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(54) **Title**: MEDICAL DEVICES HAVING A COATING OF INORGANIC MATERIAL

(57) **Abstract**: In one aspect, a medical device has a first configuration and a second configuration, a reservoir containing a therapeutic agent, and a barrier layer disposed over the reservoir, wherein the barrier layer comprises an inorganic material. In another aspect, a medical device has a reservoir containing a therapeutic agent, a barrier layer disposed over the reservoir, wherein the barrier layer comprises an inorganic material, and a swellable material disposed between the barrier layer and a surface of the medical device, wherein the swellable material is a material that swells upon exposure to an aqueous environment. In yet another aspect, a medical device has a multi-layered coating having alternating reservoir layers and barrier layers, and a plurality of excavated regions penetrating through at least a partial thickness of the multi-layered coating. In yet another aspect, a medical device has a polymer layer comprising a block co-polymer, wherein the polymer layer contains a therapeutic agent, and a barrier layer disposed over the polymer layer, wherein the barrier layer comprises an inorganic material, and wherein the barrier layer has a plurality of discontinuities. Methods of forming coatings on medical devices and methods of delivering therapeutic agents to body sites are also disclosed.

MEDICAL DEVICES HAVING A COATING OF INORGANIC MATERIAL

Cross Reference to Related Application

[0001] The present application claims priority to United States provisional application Serial No. 61/047,002 filed April 22, 2008, the disclosure of which is incorporated herein by reference in its entirety.

Technical Field

[0002] The present invention relates to medical devices, and in particular, medical devices having a coating containing a therapeutic agent.

Background

[0003] Many implantable medical devices are coated with drugs that are eluted from the medical device upon implantation. For example, some vascular stents are coated with a drug which is eluted from the stent for treatment of the vessel and/or to prevent some of the unwanted effects and complications of implanting the stent. In such drug-eluting medical devices, various methods have been proposed to provide a mechanism for drug elution. However, there is a continuing desire for improved devices and methods for providing drug elution from medical devices.

Summary

[0004] In one aspect, the present invention provides a medical device having a first configuration (e.g., unexpanded) and a second configuration (e.g., expanded), wherein the medical device comprises: (a) a reservoir containing a therapeutic agent; and (b) a barrier layer disposed over the reservoir, wherein the barrier layer comprises an inorganic material, wherein the barrier layer has a first permeability to the therapeutic agent when the medical device is in the first configuration and a second permeability to the therapeutic agent when the medical device is in the second configuration, and wherein the second permeability is greater than the first permeability.

[0005] In another aspect, the present invention provides a medical device comprising: (a) a reservoir containing a therapeutic agent; (b) a barrier layer disposed over the reservoir, wherein

the barrier layer comprises an inorganic material; and (c) a swellable material disposed between the barrier layer and a surface of the medical device, wherein the swellable material is a material that swells upon exposure to an aqueous environment.

[0006] In yet another aspect, the present invention provides a medical device having a multi-layered coating, wherein the multi-layered coating comprises: (a) a first reservoir layer over a surface of the medical device, wherein the first reservoir layer comprises a first therapeutic agent; (b) a first barrier layer over the first reservoir layer, wherein the first barrier layer comprises a first inorganic material; (c) a second reservoir layer over the first barrier layer, wherein the second reservoir layer comprises a second therapeutic agent; (d) a second barrier layer over the second reservoir layer, wherein the second barrier layer comprises a second inorganic material; and (e) a plurality of excavated regions penetrating through at least a partial thickness of the multi-layered coating.

[0007] In yet another aspect, the present invention provides a medical device comprising: (a) a polymer layer comprising a block co-polymer, wherein the polymer layer contains a therapeutic agent; and (b) a barrier layer disposed over the polymer layer, wherein the barrier layer comprises an inorganic material, and wherein the barrier layer has a plurality of discontinuities.

[0008] The present invention also provides methods for forming a coating on medical devices and methods for delivering a therapeutic agent to a body site.

Brief Description of the Drawings

[0009] FIGS. 1A-1D show various views of a stent according to an embodiment of the present invention. FIG. 1A shows a top view of a strut on the stent. FIG. 1B shows a cross-section perspective view of a portion of the stent strut in FIG. 1A. FIG. 1C shows a cross-section side view of the stent strut in FIG. 1B, before the stent is expanded. FIG. 1D shows a cross-section side view of the stent strut in FIG. 1B, after the stent is expanded.

