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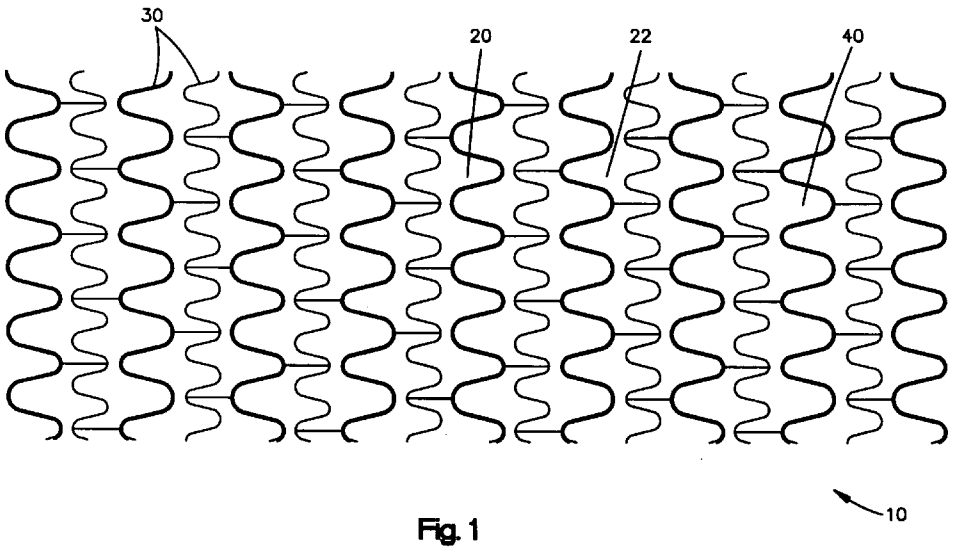

Fig. 1

(57) **Abstract:** The invention relates generally to an implantable medical device for delivering a therapeutic agent to the body tissue of a patient, and a method for making such a medical device. In particular, the invention pertains to an implantable stent, such as an intravascular stent, having a coating comprising an inorganic or ceramic oxide, metal or inert carbon and a plurality of reservoirs in such material that contain a therapeutic agent.

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COATED MEDICAL DEVICES FOR ABLUMINAL DRUG DELIVERY

FIELD OF THE INVENTION

[0001] The invention relates generally to an implantable medical device for delivering a therapeutic agent to the body tissue of a patient, and a method for making such a medical device. In particular, the invention pertains to an implantable medical device, such as an intravascular stent, having a coating comprising an inorganic or ceramic oxide, metal or inert carbon and a plurality of reservoirs in such materials that contain a therapeutic agent.

BACKGROUND

[0002] Medical devices have been used to deliver therapeutic agents locally to body tissue of a patient. For example, intravascular stents comprising a therapeutic agent have been used to locally deliver therapeutic agents to a blood vessel. Often such therapeutic agents have been used to prevent restenosis. Examples of stents comprising a therapeutic agent include stents that comprise a coating containing a therapeutic agent for delivery to a blood vessel. Studies have shown that stents having a coating with a therapeutic agent are effective in treating or preventing restenosis.

[0003] Even though medical devices having a coating with a therapeutic agent are effective in preventing or treating restenosis, many coated medical devices, in order to coat the medical device with the therapeutic agent or in order to control the release rate of the therapeutic agent, also include a polymer. The use of such polymers may have certain limitations.

[0004] For example, some polymer coatings do not actually adhere to the surface of the medical device, instead the coating encapsulates the surface, which makes the polymer coating susceptible to deformation and damage during loading, deployment and implantation of the medical device. Any damage to the polymer coating may alter the drug release profile and can lead to an undesirable and dangerous increase or decrease in the drug release rate.

[0005] For instance, balloon expandable stents must be put in an unexpanded or "crimped" state before being delivered to a body lumen. The crimping process can tear the coating or cause the coating to be completely ripped off of the stent. Once in the crimped state the polymeric coating can cause adjacent stent surfaces, such as struts, to adhere to each other. Moreover, if the coating is applied to the inner surface of the stent, it may stick

to the balloon as it contacts the inner surface during expansion. Such interference may prevent a successful deployment of the medical device.

[0006] Similar to balloon-expandable stents, polymer coatings on self-expanding stents can also interfere with the deployment mechanism. Self-expanding stents are usually deployed using a pull-back sheath system. When the system is activated to deploy the stent, the sheath is pulled back, exposing the stent and allowing the stent to expand itself. As the sheath is pulled back it slides over the outer surface of the stent. Polymer coatings located on the outer surface of the stent can adhere to the sheath as it is being pulled back and disrupt the deployment of the stent.

[0007] Since many polymeric coatings only encapsulate the surface of the medical device, not only are such coatings susceptible to deformation, they must coat the entire surface of the medical device in order to encapsulate it. Coating the entire surface with a therapeutic agent/polymer coating can result an excessive amount of a therapeutic agent being applied to the medical device. In certain instances, it is desirable that only the surfaces of the medical device that contact the body lumen are coated with a therapeutic agent. However, when the therapeutic agent is dispersed in a coating composition and the coating composition is applied to the entire surface of the medical device, the therapeutic agent is also applied to the entire surface of the medical device. Such use of excess therapeutic agents is costly.

[0008] An alternative to coating or encapsulating the surface of a medical device is to create holes in the surface of a medical device and place a therapeutic agent in the holes. Placing the therapeutic agent in the holes reduces waste and the dangers associated with coating a medical device with an excessive amount of a therapeutic agent since the therapeutic agent is placed were it is needed, instead of on the entire surface of the medical device. However, creating holes in the medical device can negatively impact the structural integrity of the medical device. For example, if holes are created in stent struts, the structural integrity of the stent struts can be compromised causing the struts to become weak. Weak struts could result in the stent failing to expand properly or, once implanted, collapsing, potentially causing re-occlusion of a body lumen.

[0009] Accordingly, there is a need for coatings for medical devices that allow greater control over placement of a therapeutic agent on the surface of the medical device as well as coatings that are not easily deformed or damaged, particularly during loading, deployment or implantation of the medical device. Moreover, there is a need for medical device coatings and a way to apply them that does not affect the structural integrity of the medical device.

SUMMARY

[0010] These and other objectives are accomplished by the present invention. The present invention, in one embodiment, provides a coating for a medical device, such as an intravascular stent. The coating comprises a first coating material comprising an inorganic or ceramic oxide, a metal or inert carbon wherein the first coating material has a plurality of reservoirs therein and a second coating material comprising a therapeutic agent and a polymer disposed in the reservoirs.

[0011] The coating is an alternative to and overcomes the limitations of present drug release coatings by allowing precise quantities of a therapeutic agent to be disposed on the surface of an implantable medical device. The coatings of the present invention also allow for precise placement of a therapeutic agent on the surface of a medical device without compromising the structural integrity of the medical device itself. Since the therapeutic agent is disposed in reservoirs in the inorganic or ceramic oxide, metal or inert carbon of the first coating material, reservoirs are not drilled in the surface of the medical device, thus preserving the structural integrity of the medical device.

[0012] One embodiment contemplated by the present invention is an implantable stent comprising: (a) a tubular stent sidewall structure having an abluminal surface and an adluminal surface; (b) a coating having an outer surface comprising a first coating material disposed on at least a portion of the abluminal surface of the stent comprising an inorganic or ceramic oxide, metal or inert carbon; a plurality of reservoirs formed within the first coating material; and a second coating material comprising a polymer and a first therapeutic agent, wherein the second coating material is disposed within the reservoirs. In certain embodiments, the adluminal surface of the stents is substantially free of the coating.

[0013] It is contemplated by the present invention that the stent sidewall can comprise a plurality of struts and openings in the sidewall structure, wherein at least one strut comprises an abluminal surface and an adluminal surface opposite the abluminal surface. In certain embodiments, the coating is capable of conforming to the stent sidewall structure so that the openings are preserved.

[0014] Stents that can be used in accordance with the present invention include intravascular balloon-expandable stents and intravascular self-expanding stents.

[0015] In addition to coating at least a portion of the abluminal surface of the stents of the present invention, the first coating material can be further disposed on the adluminal surface of the sidewall structure and wherein the first coating material disposed on the adluminal surface of the sidewall structure can comprise a plurality of reservoirs.

[0016] The first coating material used in accordance with the present invention can be radiopaque. Inorganic or ceramic oxides used in the coatings of the present invention include metal oxides. For example, the inorganic or ceramic oxide can be iridium oxide. Metals used in the coatings of the present invention can include, but are not limited to, gold, platinum or titanium.

[0017] In certain embodiments, the coating is about 1 micron to about 70 microns thick. Additionally, the first coating material can further comprise a second therapeutic agent that is different from the first therapeutic agent.

[0018] In certain embodiments of the present invention, the reservoirs can be interconnected. Additionally, the reservoirs can be in fluid communication with the outer surface of the coating. The reservoirs also can extend between the outer surface of the coating and the abluminal surface of the stent. The average diameter of the reservoirs can be about 5 microns to about 80 microns.

[0019] Polymers used in the coatings can be biostable or bioabsorbable. The polymer used in the coatings of the present invention can be a styrene-isobutylene co-polymer, polylactic glycol acid, and methylenebisacrylamide.

[0020] Suitable therapeutic agents include, but are not limited to, an anti-thrombogenic agent, anti-angiogenesis agent, anti-proliferative agent, antibiotic agent, anti-restenosis agent, growth factor, immunosuppressant, radiochemical, or combination of thereof. In certain embodiments the therapeutic agent comprises an anti-restenosis agent. Therapeutic agent can comprise paclitaxel, sirolimus, tacrolimus, pimecrolimus or everolimus.

[0021] The present invention is also directed to an intravascular stent comprising: (a) a tubular stent sidewall structure having an abluminal surface and an adluminal surface wherein, the sidewall structure has a plurality of openings therein; (b) a coating comprising a first coating material comprising gold or platinum disposed on the abluminal surface; a plurality of reservoirs formed within the first coating material; and a second coating material comprising a polymer and an anti-restinosis agent, wherein the second coating material is disposed within the reservoirs.

[0022] The present invention is further directed to a stent comprising: (a) a tubular stent sidewall structure comprising a plurality of struts and openings in the sidewall structure, and wherein at least one of the struts has an abluminal surface and an adluminal surface opposite the abluminal surface; (b) a coating having an outer surface comprising a first coating material disposed on at least a portion of the abluminal surface comprising gold or platinum disposed on the abluminal surface; a plurality of reservoirs formed within the first coating

material; and a second coating material comprising a polymer and an anti-restinosis agent, wherein the second coating material is disposed within the reservoirs.

[0023] The present invention also contemplates a method of coating an implantable stent having an abluminal surface and an adluminal surface comprising: (a) disposing a first coating material on at least a portion of an abluminal or adluminal surface of the stent wherein the first coating comprises an inorganic or ceramic oxide, inert carbon or metal; (b) forming a plurality of reservoirs in the first coating material; and (c) disposing a second coating material in the reservoirs wherein, the second coating comprises a polymer and a therapeutic agent. In certain embodiments of the methods of the present invention, the adluminal surface of the stent can be substantially free of the first coating material.

