient. The heating can, alternatively, be conducted under a vacuum condition. It is understood that essentially all of the solvent and the wetting fluid will be removed from the composition, but traces or residues may remain blended with the polymer.

[0068] The diffusion barrier layer can be formed on a designated region of the active ingredient-containing coating subsequent to the evaporation of the solvent(s) or solvent(s)/wetting fluid and the drying of the polymer for the active ingredient-containing coating. Alternatively, in embodiments in which a polymeric reservoir coating is not employed, the rate-reducing membrane may be formed directly over active-ingredient containing cavities within the surface of the prosthesis. The diffusion barrier layer can be applied by spraying the composition onto the device or immersing the device in the composition, then drying the polymer. The above-described processes can be similarly repeated for the formation of the diffusion barrier layer.

Coating

[0069] Some of the various embodiments of the present invention are illustrated by FIGS. **2**A, **2**B, and **2**C. The

Figures have not been drawn to scale, and the thickness of the various layers have been over or under emphasized for illustrative purposes.

[0070] Referring to FIG. 2A, a body of a medical substrate **20**, such as a stent, is illustrated having a surface **22**. Medical substrate **20** includes cavities or micro-pores **24** formed in the body for releasably containing an active ingredient, as illustrated by dotted region **26**. A diffusion barrier layer or rate-reducing membrane **28** is disposed on surface **22** of medical substrate **20**, covering cavities **24**. Diffusion barrier layer **28** functions to reduce the rate of release of an active ingredient from medical substrate **20**.

[0071] Referring to FIG. 2B, medical substrate **20** is illustrated having a primer layer **30** formed on surface **22**. An active ingredient-containing or reservoir coating **32** is deposited on primer layer **30**. Primer layer **30** serves as an intermediary layer for increasing the adhesion between reservoir coating **32** and surface **22**. Increasing the amount of active ingredient admixed within the polymer diminishes the adhesiveness of reservoir layer **32** to surface **22**. Accordingly, using an active ingredient-free polymer as an intermediary primer layer **30** allows for a higher active ingredient content for reservoir layer **32**. Diffusion barrier **28** is formed over at least a selected portion of reservoir layer **32**. One of ordinary skill in the art can appreciate that diffusion barrier layer **28** can be deposited only on selected areas of reservoir layer **32** so as to provide a variety of selected release parameters. Such selected patterns may become particularly useful if a combination of active ingredients are used, each of which requires a different release parameter.

[0072] FIG. 2C illustrates medical substrate **20** having a first reservoir layer **32**A disposed on a selected portion of surface **22** of medical substrate **20**. First reservoir layer **32**A contains a first active ingredient, e.g., actinomycin D. A second reservoir layer **32**B can also be disposed on surface **22**. Second reservoir layer **32**B contains a second active ingredient, e.g., taxol. First and second reservoir layers **32**A and **32**B are covered by first and second diffusion barrier layers **28**A and **28**B, respectively. In accordance with one embodiment, the polymeric material from which diffusion barrier layer **28**A is made can be different than the material from which diffusion barrier layer **28**B is made. Accordingly, a wide array of release parameters can be obtained for any selected combination of active ingredients.

[0073] Diffusion barrier layer **28** can have any suitable thickness, as the thickness of diffusion barrier layer **28** is dependent on parameters such as, but not limited to, the desired rate of release and the procedure for which the stent will be used. Diffusion barrier layer **28** can have a thickness of about 0.1 to about 10 microns, more narrowly from about 0.25 to about 5 microns.

[0074] By way of example, and not limitation, the impregnated reservoir layer **32** can have a thickness of about 0.5 microns to about 1.5 microns. The particular thickness of reservoir layer **32** is based on the type of procedure for which medical substrate **20** is employed and the amount of the active ingredient to be delivered. The amount of the active ingredient to be included on the prosthesis can be further increased by applying a plurality of reservoir layers **32** on top of one another. The optional primer layer **30** can have any suitable thickness, examples of which can be in the range of about 0.1 to about 10 microns, more narrowly about 0.1 to about 2 microns.

Method of Use

[0075] In accordance with the above-described method, the active ingredient can be applied to a device, e.g., a stent, retained on the device during delivery 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 by 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.

[0076] Briefly, an angiogram is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by injecting a radiopaque contrasting 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 layers may then be expanded at the desired area of treatment. A post insertion angiogram may also be utilized to confirm appropriate positioning.