[0010] FIGS. 2A-2C show cross-section views of a strut on a stent according to another embodiment. FIG. 2A shows the stent strut before the stent is expanded. FIG. 2B shows the stent strut after the stent is expanded. FIG. 2C shows the stent strut after degradation of the plugs.

[0011] FIGS. 3A and 3B show cross-section views of a strut on a stent according to yet another embodiment. FIG. 3A shows the stent strut before the stent is expanded. FIG. 3B shows the stent strut after the stent is expanded.

[0012] FIGS. 4A and 4B show cross-section views of a strut on a stent according to yet another embodiment. FIG. 4A shows the stent strut before the stent is expanded. FIG. 4B shows the stent strut after the stent is expanded.

[0013] FIGS. 5A and 5B show cross-section views of a strut on a stent according to yet another embodiment. FIG. 5A shows the stent strut before the stent is expanded. FIG. 5B shows the stent strut after the stent is expanded.

[0014] FIGS. 6A and 6B show cross-section views of a strut on a stent according to yet another embodiment. FIG. 6A shows the stent strut before the stent is expanded. FIG. 6B shows the stent strut after the stent is expanded.

[0015] FIGS. 7A and 7B show cross-section views of a strut on a stent according to yet another embodiment. FIG. 7A shows the stent strut before the water-swellable layer is hydrated. FIG. 7B shows the stent strut after the water-swellable layer is hydrated.

[0016] FIGS. 8A and 8B show cross-section views of a strut on a stent according to yet another embodiment. FIG. 8A shows the stent strut before the hydrogel capsules are hydrated. FIG. 8B shows the stent strut after the hydrogel capsules are hydrated.

[0017] FIG. 9 shows a cross-section view of a strut on a stent having a multi-layered coating according to yet another embodiment.

[0018] FIG. 10 shows a cross-section view of a strut on a stent having a multi-layered coating according to yet another embodiment.

[0019] FIG. 11 shows a magnified view of the surface of a sputter-deposited layer of gold.

[0020] FIG. 12 shows an atomic force microscopic image of the surface of an SIBS block polymer film.

[0021] FIG. 13 shows an example of a surface having feature elements (grooves) and feature domains (area enclosed by the grooves).

[0022] FIGS. 14A and 14B show cross-section views of a strut on a stent according to yet another embodiment. FIG. 14A shows the stent strut before dissolution of the polymer layer. FIG. 14B shows the stent strut after dissolution of the polymer layer.

[0023] FIG. 15 shows a magnified view of the surface of a layer of sputter-deposited gold with drug particles underneath.

[0024] FIG. 16 shows a magnified view of the surface of the gold layer of FIG. 15, after additional sputter-deposition of gold onto the layer.

Detailed Description

[0025] In one aspect, the present invention provides a medical device having a first configuration and a second configuration. The medical device comprises a reservoir containing a therapeutic agent. A barrier layer is disposed over the reservoir, wherein the barrier layer comprises an inorganic material.

[0026] Medical devices may have various types of first and second configurations. In some cases, the medical device is an expandable medical device having an unexpanded (first) configuration and an expanded (second) configuration. For example, the medical device may be an expandable stent or vascular graft which is delivered to the target body site in an unexpanded configuration and then expanded to the expanded configuration for implantation at the target site. Various other types of first/second configurations are also possible, including for example, unbent/bent configurations, unstretched/stretched configurations, or undeformed/deformed configurations.

[0027] The reservoir containing the therapeutic agent may be provided in various ways. The reservoir may be the therapeutic agent formulation alone, or may comprise any structure that retains or holds the therapeutic agent. For example, the reservoir may be a polymer layer or other layer over the medical device with the therapeutic agent disposed therein. In another example, the reservoir may be created in the surface of the medical device (e.g., a porous surface), or the medical device may have pits, pores, cavities, or holes that contain the therapeutic agent.

[0028] The barrier layer comprises an inorganic material, which may be selected on the basis of various considerations depending upon the particular application. For example, the inorganic material may be selected for its biologic properties (e.g., biocompatibility), structural properties (e.g., porosity), chemical properties (e.g., chemical reactivity), handling properties (e.g., storage stability), or the deposition techniques that can be used. Suitable inorganic materials for use in the barrier layer include inorganic elements, such as pure metals including aluminum, chromium,

gold, hafnium, iridium, niobium, palladium, platinum, tantalum, titanium, tungsten, zirconium, and alloys of these metals (e.g., nitinol); and inorganic compounds, such as metal oxides (e.g., iridium oxide or titanium oxide), metal nitrides, and metal carbides, as well as inorganic silicides. Other suitable inorganic materials include certain carbon-containing materials that are traditionally considered inorganic materials, such as carbonized materials, carbon nanostructure materials, (e.g., carbon nanotubes, fullerenes, etc.), and diamond-like materials.