[0024] In certain embodiments the reservoirs can be formed on the abluminal surface of the stent only, leaving the adluminal side of the stent substantially free of reservoirs. Alternatively, the reservoirs can be formed on the abluminal and adluminal surface of the stent. Reservoirs can be formed by drilling, chemical etching or laser ablation.

[0025] The first coating material used in accordance with the present invention can be radiopaque. Inorganic or ceramic oxides used in the coatings of the present invention can be a metal oxide. For example, the inorganic or ceramic oxide can be iridium oxide. Metals used in the coatings of the present invention can include, but are not limited to, gold, platinum or titanium.

[0026] The therapeutic agent used in the coatings of the present invention can be, but are not limited to, an anti-thrombogenic agent, anti-angiogenesis agent, anti-proliferative agent, antibiotic agent, anti-restenosis agent, growth factor, immunosuppressant, radiochemical, an agent that inhibits smooth muscle cell proliferation or combination of thereof. In certain embodiments the therapeutic agent comprises an anti-restenosis agent. Therapeutic agent can comprise paclitaxel, sirolimus, tacrolimus, pimecrolimus or everolimus.

[0027] Polymer used in the methods of the present invention can be biostable or bioabsorbable. Examples of suitable polymers include, but are not limited to, a styrene-isobutylene coppolymer, polylactic glycol acid, and methylenebisacrylamide.

[0028] The present invention also contemplates a method of coating an implantable stent having an abluminal surface and an adluminal surface comprising: (a) masking a portion of an adluminal or abluminal surface of the stent with a masking material; (b) disposing a first coating on the unmasked portion of the adluminal or abluminal surface, wherein the first coating comprises an inorganic or ceramic oxide, metal or inert carbon; (c) removing the masking material to create a plurality of reservoirs; and (d) disposing a second

coating material within the reservoirs wherein, the second coating comprises a polymer and a therapeutic agent.

[0029] In certain embodiments the reservoirs can be formed on the abluminal surface of the stent only, leaving the adluminal side of the stent substantially free of reservoirs. Alternatively, the reservoirs can be formed on the abluminal and adluminal surface of the stent. Reservoirs can be formed by drilling, chemical etching or laser ablation.

[0030] The first coating material used in accordance with the present invention can be radiopaque. Inorganic or ceramic oxides used in the coatings of the present invention can be a metal oxide. For example, the inorganic or ceramic oxide can be iridium oxide. Metals used in the coatings of the present invention can include, but are not limited to, gold, platinum or titanium.

[0031] The therapeutic agent used in the coatings of the present invention can comprise an agent that inhibits smooth muscle cell proliferation. Other suitable therapeutic agents include, but are not limited to, an anti-thrombogenic agent, anti-angiogenesis agent, anti-proliferative agent, antibiotic agent, anti-restenosis agent, growth factor, immunosuppressant, radiochemical, or combination of thereof. In certain embodiments the therapeutic agent comprises an anti-restenosis agent. Therapeutic agent can comprise paclitaxel, sirolimus, tacrolimus, pimecrolimus or everolimus.

[0032] Polymer used in the methods of the present invention can comprise a styrene-isobutylene coppolymer, polylactic glycol acid, and methylenebisacrylamide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The present invention will be explained with reference to the following drawings.

[0034] **Figure 1** shows an example of a medical device that is suitable for use in the present invention.

[0035] **Figure 2** shows a cross-sectional view of an embodiment of a stent having a coating disposed on the abluminal surface the medical device.

[0036] **Figure 3** shows a cross-sectional view of an embodiment of a medical device with a coating disposed on the abluminal surface.

[0037] **Figure 4** shows a cross-sectional view of an embodiment of a medical device with a coating disposed on the abluminal surface and adluminal surface of the medical device.

[0038] **Figure 5** shows a cross-sectional view of another embodiment of a coating disposed on at least a portion of a medical device.

[0039] **Figure 6** shows a cross-sectional view of yet another embodiment of a coating disposed on at least a portion of a medical device.

[0040] **Figure 7** shows a cross-sectional view of yet another embodiment of a coating disposed on at least a portion of a medical device.

[0041] **Figure 8** shows a cross-sectional view of yet another embodiment of a coating disposed on at least a portion of a medical device.

[0042] **Figure 9** shows a cross-sectional view of yet another embodiment of a coating disposed on at least a portion of a medical device.

DETAILED DESCRIPTION

[0043] In one embodiment, the medical device of the present invention comprises a surface having a coating disposed thereon. The coating comprises a first coating material comprising an inorganic or ceramic oxide, metal or inert carbon wherein the first coating material has a plurality of reservoirs formed therein and a second coating material comprising a therapeutic agent and a polymer, wherein the second coating material is disposed in the reservoirs.

[0044] The coating can be disposed on any surface of the medical device. **Figure 1** shows an example of a medical device that is suitable for use in the present invention. This figure shows an implantable intravascular stent **10** comprising a sidewall **20** which comprises a plurality of struts **30** and at least one opening **40** in the sidewall **20**. Generally, the opening **40** is disposed between adjacent struts **30**. Also, the sidewall **20** may have a first sidewall surface **22** and an opposing second sidewall surface, which is not shown in **Figure 1**. The first sidewall surface **22** can be an outer or abluminal sidewall surface, which faces the body lumen wall when the stent is implanted, or an inner or adluminal sidewall surface, which faces away from the body lumen wall. Likewise, the second sidewall surface can be an adluminal sidewall surface or an adluminal sidewall surface.

[0045] In a stent having opening in the stent sidewall structure, in certain embodiments, it is preferable that the coating applied to the stent conforms to the surface of the stent so that the openings in the sidewall stent structure are preserved, *e.g.* the openings are not entirely or partially occluded with coating material.

[0046] **Figure 2** shows a cross-sectional view of a stent **50** having a plurality of struts **60**. Each strut has a abluminal surface **62** and an adluminal surface **64**. In this embodiment, a coating **70** is disposed on the abluminal surface **62** of stent **50**.

[0047] In certain embodiments, as shown in **Figure 2**, the coating is disposed on the abluminal surface **62** which is the portion of the surface of the medical device that contacts

the body lumen. Coating only the surfaces that contact the body lumen will reduce the use of excess materials, such as therapeutic agents.

[0048] **Figure 3** shows a cross-sectional view of a stent strut **60** having an abluminal surface **62** and an adluminal surface **64.** Disposed on at least a portion of the abluminal surface **62** is a coating **70** having an outer surface **72**. The coating **70** comprises a first coating material **74** comprising an inorganic or ceramic oxide, metal or inert carbon having reservoirs **76** therein and a second coating material **80** comprising a polymer **82** and a therapeutic agent **90** disposed in the reservoirs **76**. In accordance with the present invention, the reservoirs **76** do not extend into the surface **62** of the strut **60** and therefore, do not compromise the structural integrity of the medical device.

[0049] In an alternative embodiment the coating can cover a greater portion of the surface of a medical device than the portion of the surface that contacts the body lumen. Such embodiments having a greater portion of the surface covered than the portion of the surface that contacts the body lumen can be useful when, in addition to administering a therapeutic agent to a body lumen, it is also beneficial to introduce a therapeutic agent into the blood stream. For example an intravascular stent having an abluminal and adluminal surface can have the coating of the present invention on both the abluminal and adluminal surfaces. The coating on the abluminal surface can administer a therapeutic agent to a body lumen and the coating on the adluminal surface can introduce a therapeutic agent into the blood stream.

[0050] **Figure 4** shows a cross-sectional view of a stent strut **60**. Stent strut **60** has an abluminal surface **62** and an adluminal surface **64**. In this embodiment, coating **70** having an outer surface **72** is disposed on at least a portion of the abluminal surface **62** and adluminal surface **64**. The coating **70** comprises a first coating material **74** comprising an inorganic or ceramic oxide, metal or inert carbon wherein the first coating material has a plurality of reservoirs **76** therein and a second coating material **80** comprising a polymer **82** and a therapeutic agent **90** disposed in the reservoirs **76**.

[0051] When a coating is disposed on both the abluminal and adluminal surfaces of a stent, the coating disposed on the abluminal surface can be the same or different than the coating disposed on the adluminal surface of the stent. Also, the therapeutic agent disposed in the reservoirs of the coating on the abluminal and adluminal sides can be the same or different. Moreover, in some embodiments the coating can be disposed on the entire surface of the medical device. Alternatively, the first coating material can be disposed on the entire surface of the medical device but the reservoirs, however, can be located only on the portion of the medical device that contacts the body lumen.

[0052] As shown in **Figure 3** and **Figure 4**, the reservoirs **76** can be distributed throughout the first coating material **74**. In certain embodiments the reservoirs may be discrete or disposed in a pattern. Patterns can be random or uniform.

[0053] **Figure 5** shows a cross-sectional view of a stent **100.** Stent **100** has an abluminal surface **102** and an adluminal surface **104,** as well as, a front end **106** and a back end **108**. Disposed on at least a portion of abluminal surface **102** is a coating **110**. In certain embodiments wherein the stent comprises a plurality of struts, the abluminal surfaces of the struts comprise the abluminal surface of the stent and the adluminal surfaces of the struts comprise the adluminal surface of the stent. Disposed on at least a portion of the abluminal surface **102** is a coating **110** having an outer surface **112**. The coating **110** comprises a first coating material **114** comprising an inorganic or ceramic oxide, metal or inert carbon wherein the first coating material **114** has a plurality of reservoirs **116** therein and a second coating material **120** comprising a polymer **122** and a therapeutic agent **130**. In this embodiment the reservoirs **116** are positioned in the coating at the front end **106** and back end **108** of stent **100.** In embodiments wherein the stent comprises a plurality of struts, the reservoirs can be positioned on the struts at the end of the stent.

[0054] Also, some or all of the reservoirs in the coating may be in fluid communication with the outer surface of the coating. For example, in **Figure 3** and **Figure 4**, the reservoirs **76** are in fluid communication with the outer surface **72** of the coating **70**. Such communication with the outer surface can facilitate release of the therapeutic agent from the medical device.

[0055] In some embodiments the reservoirs may also be in contact with the surface of the medical device. Not only are the reservoirs in **Figure 3** in fluid communication with the outer surface **72** of the coating **70** they are also in contact with the surface **62** of strut **50**.

[0056] In an alternative embodiment the reservoirs may not be in contact with the surface of the medical device. **Figure 6** shows a cross-sectional view of a strut **60**, wherein the strut has an abluminal surface **62** and an adluminal surface **64**. Disposed on at least a portion of the abluminal surface **62** is a coating **70**. The coating **70** comprises a first coating material **74** comprising an inorganic or ceramic oxide, metal or inert carbon and wherein the first coating material **74** has a plurality of reservoirs **76** therein and wherein the reservoirs **76** are different sizes and do not extend through the coating to the surface of the strut **62**. The coating **70** also comprises a second coating material **80** comprising a polymer **82** and a therapeutic agent **90** disposed within the reservoirs **76**.