EXAMPLES

[0077] The embodiments of the invention will be illustrated by the following set forth prophetic examples which are being given by way of illustration only and not by way of limitation. All parameters and data are not to be construed to unduly limit the scope of the embodiments of the invention.

Example 1

[0078] A 13 mm, 316L stainless steel TETRA stent is primer coated by spraying with a 2% (w/w) solution of poly(ethylene-co-vinyl alcohol) (44 mole % ethylene) in dimethylacetamide. The solvent is removed by baking at 140° C. for 1 hour. A solution of 2% (w/w) EVAL and 0.25% (w/w) actinomycin D in dimethylacetamide is spray coated onto the stent to a thickness that gives 25 μg of actinomycin D on the stent. The stent is then baked at 50° C. for two hours. A hydrophobic release rate limiting membrane is formed by spraying the stent with a 2% (w/w) solution of polybutylmethacrylate in a ⅓ (w/w) mixture of ethyl acetate and cyclohexanone. A second two hour bake at 50° C. is performed to remove the solvent.

Example 2

[0079] A 13 mm, 316L stainless steel TETRA stent is primer coated by spraying with a 2% (w/w) solution of poly(ethylene-co-vinyl alcohol) (44 mole % ethylene) in dimethylacetamide. The solvent is removed by baking at

140° C. for 1 hour. A solution of 2% (w/w) EVAL and 0.5% (w/w) paclitaxel in dimethylacetamide is spray coated onto the stent to a thickness that gives 50 μg of paclitaxel on the stent. The stent is then baked at 50° C. for two hours. A hydrophobic release rate limiting membrane is formed by spraying on a 2% (w/w) solution of poly(ethylene-co-vinylacetate) (25 mole % acetate content) in a 1/1 (w/w) solution of toluene and n-butyl acetate. Another two hour bake at 50° C. is performed to remove the solvent.

Example 3

[0080] A 13 mm, 316L stainless steel TETRA stent is primer coated by spraying with a 2% (w/w) solution of poly(ethylene-co-vinyl alcohol) (44 mole % ethylene) in dimethylacetamide. The solvent is removed by baking at 140° C. for 1 hour. A solution of 2% (w/w) EVAL and 0.67% (w/w) clobetasol propionate in dimethylacetamide is spray coated onto the stent to a thickness that gives 150 μg of clobetasol propionate on the stent. The stent is then baked at 50° C. for two hours. A hydrophobic release rate limiting membrane is formed by coating on a 5% (w/w) solution of Nusil MED3-6605 silicone dispersion in a 1/1 (w/w) of trichloroethylene and cyclohexane. This process is accomplished by placing the stent on a section of 0.070 inch OD stainless steel tubing. The coating is then applied to the stent via syringe. With the stent covered with fluid, it is pushed along the length of the tube with a short section of TEFLON tubing, while simultaneously rotating the stainless steel tube. The coating is left to air cure at ambient temperature for 18 hours.

[0081] 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. For example, while much of the above discussion focuses on the reduction of the rate of diffusion of a polar active ingredient, one of ordinary skill in the art will understand that the diffusion barriers described are also applicable for use with non-polar active ingredients. 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.

What is claimed is:

1. A method of forming a coating for a medical device carrying an agent, comprising:

applying a first composition including a polymer to at least a portion of a medical device to form a first coating, said polymer having a solubility parameter not greater than approximately 11.5 $(cal/cm^3)^{1/2}$, and

wherein said first coating reduces the rate of release of said agent from said medical device.

2. A coating for a medical device produced in accordance with the method of claim 1.

3. The method of claim 1, wherein said medical device is a balloon expandable stent, a self-expandable stent, a stent-graft, or a graft.

4. The method of claim 1, wherein said medical device is a metallic stent having cavities containing said agent for the release of said agent subsequent to the implantation of said stent in a mammalian lumen, and wherein said first coating is formed on the surface of said metallic stent and covering said cavities.

5. The method of claim 1, wherein said agent is a polar substance.

6. The method of claim 1, wherein said first coating is hydrophobic, and wherein said agent is a polar substance.

7. The method of claim 1, wherein said first composition additionally includes a solvent capable of dissolving said polymer, said method additionally comprising evaporating said solvent to form said first coating.

8. The method of claim 7, wherein said solvent is non-polar and capable of dissolving said polymer.

9. The method of claim 7, wherein said solvent is non-polar and capable of dissolving the polymer but not the agent.

10. The method of claim 1, wherein said agent is selected from a group of actinomycin D, docetaxel, paclitaxel, and rapamycin.

11. The method of claim 1, wherein said polymer has an equilibrium water absorption factor of less than about 5% by weight under physiologic conditions.