[0029] By being comprised of an inorganic material, the barrier layer may be useful in improving the biocompatibility or therapeutic effectiveness of the medical device. For example, the barrier layer may be useful in protecting body tissue from direct exposure to an underlying polymer layer that is less biocompatible than the barrier layer. Also, the barrier layer may present a more attractive surface for body tissue. For example, in the case of a vascular stent, the barrier layer may present a surface that promotes the migration and growth of endothelial cells, which can help to reduce the incidence of adverse effects related to stent implantation.

[0030] In some cases, the barrier layer may be formed using any of various layer deposition processes. For example, layer deposition processes that may be suitable for forming the barrier layer include: chemical vapor deposition, plasma vapor deposition, sputtering, pulsed laser deposition, sol-gel, evaporation (thermal, electron beam, etc.), molecular beam epitaxy, solution process (e.g., spray coating, dip coating, roll coating, etc.), or electrodeposition (e.g., electroplating, electrospray, etc.). The barrier layer may also be formed by carbonization (e.g., by laser heating or ion bombardment) of a precursor carbon material (e.g., a polymer) to form a barrier layer formed of an inorganic carbonized material.

[0031] The process used to form the barrier layer can be selected on the basis of various considerations, such as the type of medical device, the vulnerability of the therapeutic agent to heat degradation, or the type of inorganic material being used in the barrier layer. The thickness of the barrier layer will vary, depending upon the particular application. In some cases, the thickness of the barrier layer is in the range of 20 nm to 10 μm, but other thicknesses are also possible.

[0032] The barrier layer has a first permeability to the therapeutic agent when the medical device is in the first configuration and a second permeability to the therapeutic agent when the medical device is in the second configuration, with the second permeability being greater than the first permeability. Various possible degrees of permeability are possible for the first and

second permeabilities of the barrier layer. In some cases, the first permeability does not provide a therapeutically effective release profile of the therapeutic agent (e.g., negligible or zero permeability), whereas the second permeability does provide a therapeutically effective release profile of the therapeutic agent. In some cases, the second permeability is at least 1.5-fold greater; and in some cases, at least 3.0-fold greater than the first permeability (where the first permeability is non-zero).

[0033] The second permeability is provided by discontinuities that are formed in the barrier layer when the medical device changes from the first configuration (e.g., unexpanded) to the second configuration (e.g., expanded). As used herein, the term "discontinuities" refers to discrete defects in the barrier layer that allow the passage of therapeutic agents through the barrier layer. Examples of such discrete defects include fractures lines, cracks, breaks, gaps, faults, holes, perforations, and other openings through the full thickness of the barrier layer. These discontinuities may have various dimensions and geometries, which can affect the permeability of the barrier layer. For example, wider discontinuities can increase the permeability of the barrier layer, and thus, increase the rate at which the therapeutic agent diffuses through the barrier layer. The discontinuities may be linear or curved, jagged or smooth, irregular or regular, or have any of various other patterns.

[0034] In addition to providing the second permeability, the discontinuities may also serve to relieve any stress on the adhesive bond between the barrier layer and the underlying substrate when the medical device undergoes deformation. By allowing the formation of discontinuities in the barrier layer, the barrier layer is made less sensitive to strain, thus relieving stress on the adhesive bond when the medical device undergoes deformation.

[0035] In certain embodiments, the medical device is provided in the first configuration (e.g., unexpanded) with the barrier layer having a plurality of regions of structural weakness. As used herein, "regions of structural weakness" refers to regions of relative weakness in the barrier layer such that when the barrier layer is strained, discontinuities will form and/or propagate in the regions of structural weakness. In certain embodiments, the regions of structural weakness are excavated regions in the barrier layer. As used herein, "excavated regions" refers to voids (e.g., holes, slots, grooves, channels, etchings, scribe lines, perforations, pits, etc.) that are created by removal of material using techniques that control the size, shape, and location of the voids. For

example, such techniques include direct-write etching using energetic beams (e.g., laser, ion, or electron), micromachining, microdrilling, or lithographic processes.