[0057] Additionally, some or all of the reservoirs in the coating can be interconnected to other reservoirs. **Figure 7** shows a cross-sectional view of stent strut **60** having an

abluminal surface **62** and an adluminal surface **64.** A coating **70** is disposed on at least a portion of surface **62**. The coating **70** comprises a first coating material **74** comprising an inorganic or ceramic oxide, metal or inert carbon wherein the first coating material has a plurality of reservoirs **76** therein and wherein the reservoirs **76** are interconnected. The coating **70** further comprises a second coating material **80** comprising a polymer **82** and a therapeutic agent **90** disposed within the reservoirs **76**.

[0058] In addition, the reservoirs in the inorganic or ceramic oxide, metal or inert carbon can have any shape. For example, the reservoirs can be shaped like cylinders, circles or hemispheres. Reservoirs can also be non-circular in shape or a mix of various shapes. Reservoirs can also be shaped like conduits, channels or void pathways. Varying the pore shape can be utilized to maximize or optimize the amount of therapeutic agent that can be loaded onto the surface of a medical device. In certain embodiments the reservoirs can be narrow at the top, near the surface of the coating and then become broad near the surface of the medical device.

[0059] For example, **Figure 8** shows a cross-sectional view of a stent strut **60** has an abluminal surface **62** and an adluminal surface **64**. Disposed on at least a portion of the abluminal surface **62** is a coating **70**. The coating **70** comprises a first coating material **74** comprising an inorganic or ceramic oxide, metal or inert carbon wherein the first coating material **74** has a plurality of reservoirs **76** and wherein the reservoirs **76** are narrow near the surface **72** of the coating and broad near the surface **62** of the stent strut **60**. The coating **70** also comprises a second coating material **80** comprising a polymer **82** and a therapeutic agent **90** disposed within the reservoirs **76**.

[0060] Additionally, the reservoirs in the first coating material may have any size or range of sizes. In some instances, the reservoirs can be micro-size reservoirs or nano-size reservoirs. Also, in some embodiments, it may be preferable that the average width or diameter of the reservoirs is between about 1 nm and about 10 μm. Preferably, the average width or diameter is between about 3 microns and about 70 microns.

[0061] The size of the reservoirs can also be used to control the release rate of the therapeutic agent. For example, reservoirs having larger average width will allow the therapeutic agent to be released more quickly than reservoirs with a smaller average width. Also, the number of reservoirs in the first coating material can be adjusted to better control the release rate of the therapeutic agent. For example, the presence of more reservoirs per unit volume or weight of the first coating material can allow for a higher release rate of the therapeutic agent than a material having fewer reservoirs therein.

[0062] The first coating material can be an inorganic or ceramic oxide, metal or inert carbon. The first coating material can also be radiopaque and/or have MRI compatibility. In certain embodiments the first coating material comprises an inorganic or ceramic oxide. Examples of inorganic or ceramic oxides include without limitation, platinum oxides, tantalum oxides, titanium oxides, tantalum oxides, zinc oxides, iron oxides, magnesium oxides, aluminum oxides, iridium oxides, niobium oxides, zirconium oxides, tungsten oxides, rhodium oxides, ruthenium oxides, silicone oxides such as, silicon dioxide; inorganic-organic hybrids such as, titanium poly[(oligoethylene glycol) dihydroxytitanate] or combinations thereof. In other embodiments the inorganic or ceramic oxide is a metal oxide. In certain embodiments preferred inorganic or ceramic oxides include without limitation, iridium oxide and titanium oxide.

[0063] In certain embodiments of the present invention, the first coating material comprises a metal. Suitable metals include alkali metals, alkaline earth metals, transition metals, metal alloys and metalloids. Examples of metals include without limitation, titanium, scandium, stainless steel, tantalum, nickel, silicon, chrome, cobalt, chromium, manganese, iron, platinum, iridium, niobium, vanadium, zirconium, tungsten, rhodium, ruthenium, gold, copper, zinc, yttrium, molybdenum, technetium, palladium, cadmium, hafnium, rhenium and combinations thereof. In certain embodiments preferred metals include without limitation, platinum, gold, titanium and stainless steel.

[0064] In other embodiments the first coating material can comprise inert carbon. Suitable forms of inert carbon can include with out limitation, pyrolitic carbon and porous vitreous carbon. Use of porous carbon can help prevent thrombosis and encourage endothelial cell growth.

[0065] In some embodiments, the inorganic or ceramic oxide, metal or inert carbon can comprise at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 99% or more by weight of the coating. Preferably, the inorganic or ceramic oxide, metal or inert carbon is about 20% to about 70% by weight of the coating.

[0066] In addition to the reservoirs in which the second coating material is disposed in the first coating material can further comprise additional pores. A second therapeutic agent can be disposed in the additional pores. For example, **Figure 9** shows a cross-sectional view of a stent strut **60** having an abluminal surface **62** and an adluminal surface **64**. Disposed on at least a portion of the abluminal surface **62** is a coating **70**. The coating comprises a first coating material **74**, wherein the first coating material **74** due to its nature already has a plurality of pores therein **78**. For example, a first coating material comprising

carbon having a plurality of pores can be used. In addition to the pores **78** in the first coating material **74,** a plurality of reservoirs **76** can be formed in the first coating material **74**. A second coating material **80** comprising a polymer **82** and a first therapeutic agent **90** disposed in at least some of the reservoirs **76** and a second therapeutic agent **92** is disposed in some of the pores **78**.

[0067] The coating may be of any thickness. In some embodiments, the coating preferably has a thickness of about 1 to about 10 microns. In some instances, a relatively thicker film may be preferred to incorporate a higher number of reservoirs and greater amounts of the therapeutic agent.

A. Medical Devices

[0068] Suitable medical devices for the present invention include, but are not limited to, stents, surgical staples, cochlear implants, catheters, such as central venous catheters and arterial catheters, guidewires, cannulas, cardiac pacemaker leads or lead tips, cardiac defibrillator leads or lead tips, implantable vascular access ports, blood storage bags, blood tubing, vascular or other grafts, intra-aortic balloon pumps, heart valves, cardiovascular sutures, total artificial hearts and ventricular assist pumps, extra-corporeal devices such as blood oxygenators, blood filters, hemodialysis units, hemoperfusion units or plasmapheresis units.

[0069] Medical devices which are particularly suitable for the present invention include any stent for medical purposes, which are known to the skilled artisan. Suitable stents include, for example, vascular stents such as self-expanding stents and balloon expandable stents. Examples of self-expanding stents are illustrated in U.S. Patent Nos. 4,655,771 and 4,954,126 issued to Wallsten and 5,061,275 issued to Wallsten *et al.* Examples of appropriate balloon-expandable stents are shown in U.S. Patent No. 5,449,373 issued to Pinchasik *et al.* In preferred embodiments, the stent suitable for the present invention is an Express stent. More preferably, the Express stent is an Express™ stent or an Express2™ stent (Boston Scientific, Inc. Natick, Mass.).

[0070] The framework of the suitable stents may be formed through various methods as known in the art. The framework may be welded, molded, laser cut, electro-formed, or consist of filaments or fibers which are wound or braided together in order to form a continuous structure.

[0071] Medical devices that are suitable for the present invention may be fabricated from metallic, ceramic, polymeric or composite materials or a combination thereof. Preferably, the materials are biocompatible. Metallic material is more preferable. Suitable

metallic materials include metals and alloys based on titanium (such as nitinol, nickel titanium alloys, thermo-memory alloy materials); stainless steel; tantalum, nickel-chrome; or certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®; PERSS (Platinum EnRiched Stainless Steel) and Niobium. Metallic materials also include clad composite filaments, such as those disclosed in WO 94/16646.

[0072] Suitable ceramic materials include, but are not limited to, oxides, carbides, or nitrides of the transition elements such as titanium, hafnium, iridium, chromium, aluminum, and zirconium. Silicon based materials, such as silica, may also be used.

[0073] Suitable polymers for forming the medical devices may be biostable. Also, the polymer may be biodegradable. Suitable polymers include, but are not limited to, styrene isobutylene styrene, polyetheroxides, polyvinyl alcohol, polyglycolic acid, polylactic acid, polyamides, poly-2-hydroxy-butyrate, polycaprolactone, poly(lactic-co-glycolic)acid, and Teflon.

[0074] Polymers may be used for forming the medical device in the present invention include without limitation isobutylene-based polymers, polystyrene-based polymers, polyacrylates, and polyacrylate derivatives, vinyl acetate-based polymers and its copolymers, polyurethane and its copolymers, silicone and its copolymers, ethylene vinyl-acetate, polyethylene terephtalate, thermoplastic elastomers, polyvinyl chloride, polyolefins, cellulosics, polyamides, polyesters, polysulfones, polytetrafluorethylenes, polycarbonates, acrylonitrile butadiene styrene copolymers, acrylics, polylactic acid, polyglycolic acid, polycaprolactone, polylactic acid-polyethylene oxide copolymers, cellulose, collagens, and chitins.

[0075] Other polymers that are useful as materials for medical devices include without limitation dacron polyester, poly(ethylene terephthalate), polycarbonate, polymethylmethacrylate, polypropylene, polyalkylene oxalates, polyvinylchloride, polyurethanes, polysiloxanes, nylons, poly(dimethyl siloxane), polycyanoacrylates, polyphosphazenes, poly(amino acids), ethylene glycol I dimethacrylate, poly(methyl methacrylate), poly(2-hydroxyethyl methacrylate), polytetrafluoroethylene poly(HEMA), polyhydroxyalkanoates, polytetrafluorethylene, polycarbonate, poly(glycolide-lactide) co-polymer, polylactic acid, poly(γ-caprolactone), poly(γ -hydroxybutyrate), polydioxanone, poly(γ -ethyl glutamate), polyiminocarbonates, poly(ortho ester), polyanhydrides, alginate, dextran, chitin, cotton, polyglycolic acid, polyurethane, or derivatized versions thereof, i.e., polymers which have been modified to include, for example, attachment sites or cross-linking groups, e.g., RGD, in which the polymers retain their structural integrity while allowing for attachment of cells and molecules, such as proteins, nucleic acids, and the like.