12. The method of claim 1, additionally comprising prior to said applying a first composition:

(a) applying a second composition including a solvent and a polymer to the surface of said medical device;

(b) evaporating said solvent of said second composition to form a second coating on the surface of said medical device;

(c) applying a third composition including a solvent, a polymer, and an agent on said second coating; and

(d) evaporating said solvent of said third composition to form a third coating containing said agent in said second coating,

wherein said first coating reduces the rate of release of said agent.

13. The method of claim 1, additionally comprising prior to said applying a first composition:

(a) applying a second composition including a solvent, a polymer, and an agent to the surface of said medical device; and

(b) evaporating said solvent of said second composition to form a second coating containing said agent on the surface of said medical device,

wherein said first coating reduces the rate of release of said agent.

14. The method of claim 1, wherein said polymer has a solubility parameter not greater than approximately 10 $(cal/cm^3)^{1/2}$.

15. The method of claim 1, wherein said polymer has a solubility parameter not greater than approximately 8.5 $(cal/cm^3)^{1/2}$.

16. A composition for forming a coating on a medical device comprising:

(a) a solvent; and

(b) a hydrophobic polymer dissolved in said solvent, wherein said polymer has an equilibrium water absorption factor of less than about 5% by weight by weight under physiological conditions.

17. The composition of claim 16, wherein said solvent is non-polar and capable of dissolving said polymer.

18. A polymeric coating produced by the evaporation of said solvent from said composition of claim 16.

19. The composition of claim 16, wherein said polymer is selected from a group of polytetrafluoroethylene, perfluoro elastomers, fluoropolymers, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropylene, low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, atactic polypropylene, polyisobutene, polybutylenes, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butlene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-anhydride copolymers, ethylene vinyl acetate copolymers, ethylene-acrylic acid copolymers, ethylene methacrylic acid copolymers, polyurethanes with a polydimethylsiloxane soft segment, ethylene vinyl alcohol copolymers with an ethylene content greater than 48 mole percent, and cross-linked silicone elastomers.

20. The composition of claim 16, wherein said medical device is a radially expandable stent.

21. The composition of claim 16, wherein said coating formed from said composition is used for reducing the rate of release of a therapeutic agent from said medical device.

22. The composition of claim 16, wherein said polymer has a solubility parameter not greater than approximately 11.5 $(cal/cm^3)^{1/2}$.

23. The composition of claim 16, wherein said polymer has a solubility parameter not greater than approximately 8.5 $(cal/cm^3)^{1/2}$.

24. An implantable medical device for carrying a therapeutic agent, comprising:

a first coating including a polymeric material, said polymeric material having a solubility parameter not greater that approximately 11.5 $(cal/cm^3)^{1/2}$, wherein said first coating reduces the rate of release of said agent.

25. The device of claim 24, wherein said polymeric material is hydrophobic and said therapeutic agent is polar.

26. The device of claim 24, wherein said polymeric material is non-polar and said therapeutic agent is polar.

27. The device of claim 24, additionally comprising:

(a) a second polymeric coating formed on the surface of said medical device; and

(b) a third polymeric coating including an agent formed on said second polymeric coating and beneath said first polymeric coating,

wherein said first polymeric coating reduces the rate of release of said agent.

28. The device of claim 24, additionally comprising:

(a) a second polymeric coating including an agent formed on the surface of said medical device and beneath said first polymeric coating,

wherein said first polymeric coating reduces the rate of release of said agent.

29. The device of claim 24, wherein said polymeric material is selected from a group of polytetrafluoroethylene, perfluoro elastomers, fluoropolymers, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropylene, low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, atactic polypropylene, polyisobutene, polybutylenes, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butlene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-anhydride copolymers, ethylene vinyl acetate copolymers, ethylene-acrylic acid copolymers, ethylene methacrylic acid copolymers, polyurethanes with a polydimethylsiloxane soft segment, ethylene vinyl alcohol copolymers with an ethylene content greater than 48 mole percent, and cross-linked silicone elastomers.

30. The device of claim 24, wherein said implantable medical device is a radially expandable metallic stent.

31. The device of claim 30, wherein said metallic stent includes cavities containing said agent for the release of said agent subsequent to the implantation of said stent in a mammalian lumen, and wherein said first polymeric coating is formed on the surface of said metallic stent and covering said cavities.

32. The device of claim 24, wherein said polymeric material has an equilibrium water absorption factor of less than about 5% by weight under physiologic conditions.

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