[0036] The excavated regions may have various geometries and dimensions, which may be adjusted to achieve the desired amount of weakness in that particular region of the barrier layer. The excavated regions may extend partially or completely through the barrier layer. Increasing the depth of penetration of the excavated regions can increase the amount of weakness in that particular region of the barrier layer. In some cases, the excavated regions have an average penetration depth of 10% - 90% through the thickness of the layer, but other average penetration depths are also possible. In some cases, the average penetration depth of the excavated regions is greater than 10% of the thickness of the barrier layer; and in some cases, greater than 33%; and in some cases, greater than 50%. Increasing the width of the excavated regions can also increase the amount of weakness in the barrier layer in that particular region. In some cases, the excavated regions have an average width in the range of 10 nm to 1 μm, but other average widths are also possible. The overall ratio between the surface area of the excavated regions and the non-excavated regions will vary depending upon the particular application. In some cases, the excavated regions may constitute 5-90%; and in some cases, 30-70% of the overall surface area, but other ratios are also possible Also, the surface area ratio of the excavated regions to the non-excavated regions may be different at different portions of the medical device.

[0037] For example, referring to the embodiment shown in FIGS. 1A-1D, a strut 20 of an expandable stent 10 is coated with a polymer layer 30 containing a therapeutic agent. Polymer layer 30 is coated with a barrier layer 40 formed of iridium oxide. Referring to FIG. 1A, showing a top view of a portion of stent strut 20, barrier layer 40 over stent strut 20 has multiple scribe lines 42 that are formed by laser etching. FIG. 1B is a cross-section perspective view and FIG. 1C is a cross-section side view of portion 16 in FIG. 1A, showing barrier layer 40, polymer layer 30, and stent strut 20 when stent 10 is in an unexpanded configuration. In this particular embodiment, scribe lines 42 penetrate partially through barrier layer 40.

[0038] In operation, stent 10 is delivered to a body site in an unexpanded configuration. Once at the target body site, stent 10 is expanded. As shown in FIG. 1D, upon expansion, deformation of the stent struts imposes strain on barrier layer 40, causing the formation of cracks 44 in barrier layer 40 along scribe lines 42. These cracks 44 allow the passage of therapeutic agent from polymer layer 30 through barrier layer 40 to the external environment.

[0039] The laser used in the etching process may be any of various lasers capable of ablating inorganic material, including excimer lasers. Various parameters, including for example, the wavelength, pulse energy, and/or pulse frequency of the laser, may be adjusted to achieve the desired result. The laser can be applied using direct-write techniques or by using masking techniques (e.g., laser lithography). In some cases, a cold ablation technique is used (e.g., using a femtosecond laser or a short wavelength excimer laser), which may be useful in reducing any damage to the therapeutic agent or, where a polymeric material is used in the medical device, in reducing damage to the polymeric material.

[0040] In certain embodiments, the excavated regions may extend through the full thickness of the barrier layer, with the excavated regions being filled with a biodegradable filler material. For example, referring to the embodiment shown in FIGS. 2A and 2B, a stent strut 20 of an expandable stent is coated with a polymer layer 30 containing a therapeutic agent. Polymer layer 30 is coated with a barrier layer 50, which has multiple perforations 52. Perforations 52 are filled with plugs 54, which comprises a biodegradable filler material, such as a biodegradable polymer, pharmaceutically acceptable salt or sugar, or a biodegradable metal (e.g., magnesium).

[0041] In operation, the stent is delivered to a body site in an unexpanded state. Once at the target body site, the stent is expanded. As shown in FIG. 2B, upon expansion, deformation of the stent struts imposes strain upon barrier layer 50. This causes plugs 54 to partially detach or fracture, increasing the exposure of plugs 54 to the physiologic fluid. As shown in FIG. 2C, plugs 54 then undergo biodegradation such that perforations 52 are made patent. This allows the passage of therapeutic agent from polymer layer 30 through perforations 52 to the external environment.

[0042] In certain embodiments, the regions of structural weakness are regions where the barrier layer has reduced thickness relative to the full thickness of the barrier layer. The regions of reduced thickness may be created in various ways during the formation of the barrier layer. In one example, the regions of reduced thickness may be created by disposing the barrier layer on a textured surface such that the barrier layer has reduced thickness in the regions that are located over the protruding features of the textured surface. The protruding features may be bumps, ridges, ribs, folds, corrugations, projections, prominences, elevations, or other features that protrude from the textured surface. The textured surface may form a pattern that is regular or irregular.