[0076] Medical devices may also be made with non-polymers. Examples of useful non-polymers include sterols such as cholesterol, stigmasterol, β-sitosterol, and estradiol; cholesteryl esters such as cholesteryl stearate; C_{12} -C_{24} fatty acids such as lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, and lignoceric acid; C_{18} -C_{36} mono-, di- and triacylglycerides such as glyceryl monooleate, glyceryl monolinoleate, glyceryl monolaurate, glyceryl monodocosanoate, glyceryl monomyristate, glyceryl monodicenoate, glyceryl dipalmitate, glyceryl didocosanoate, glyceryl dimyristate, glyceryl didecenoate, glyceryl tridocosanoate, glyceryl trimyristate, glyceryl tridecenoate, glycerol tristearate and mixtures thereof; sucrose fatty acid esters such as sucrose distearate and sucrose palmitate; sorbitan fatty acid esters such as sorbitan monostearate, sorbitan monopalmitate and sorbitan tristearate; C_{16} -C_{18} fatty alcohols such as cetyl alcohol, myristyl alcohol, stearyl alcohol, and cetostearyl alcohol; esters of fatty alcohols and fatty acids such as cetyl palmitate and cetearyl palmitate; anhydrides of fatty acids such as stearic anhydride; phospholipids including phosphatidylcholine (lecithin), phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol, and lysoderivatives thereof; sphingosine and derivatives thereof; sphingomyelins such as stearyl, palmitoyl, and tricosanyl sphingomyelins; ceramides such as stearyl and palmitoyl ceramides; glycosphingolipids; lanolin and lanolin alcohols; and combinations and mixtures thereof. Non-polymers may also include biomaterials such as stem sells, which can be seeded into the medical device prior to implantation. Preferred non-polymers include cholesterol, glyceryl monostearate, glycerol tristearate, stearic acid, stearic anhydride, glyceryl monooleate, glyceryl monolinoleate, and acetylated monoglycerides.

B. Therapeutic Agents

[0077] The term "therapeutic agent" as used in the present invention encompasses drugs, genetic materials, and biological materials and can be used interchangeably with "biologically active material". In one embodiment, the therapeutic agent is an anti-restenotic agent. In other embodiments, the therapeutic agent inhibits smooth muscle cell proliferation, contraction, migration or hyperactivity. Non-limiting examples of suitable therapeutic agent include heparin, heparin derivatives, urokinase, dextrophenylalanine proline arginine chloromethylketone (PPack), enoxaprin, angiopeptin, hirudin, acetylsalicylic acid, tacrolimus, everolimus, rapamycin (sirolimus), pimecrolimus, amlodipine, doxazosin, glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, sulfasalazine, rosiglitazone, mycophenolic acid, mesalamine, paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, methotrexate,

azathioprine, adriamycin, mutamycin, endostatin, angiostatin, thymidine kinase inhibitors, cladribine, lidocaine, bupivacaine, ropivacaine, D-Phe-Pro-Arg chloromethyl ketone, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, aspirin, dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors, trapidil, liprostin, tick antiplatelet peptides, 5-azacytidine, vascular endothelial growth factors, growth factor receptors, transcriptional activators, translational promoters, antiproliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin, cholesterol lowering agents, vasodilating agents, agents which interfere with endogenous vasoactive mechanisms, antioxidants, probucol, antibiotic agents, penicillin, cefoxitin, oxacillin, tobranycin, angiogenic substances, fibroblast growth factors, estrogen, estradiol (E2), estriol (E3), 17-beta estradiol, digoxin, beta blockers, captopril, enalopril, statins, steroids, vitamins, paclitaxel (as well as its derivatives, analogs or paclitaxel bound to proteins, *e.g.* Abraxane™) 2'-succinyl-taxol, 2'-succinyl-taxol triethanolamine, 2'-glutaryl-taxol, 2'-glutaryl-taxol triethanolamine salt, 2'-O-ester with N-(dimethylaminoethyl) glutamine, 2'-O-ester with N-(dimethylaminoethyl) glutamide hydrochloride salt, nitroglycerin, nitrous oxides, nitric oxides, antibiotics, aspirins, digitalis, estrogen, estradiol and glycosides. In one embodiment, the therapeutic agent is a smooth muscle cell inhibitor or antibiotic. In a preferred embodiment, the therapeutic agent is taxol (*e.g.*, Taxol®), or its analogs or derivatives. In another preferred embodiment, the therapeutic agent is paclitaxel, or its analogs or derivatives. In yet another preferred embodiment, the therapeutic agent is an antibiotic such as erythromycin, amphotericin, rapamycin, adriamycin, etc.

[0078] The term "genetic materials" means DNA or RNA, including, without limitation, of DNA/RNA encoding a useful protein stated below, intended to be inserted into a human body including viral vectors and non-viral vectors.

[0079] The term "biological materials" include cells, yeasts, bacteria, proteins, peptides, cytokines and hormones. Examples for peptides and proteins include vascular endothelial growth factor (VEGF), transforming growth factor (TGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), cartilage growth factor (CGF), nerve growth factor (NGF), keratinocyte growth factor (KGF), skeletal growth factor (SGF), osteoblast-derived growth factor (BDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), cytokine growth factors (CGF), platelet-derived growth factor (PDGF), hypoxia inducible factor-1

(HIF-1), stem cell derived factor (SDF), stem cell factor (SCF), endothelial cell growth supplement (ECGS), granulocyte macrophage colony stimulating factor (GM-CSF), growth differentiation factor (GDF), integrin modulating factor (IMF), calmodulin (CaM), thymidine kinase (TK), tumor necrosis factor (TNF), growth hormone (GH), bone morphogenic protein (BMP) (*e.g.*, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (PO-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-14, BMP-15, BMP-16, etc.), matrix metalloproteinase (MMP), tissue inhibitor of matrix metalloproteinase (TIMP), cytokines, interleukin (*e.g.*, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-15, etc.), lymphokines, interferon, integrin, collagen (all types), elastin, fibrillins, fibronectin, vitronectin, laminin, glycosaminoglycans, proteoglycans, transferrin, cytotactin, cell binding domains (*e.g.*, RGD), and tenascin. Currently preferred BMP's are BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered, if desired, to deliver proteins of interest at the transplant site. The delivery media can be formulated as needed to maintain cell function and viability. Cells include progenitor cells (*e.g.*, endothelial progenitor cells), stem cells (*e.g.*, mesenchymal, hematopoietic, neuronal), stromal cells, parenchymal cells, undifferentiated cells, fibroblasts, macrophage, and satellite cells.

[0080] Other non-genetic therapeutic agents include:

- anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone);
- anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, acetylsalicylic acid, tacrolimus, everolimus, amlodipine and doxazosin;
- anti-inflammatory agents such as glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, rosiglitazone, mycophenolic acid and mesalamine;
- anti-neoplastic/anti-proliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, methotrexate, azathioprine, adriamycin and mutamycin; endostatin, angiostatin and thymidine kinase inhibitors, cladribine, taxol and its analogs or derivatives;
- anesthetic agents such as lidocaine, bupivacaine, and ropivacaine;
- anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-

thrombin antibodies, anti-platelet receptor antibodies, aspirin (aspirin is also classified as an analgesic, antipyretic and anti-inflammatory drug), dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors, antiplatelet agents such as trapidil or liprostin and tick antiplatelet peptides;

- DNA demethylating drugs such as 5-azacytidine, which is also categorized as a RNA or DNA metabolite that inhibit cell growth and induce apoptosis in certain cancer cells;
- vascular cell growth promoters such as growth factors, vascular endothelial growth factors (VEGF, all types including VEGF-2), growth factor receptors, transcriptional activators, and translational promoters;
- vascular cell growth inhibitors such as anti-proliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin;
- cholesterol-lowering agents, vasodilating agents, and agents which interfere with endogenous vasoactive mechanisms;
- anti-oxidants, such as probucol;
- antibiotic agents, such as penicillin, cefoxitin, oxacillin, tobranycin, rapamycin (sirolimus);
- angiogenic substances, such as acidic and basic fibroblast growth factors, estrogen including estradiol (E2), estriol (E3) and 17-beta estradiol;
- drugs for heart failure, such as digoxin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors including captopril and enalopril, statins and related compounds; and
- macrolides such as sirolimus or everolimus.

[0081] Preferred biological materials include anti-proliferative drugs such as steroids, vitamins, and restenosis-inhibiting agents. Preferred restenosis-inhibiting agents include microtubule stabilizing agents such as Taxol®, paclitaxel (*i.e.*, paclitaxel, paclitaxel analogs, or paclitaxel derivatives, and mixtures thereof). For example, derivatives suitable for use in the present invention include 2'-succinyl-taxol, 2'-succinyl-taxol triethanolamine, 2'-glutaryl-taxol, 2'-glutaryl-taxol triethanolamine salt, 2'-O-ester with N-(dimethylaminoethyl) glutamine, and 2'-O-ester with N-(dimethylaminoethyl) glutamide hydrochloride salt.

[0082] Other suitable therapeutic agents include tacrolimus; halofuginone; inhibitors of HSP90 heat shock proteins such as geldanamycin; microtubule stabilizing agents such as epothilone D; phosphodiesterase inhibitors such as cliostazole; Barkct inhibitors; phospholamban inhibitors; and Serca 2 gene/proteins.

[0083] Other preferred therapeutic agents include nitroglycerin, nitrous oxides, nitric oxides, aspirins, digitalis, estrogen derivatives such as estradiol and glycosides.

[0084] In one embodiment, the therapeutic agent is capable of altering the cellular metabolism or inhibiting a cell activity, such as protein synthesis, DNA synthesis, spindle fiber formation, cellular proliferation, cell migration, microtubule formation, microfilament formation, extracellular matrix synthesis, extracellular matrix secretion, or increase in cell volume. In another embodiment, the therapeutic agent is capable of inhibiting cell proliferation and/or migration.

[0085] In certain embodiments, the therapeutic agents for use in the medical devices of the present invention can be synthesized by methods well known to one skilled in the art. Alternatively, the therapeutic agents can be purchased from chemical and pharmaceutical companies.

[0086] In some embodiments, the therapeutic agent comprises at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 99% or more by weight of the second coating material. Preferably, the therapeutic agent is about 5 to about 15 % by weight of the second coating material. More preferably, the therapeutic agent is about 8 to about 10% by weight of the coating that contains the therapeutic agent. In certain embodiments, the therapeutic agent is about 8.8% by weight of the coating that contains the therapeutic agent.

C. Polymers

[0087] Polymers useful for forming the second coating material should be ones that are biocompatible, particularly during insertion or implantation of the device into the body and avoids irritation to body tissue. Examples of such polymers include, but not limited to, polyurethanes, polyisobutylene and its copolymers, silicones, and polyesters. Other suitable polymers include polyolefins, polyisobutylene, 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, copolymers of vinyl monomers and olefins such as

ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66 and polycaprolactone, alkyd resins, polycarbonates, polyoxyethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, and polylactic acid-polyethylene oxide copolymers.

[0088] In certain embodiment hydrophobic polymers can be used. Examples of suitable hydrophobic polymers or monomers include, but not limited to, polyolefins, such as polyethylene, polypropylene, poly(1-butene), poly(2-butene), poly(1-pentene), poly(2-pentene), poly(3-methyl-1-pentene), poly(4-methyl-1-pentene), poly(isoprene), poly(4-methyl-1-pentene), ethylene-propylene copolymers, ethylene-propylene-hexadiene copolymers, ethylene-vinyl acetate copolymers, blends of two or more polyolefins and random and block copolymers prepared from two or more different unsaturated monomers; styrene polymers, such as poly(styrene), styrene-isobutylene copolymers, poly(2-methylstyrene), styrene-acrylonitrile copolymers having less than about 20 mole-percent acrylonitrile, and styrene-2,2,3,3,-tetrafluoropropyl methacrylate copolymers; halogenated hydrocarbon polymers, such as poly(chlorotrifluoroethylene), chlorotrifluoroethylene-tetrafluoroethylene copolymers, poly(hexafluoropropylene), poly(tetrafluoroethylene), tetrafluoroethylene, tetrafluoroethylene-ethylene copolymers, poly(trifluoroethylene), poly(vinyl fluoride), and poly(vinylidene fluoride); vinyl polymers, such as poly(vinyl butyrate), poly(vinyl decanoate), poly(vinyl dodecanoate), poly(vinyl hexadecanoate), poly(vinyl hexanoate), poly(vinyl propionate), poly(vinyl octanoate), poly(heptafluoroisopropoxyethylene), poly(heptafluoroisopropoxypropylene), and poly(methacrylonitrile); acrylic polymers, such as poly(n-butyl acetate), poly(ethyl acrylate), poly(1-chlorodifluoromethyl)tetrafluoroethyl acrylate, poly di(chlorofluoromethyl)fluoromethyl acrylate, poly(1,1-dihydroheptafluorobutyl acrylate), poly(1,1-dihydropentafluoroisopropyl acrylate), poly(1,1-dihydropentadecafluorooctyl acrylate), poly(heptafluoroisopropyl acrylate), poly 5-(heptafluoroisopropoxy)pentyl acrylate, poly 11-(heptafluoroisopropoxy)undecyl acrylate, poly 2-(heptafluoropropoxy)ethyl acrylate, and poly(nonafluoroisobutyl acrylate); methacrylic polymers, such as poly(benzyl methacrylate), poly(n-butyl methacrylate), poly(isobutyl methacrylate), poly(t-butyl methacrylate), poly(t-butylaminoethyl methacrylate), poly(dodecyl methacrylate), poly(ethyl methacrylate), poly(2-ethylhexyl methacrylate), poly(n-hexyl methacrylate), poly(phenyl methacrylate), poly(n-propyl methacrylate),

poly(octadecyl methacrylate), poly(1,1-dihydropentadecafluorooctyl methacrylate), poly(heptafluoroisopropyl methacrylate), poly(heptadecafluorooctyl methacrylate), poly(1-hydrotetrafluoroethyl methacrylate), poly(1,1-dihydrotetrafluoropropyl methacrylate), poly(1-hydrohexafluoroisopropyl methacrylate), and poly(t-nonafluorobutyl methacrylate); polyesters, such a poly(ethylene terephthalate) and poly(butylene terephthalate); condensation type polymers such as and polyurethanes and siloxane-urethane copolymers; polyorganosiloxanes, i.e., polymers characterized by repeating siloxane groups, represented by Ra SiO 4-a/2, where R is a monovalent substituted or unsubstituted hydrocarbon radical and the value of a is 1 or 2; and naturally occurring hydrophobic polymers such as rubber.

[0089] In alternative embodiments, hydrophilic polymers can be used. Examples of suitable hydrophilic polymers or monomers include, but not limited to; (meth)acrylic acid, or alkaline metal or ammonium salts thereof; (meth)acrylamide; methylenebisacrylamide; (meth)acrylonitrile; polylactic acide; polyglycolic acid; polylactic-glycolic acid; those polymers to which unsaturated dibasic, such as maleic acid and fumaric acid or half esters of these unsaturated dibasic acids, or alkaline metal or ammonium salts of these dibasic adds or half esters, is added; those polymers to which unsaturated sulfonic, such as 2-acrylamido-2-methylpropanesulfonic, 2-(meth)acryloylethanesulfonic acid, or alkaline metal or ammonium salts thereof, is added; and 2-hydroxyethyl (meth)acrylate and 2-hydroxypropyl (meth)acrylate.

[0090] Polyvinyl alcohol is also an example of hydrophilic polymer. Polyvinyl alcohol may contain a plurality of hydrophilic groups such as hydroxyl, amido, carboxyl, amino, ammonium or sulfonyl (-SO3). Hydrophilic polymers also include, but are not limited to, starch, polysaccharides and related cellulosic polymers; polyalkylene glycols and oxides such as the polyethylene oxides; polymerized ethylenically unsaturated carboxylic acids such as acrylic, mathacrylic and maleic acids and partial esters derived from these acids and polyhydric alcohols such as the alkylene glycols; homopolymers and copolymers derived from acrylamide; and homopolymers and copolymers of vinylpyrrolidone.

[0091] Additional suitable polymers include, but are not limited to, thermoplastic elastomers in general, polyolefins, polyisobutylene, 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, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS

(acrylonitrile-butadiene-styrene) resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66 and polycaprolactone, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, polyether block amides, epoxy resins, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, polylactic acid-polyethylene oxide copolymers, EPDM (ethylene-propylene-diene) rubbers, fluoropolymers, fluorosilicones, polyethylene glycol, polysaccharides, phospholipids, and combinations of the foregoing.

[0092] Other polymers which can be used include ones that can be easily dissolved in water or organic solvents, cured or polymerized in the reservoirs of the first coating material, have relatively low melting points and/or can be blended with therapeutic agents. Also bioabsorbable polymers may be used wherein the therapeutic agent is release as the polymer is absorbed into the body. An additional advantage of using a bioabsorbable material is that once the polymer is absorbed, the empty reservoirs can help prevent thromboses and encourage endothelial cell growth.

[0093] In certain embodiments preferred polymers include, but are not limited to, a styrene-isobutylene copolymer, polylactic glycol acid, and methylenebisacrylamide.

D. Methods of Making Coatings

[0094] The medical device coatings of the present invention can be made by disposing a first coating material on at least a portion of a surface of a medical device wherein the first coating material comprises an inorganic or ceramic oxide, metal or inert carbon; forming a plurality of reservoirs in the first coating material; and disposing a second coating in the reservoirs wherein, the second coating comprises a polymer and a therapeutic agent.

[0095] The first coating material can be disposed on at least a portion of the surface of the medical device by any suitable method such as, but not limited to, dipping, spraying, painting, electroplating, evaporation, plasma-vapor deposition, cathodic-arc deposition, sputtering, ion implantation, electrostatically, electroplating, electrochemically, a combination of the above, or the like.

[0096] The reservoirs in the first coating composition can be formed by any method known in the art as well. These methods include, but are not limited to, laser ablation, drilling, or chemical etching, microcontact printing, inkjet printing, screen printing, replica molding, microtransfer molding, micromolding in capillaries, solvent-assisted micromolding, proximal probe lithography, photolithography, scanning probe lithography, and embossing techniques.

[0097] Additionally, reservoirs can be formed by removing a secondary material from the first coating material. Techniques for removing material include, but are not limited to, dealloying or anodization processes. To make a medical device coated with the coating of the present invention, a first coating material and a secondary material are disposed on a portion of a surface of a medical device. The first coating material comprises an inorganic or ceramic oxide, metal or inert carbon. The secondary material can be any material to long as is can be removed from the first coating material. For example, the secondary material can be more electrochemically active than the first metal. Preferably, the secondary material is a metal. Suitable metals include, but are not limited to, silver, gold, tantalum, platinum, bismuth, iridium, zirconium, iodine, titanium, and barium. After the first coating composition and secondary material is disposed on the surface of the medical device, a plurality of reservoirs are formed in the first coating composition by removing the secondary material.

[0098] The secondary material can be removed from the first coating material by a dealloying process such as selective dissolution of the secondary material. In this method, the first coating material and the secondary material are exposed to an acid which removes the secondary metal. Thus, the first coating material is preferably one that will not dissolve when exposed to the acid, while the secondary metal is one that will dissolve. Any suitable acid can be used to remove the second metal. One of ordinary skill in the art would recognize the appropriate concentration and reaction conditions to use to remove the second metal.

[0099] Alternatively, the secondary material can be removed anodically. For example, silver may be removed anodically using a dilute nitric acid bath comprising up to 15% nitric acid, wherein the anode is the plated stent, and the cathode is platinum. Voltages up to 10V DC can be applied across the electrodes. The bath chemistry, temperature, applied voltage, and process time may be varied to vary the geometry, distribution, and depth of the coating layer. In another example, a Technic Envirostrip Ag 10-20 amps per square foot may be used with a stainless steel cathode.

[0100] Once reservoirs are formed in the first coating material, a second coating material is disposed in the reservoirs. The second coating material comprises a polymer and a therapeutic agent. The second coating material can be disposed in the reservoirs of the first coating composition in any suitable way known in the art. Such methods include, but are not limited to, inkjet printing or vacuum impregnation. Additional methods include coating the medical device with the second coating material and removing the excess. For example, the second coating material can be applied to a portion of a surface of a medical

device by such methods as dipping, spraying, painting, roll coating, or a combination thereof and then removing the excess.

[0101] To facilitate disposing the second coating material within the reservoirs, the polymer and the therapeutic agent can be pre-mixed together before applying or a solution or suspension of a polymer and a therapeutic agent can be formed by dissolving or suspending the polymer and the therapeutic agent in an organic or aqueous solvent which is then used to coat a portion of a surface of a medical device.

[0102] In an alternative embodiment, a therapeutic agent and a monomer can be mixed together and disposed in the reservoirs. Additionally an initiator can be added to the monomer and the therapeutic agent. Once in the reservoirs the monomer can be polymerized by such methods as exposure to UV radiation or heat. The degree of polymerization, monomer and initiator used will be determined by the desired rate of release of the therapeutic agent.

[0103] In another embodiment, the method of coating a medical device comprises masking a portion of a surface of a medical device, such as a stent, with a masking material; disposing a first coating on the surface of the medical device, wherein the first coating comprises a metal, inorganic or ceramic oxide or inert carbon; removing the masking material, creating a plurality of reservoirs; and disposing a second coating in the reservoirs wherein, the second coating comprises a polymer and a therapeutic agent.

[0104] Before the first coating material is disposed on a portion of the surface of the medical device, polymer droplets can be applied to a portion of a surface of a medical device to mask the portion of the surface which that will comprise the reservoirs. The polymer droplets can be applied by methods such as inkjet printing and lithography. Once the first coating material is disposed on the surface of the medical device, the polymer is removed, forming a plurality of reservoirs. The second coating material is disposed in the reservoirs using methods described above.

[0105] The medical devices and stents of the present invention may be used for any appropriate medical procedure. Delivery of the medical device can be accomplished using methods well known to those skilled in the art.

[0106] The description contained herein is for purposes of illustration and not for purposes of limitation. Changes and modifications may be made to the embodiments of the description and still be within the scope of the invention. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

WHAT IS CLAIMED IS:

1. An implantable stent comprising:

(a) a tubular stent sidewall structure having an abluminal surface and an adluminal surface;

(b) a coating having an outer surface comprising:

(i) a first coating material disposed on at least a portion of the abluminal surface of the stent comprising an inorganic or ceramic oxide, metal or inert carbon;

(ii) a plurality of reservoirs formed within the first coating material; and

(iii) a second coating material comprising a polymer and a first therapeutic agent, wherein the second coating material is disposed within the reservoirs.