[0043] For example, referring to the embodiment shown in FIGS. 3A and 3B, a stent strut 20 of an expandable stent is coated with a polymer layer 32. The surface of polymer layer 32 has a plurality of ridges 34. Polymer layer 32 is coated with a barrier layer 60. The portions of barrier layer 60 overlying ridges 34 are thinner portions 62 that have reduced thickness compared to the full thickness barrier layer 60.

[0044] In operation, the expandable stent is delivered to a body site in an unexpanded state. Once at the target body site, the expandable stent is expanded. As shown in FIG. 3B, when the expandable stent is expanded, deformation of the stent struts imposes strain on barrier layer 60, causing the formation of cracks 64 in the thinner portions 62 of barrier layer 60. These cracks 64 allow the passage of therapeutic agent from polymer layer 30 through barrier layer 62 to the external environment.

[0045] The regions of structural weakness may be distributed in various ways on different portions of the medical device. In certain embodiments, the regions of structural weakness are distributed uniformly throughout the medical device. In certain embodiments, the regions of structural weakness in the barrier layer at one portion of the medical device has different characteristics than those at a different portion of the medical device. In some cases, the regions of structural weakness are arranged and/or constructed to accommodate the location-dependent variation in strain forces that the barrier layer will experience when the medical device is changed from the first configuration to the second configuration. For example, in the expandable stent 10 of FIG. 1A, different portions of stent strut 20 will undergo varying amounts of deformation when stent 10 is expanded. In this particular stent, portion 12 of stent strut 20 will undergo more deformation than portion 14, causing more strain in barrier layer 40 over portion 12 than over portion 14. As such, the regions of structural weakness can be made weaker in areas where barrier layer 40 undergoes less strain in order to achieve the desired amount of second permeability in those areas of barrier layer 40.

[0046] For example, referring to the embodiment shown in FIGS. 4A and 4B, a stent strut 20 of an expandable stent is coated with a polymer layer 30 containing a therapeutic agent. Polymer layer 30 is coated with a barrier layer 70. Referring to FIG. 4A, in portions of the stent where the stent struts experience greater deformation during expansion, barrier layer 70 has shallow scribe lines 72. Referring to FIG. 4B, in portions of the stent where the stent struts experience less deformation during expansion, barrier layer 70 has deep scribe lines 74. In another example,

referring to the embodiment shown in FIGS. 5A and 5B, a stent strut 20 of an expandable stent is coated with a polymer layer 30 containing a therapeutic agent. Polymer layer 30 is coated with a barrier layer 80. The shape of the base of the scribe lines can also have an effect on crack propagation, with blunt or larger radius tips sustaining less stress concentration than sharp or smaller radius tips. Thus, referring to FIG. 5A, in portions of the stent where the stent struts experience less deformation during expansion, barrier layer 80 has narrow scribe lines 82. Referring to FIG. 5B, in portions of the stent where the stent struts experience greater deformation during expansion, barrier layer 80 has wide scribe lines 84. In yet another example, referring to the embodiment shown in FIGS. 6A and 6B, a stent strut 20 of an expandable stent is coated with a polymer layer 30 containing a therapeutic agent. Polymer layer 30 is coated with a barrier layer 90. Referring to FIG. 6A, in portions of the stent where the stent struts experience greater deformation during expansion, barrier layer 90 has a lower density of scribe lines 92. Referring to FIG. 6B, in portions of the stent where the stent struts experience less deformation during expansion, barrier layer 90 has a higher density of scribe lines 92.

[0047] In another aspect, the present invention provides a medical device having a reservoir containing a therapeutic agent. Further, a barrier layer is disposed over the reservoir, wherein the barrier layer comprises an inorganic material. Further, a swellable material is disposed between the barrier layer and a surface of the medical device, wherein the swellable material is a material which swells upon exposure to an aqueous environment. Such swellable materials include water-swellable polymers and oxidizable metals. The composition and structure of the reservoir, as well as the manner in which it may be formed, are as described above. The composition and structure of the barrier layer, as well as the manner in which it may be formed, are as described above.