2. The stent of claim 1, wherein the adluminal surface of the stent is substantially free of the coating.

3. The stent of claim 1, wherein the sidewall structure comprises a plurality of struts and openings in the sidewall structure, and wherein at least one strut comprises an abluminal surface and an adluminal surface opposite the abluminal surface.

4. The stent of claim 1, wherein the coating conforms to the stent sidewall structure so that the openings are preserved.

5. The stent of claim 1, wherein the first coating material is further disposed on the adluminal surface of the sidewall structure and wherein the first coating material disposed on the adluminal surface of the sidewall structure comprises a plurality of reservoirs.

6. The stent of claim 1, wherein the inorganic or ceramic oxide comprises iridium oxide.

7. The stent of claim 1, wherein the metal comprises gold, platinum or titanium.

8. The stent of claim 1, wherein the coating is about 1 micron to about 70 microns thick.

9. The stent of claim 1, wherein the first coating material further comprises a second therapeutic agent and wherein the first therapeutic agent and second therapeutic agent are different.

10. The stent of claim 1, wherein the reservoirs are interconnected.

11. The stent of claim 1, wherein the reservoirs are in fluid communication with the outer surface of the coating.

12. The stent of claim 1, wherein the reservoirs extend between the outer surface of the coating and the abluminal surface of the stent.

13. The stent of claim 1, wherein the average diameter of the reservoirs is about 5 microns to about 80 microns.

14. The stent of claim 1, wherein the polymer is biostable.

15. The stent of claim 1, wherein the polymer is bioabsorbable

16. The stent of claim 1, polymer comprises a styrene-isobutylene copolymer, polylactic glycol acid, and methylenebisacrylamide.

17. The stent of claim 1, wherein the therapeutic agent comprises an anti-thrombogenic agent, anti-angiogenesis agent, anti-proliferative agent, antibiotic, anti-restenosis agent, growth factor, immunosuppressant, or a radiochemical.

18. The stent of claim 1, wherein the therapeutic agent comprises an anti-restenosis agent.

19. The stent of claim 1, wherein the therapeutic agent comprises paclitaxel.

20. The stent of claim 1, wherein the therapeutic agent comprises sirolimus, tacrolimus, pimecrolimus or everolimus.

21. An intravascular stent comprising:

(a) a tubular stent sidewall structure having an abluminal surface and an adluminal surface wherein, the sidewall structure has a plurality of openings therein;

(b) a coating comprising:

(i) a first coating material comprising gold or platinum disposed on the abluminal surface;

(ii) a plurality of reservoirs formed within the first coating material; and

(iii) a second coating material comprising a polymer and an anti-restinosis agent, wherein the second coating material is disposed with in the reservoirs.

22. A stent comprising:

(a) a tubular stent sidewall structure comprising a plurality of struts and openings in the sidewall structure, and wherein at least one strut comprises an abluminal surface and an adluminal surface opposite the abluminal surface;

(b) a coating having an outer surface comprising:

(i) a first coating material disposed on at least a portion of the abluminal surface comprising gold or platinum;

(ii) a plurality of reservoirs formed within the first coating material; and

(iii) a second coating material comprising a polymer and an anti-restenosis agent, wherein the second coating material is disposed within the reservoirs.

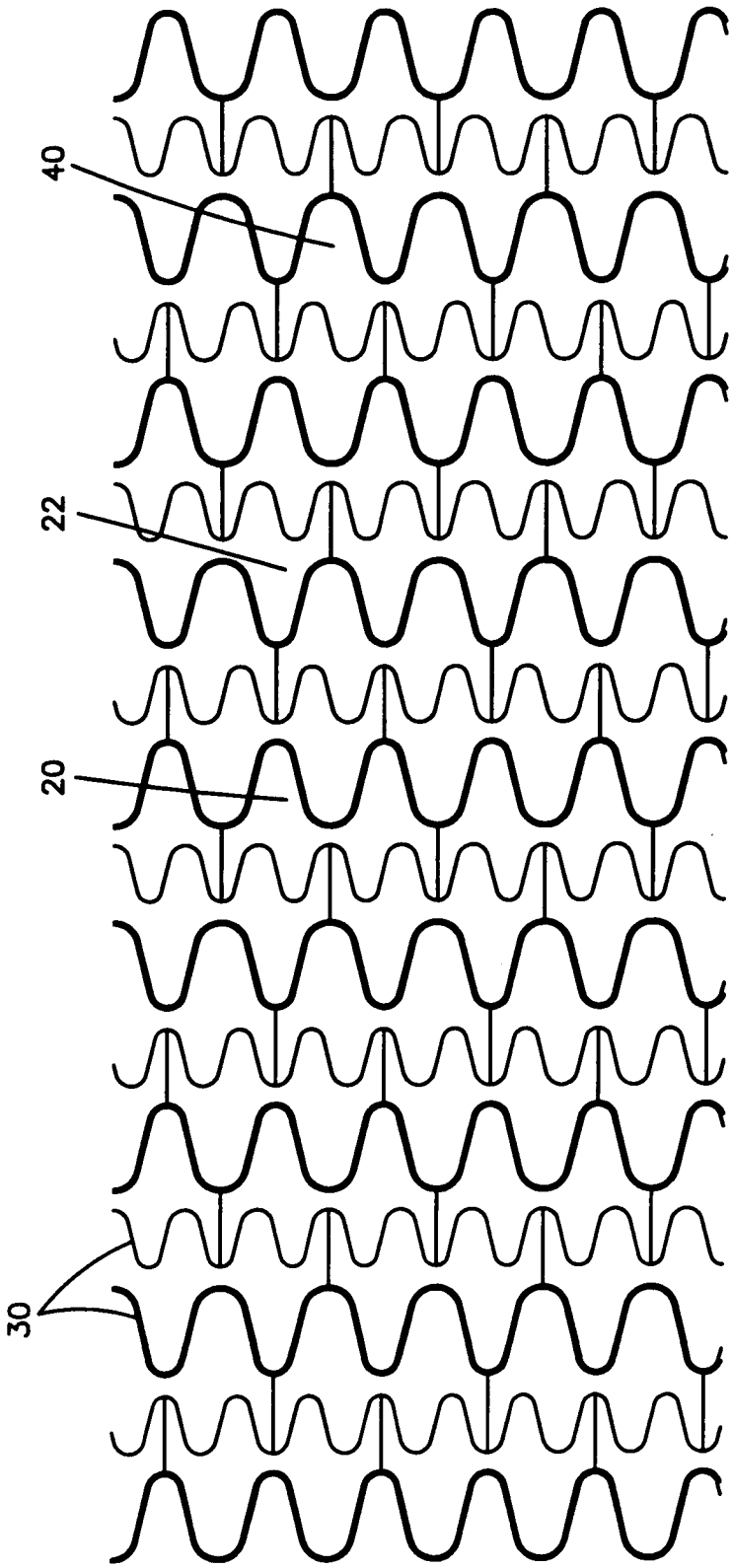

Fig. 1

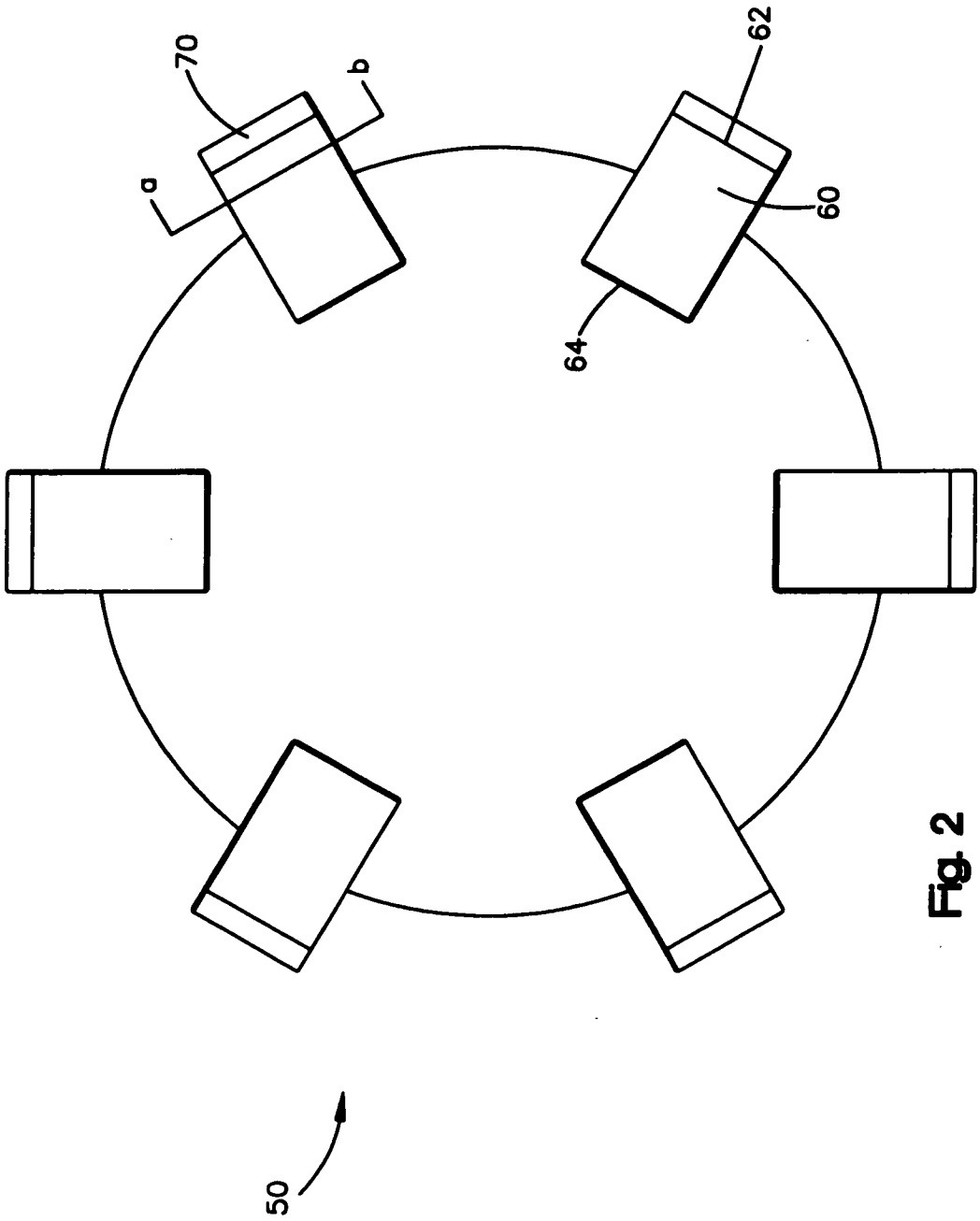

Fig. 2

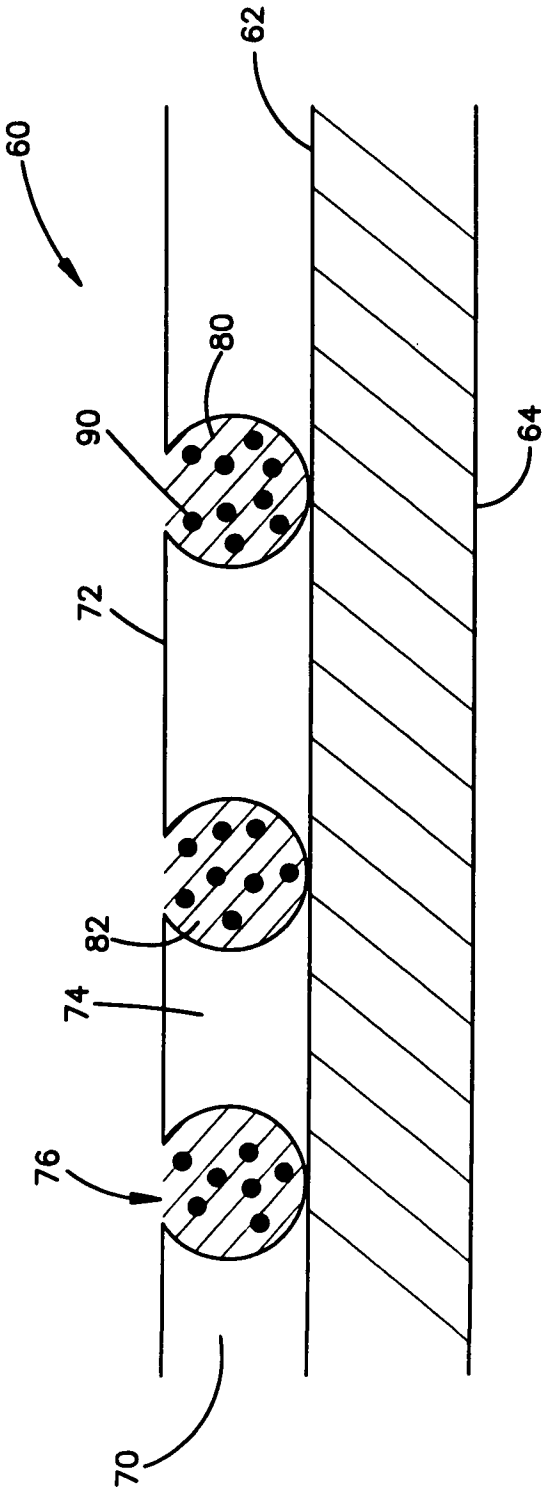

Fig. 3

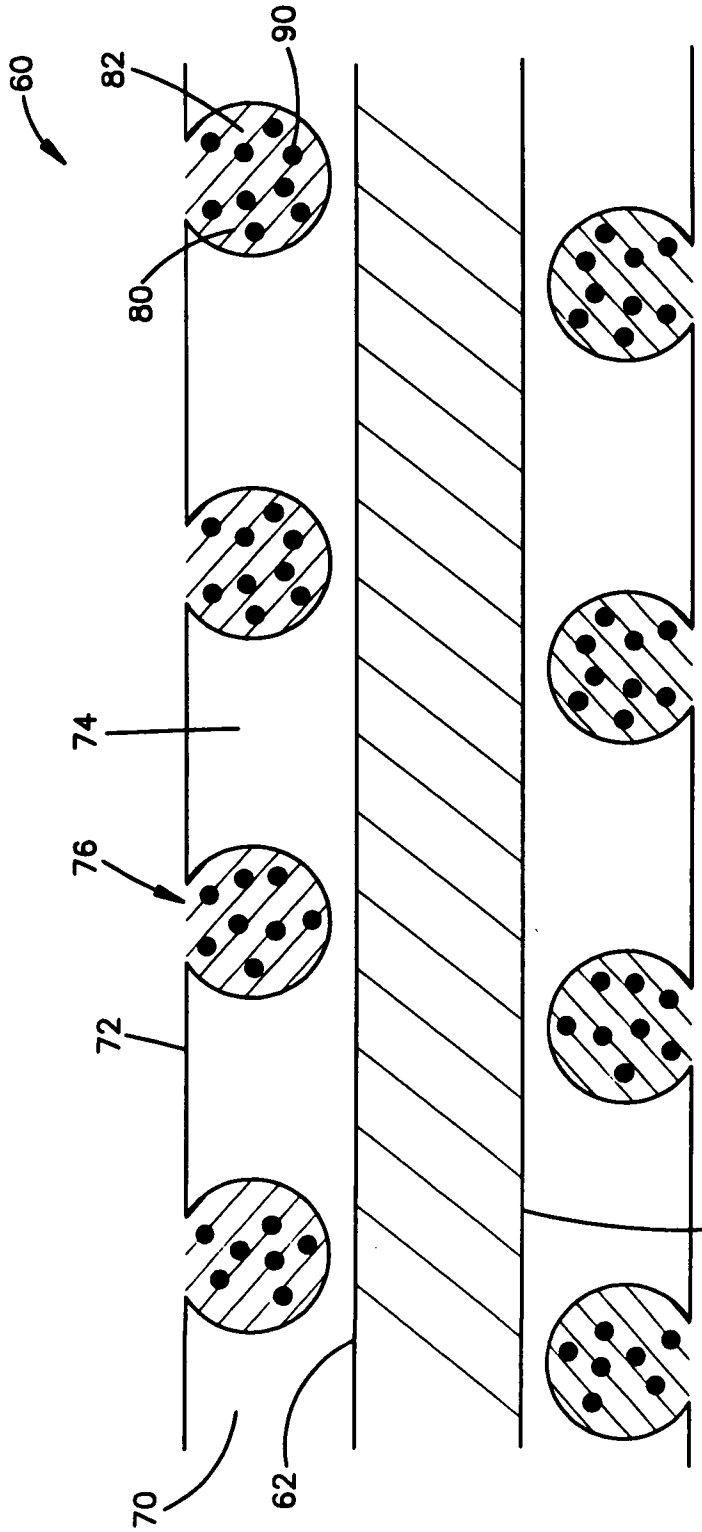

Fig. 4

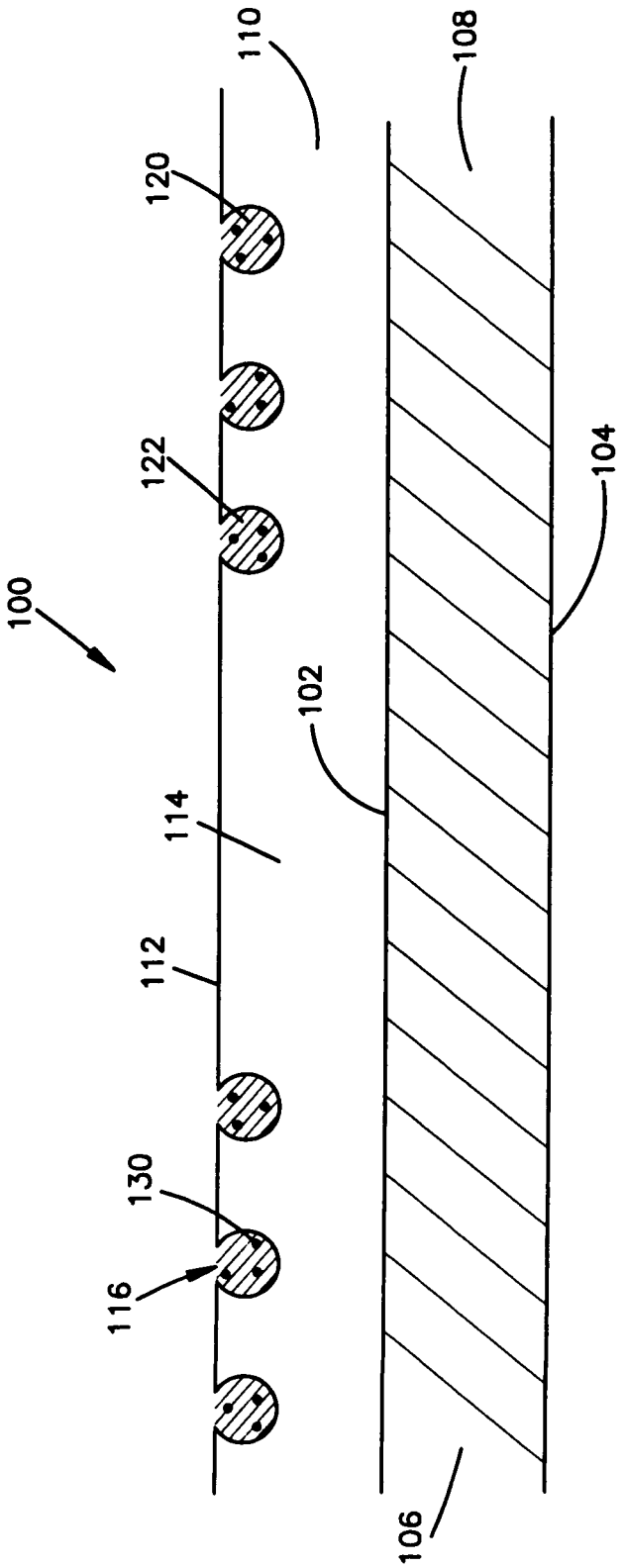

Fig. 5

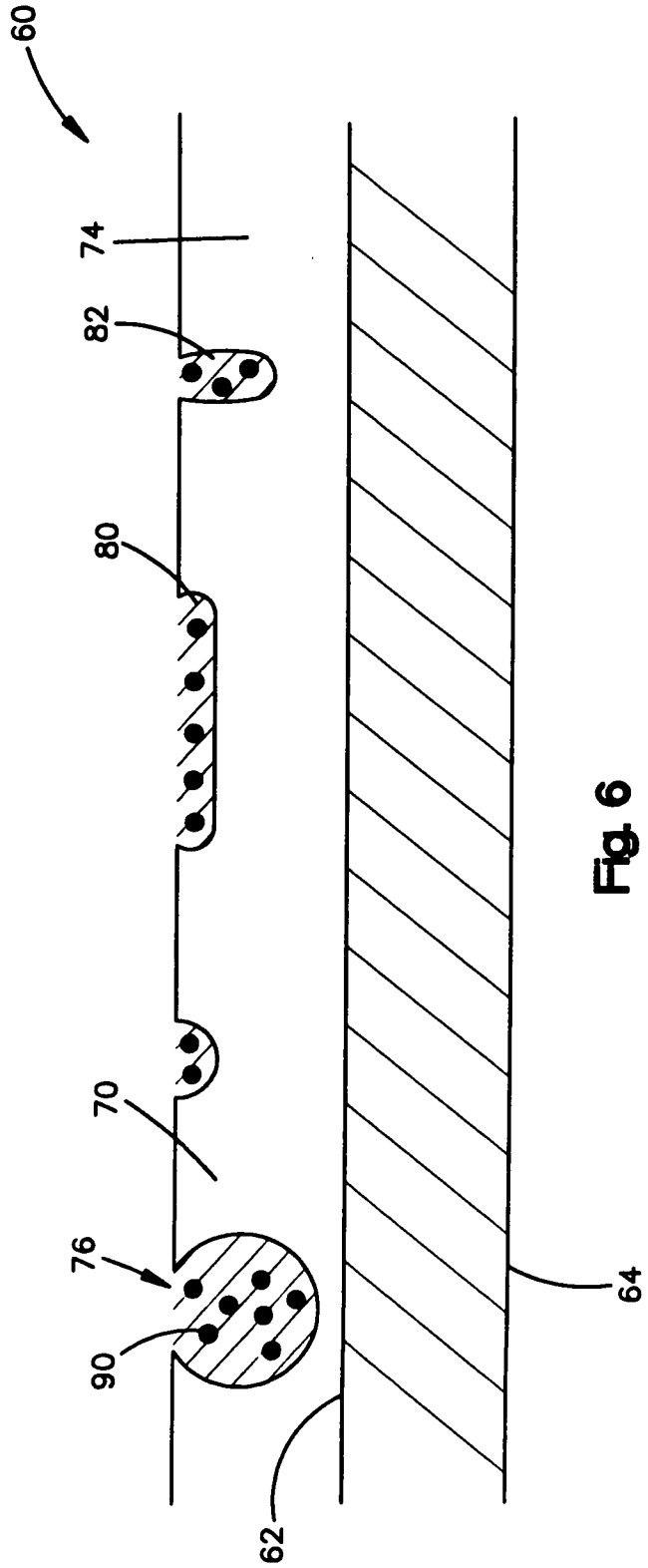

Fig. 6

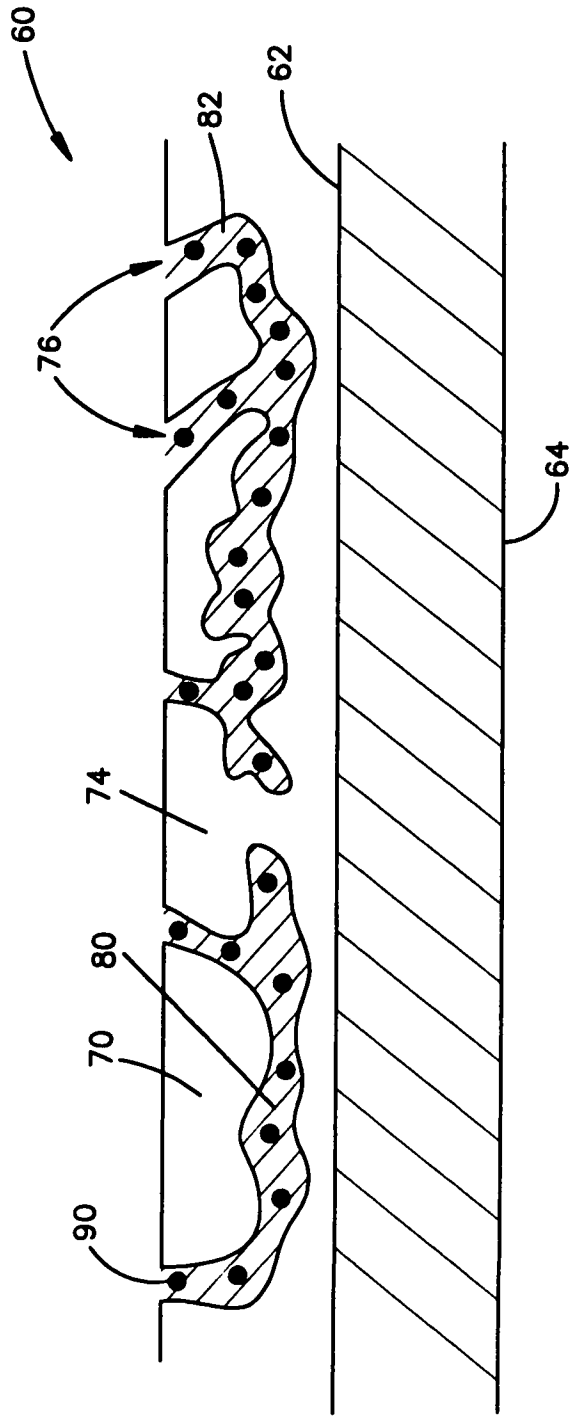

Fig. 7

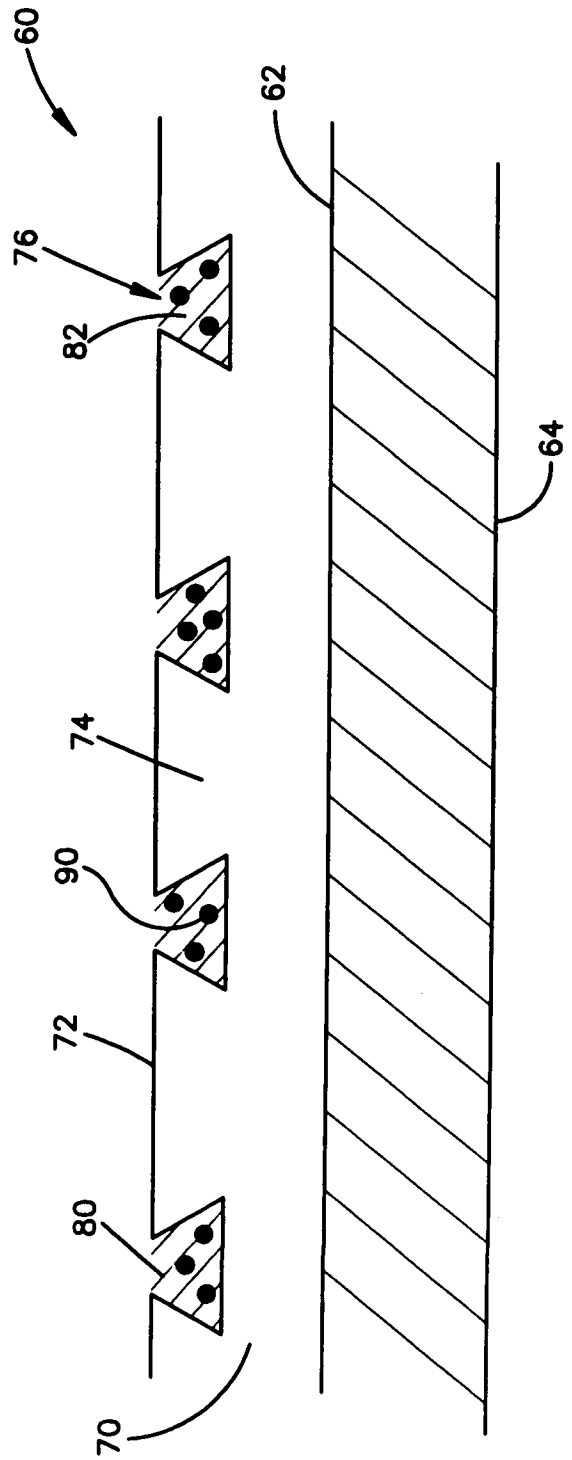

Fig. 8

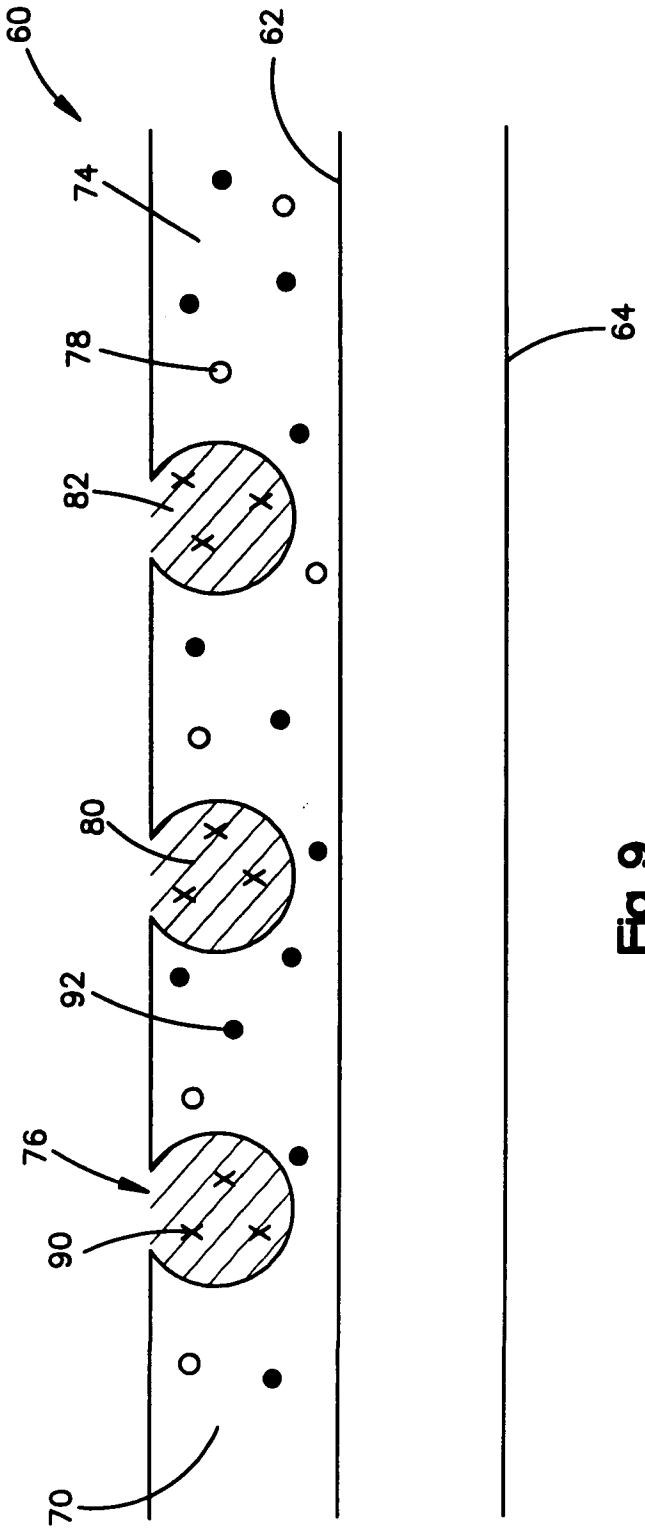

Fig. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/002713

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 02/060506 A (ADVANCED BIO PROSTHETIC SURFAC [US]; BOYLE CHRISTOPHER T [US]) 8 August 2002 (2002-08-08) page 6, line 8 - page 9, line 9 page 12, line 20 - page 13, line 11	1-4,6-22
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2008	25/06/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/002713

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No
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