[0048] The barrier layer has a first permeability to the therapeutic agent prior to swelling of the swellable material and a second permeability to the therapeutic agent after swelling of the swellable material, with the second permeability being greater than the first permeability. In certain embodiments, the barrier layer may have regions of structural weakness as described above. When the swellable material swells, it applies outward pressure against the barrier layer. The strain imposed by this pressure causes the formation of discontinuities in the barrier layer, which increases the permeability of the barrier layer. Thus, the second permeability of the barrier layer is provided by discontinuities that form in the barrier layer upon swelling of the

swellable material. Where the barrier layer has a plurality of regions of structural weakness, the discontinuities may form in these regions.

[0049] In certain embodiments, the swellable material is a water-swellable polymer that swells when it becomes hydrated. In such cases, the medical device is designed such that the water-swellable polymer becomes hydrated when the medical device is exposed to an aqueous environment (e.g., body fluid or tissue). The aqueous fluid may be distributed to the water-swellable polymer through various pathways. In certain embodiments, aqueous fluid has access to the water-swellable polymer via a pathway that does not involve the barrier layer. For example, aqueous fluid may have access to the water-swellable polymer through another portion of the medical device, or aqeuous fluid may be actively supplied to the water-swellable polymer by the medical device.

[0050] In certain embodiments, aqueous fluid from the external environment accesses the water-swellable polymer by passing through the barrier layer, which is allowed by a first, initial permeability of the barrier layer. This first, initial permeability of the barrier layer may be provided in various ways. In some cases, the barrier layer may be porous or semi-permeable. In some cases, the barrier layer may have one or more initially present discontinuities that allow the penetration of aqueous fluid through the barrier layer. These initially present discontinuities may be formed in various ways. One such method involves heating and/or cooling the barrier layer, which would cause thermal expansion and/or contraction of the barrier layer and result in the formation of discontinuities. For example, the barrier layer may be cooled by dipping the medical device into a cold solvent mixture or a cryogenic liquid (e.g., liquid nitrogen). In another example, the barrier layer may be subjected to alternating cycles of heating and cooling (or vice versa).

[0051] Any of a number of various types of water-swellable polymers known in the art may be used, including those that form hydrogels. Other examples of water-swellable polymers include polyethylene oxide, hydroxypropyl methylcellulose, poly(hydroxyalkyl methacrylate), polyvinyl alcohol, and polyacrylic acid. The water-swellable polymer may be applied to the medical device in various ways. For example, the water-swellable polymer may be provided in the form of gels, layers, fibers, agglomerates, blocks, granules, particles, capsules, or spheres. In some cases, the water-swellable polymer is contained within or underneath a polymer layer

containing the therapeutic agent. In such cases, the polymer layer may serve to control the rate at which the water-swellable polymer becomes hydrated.

[0052] The following non-limiting examples further illustrate various embodiments of this aspect of the present invention. In one example, referring to the embodiment shown in FIGS. 7A and 7B, a stent strut 20 of a stent is coated with a water-swellable layer 100 formed of a hydrogel. Water-swellable layer 100 is coated with a polymer layer 110 containing a therapeutic agent. Polymer layer 110 is coated with a barrier layer 120, which has multiple small pores 122 to allow the passage of fluids through barrier layer 120 so that water-swellable layer 100 can become hydrated when the stent is exposed to an aqueous environment. In alternate embodiments, the positions of water-swellable layer 100 and polymer layer 110 may be switched.

[0053] In operation, when the stent is delivered to a target body site, body fluid flows through pores 122 of barrier layer 120, diffuses through polymer layer 110, and hydrates the hydrogel in water-swellable layer 100. As shown in FIG. 7B, hydration of the hydrogel causes volume expansion of water-swellable layer 100, which causes the formation of cracks 124 in barrier layer 120. These cracks 124 allow the passage of therapeutic agent from polymer layer 110 through barrier layer 120 to the external environment.

[0054] In another example, referring to the embodiment shown in FIGS. 8A and 8B, a stent strut 20 of a stent is coated with a polymer layer 114 containing a therapeutic agent. Embedded in polymer layer 114 are capsules 102 which contain a hydrogel. Polymer layer 114 is coated with a barrier layer 130, which is semi-permeable to allow the passage of fluids through barrier layer 130.

[0055] In operation, when the stent is delivered to a target body site, body fluid flows through semi-permeable barrier layer 130, diffuses through polymer layer 114, and hydrates the hydrogel in capsules 102. As shown in FIG. 8B, hydration of the hydrogel causes the volume expansion of capsules 102, which in turn, causes volume expansion of polymer layer 114. This volume expansion of polymer layer 114 causes the formation of cracks 132 in barrier layer 130. These cracks 132 allow the passage of therapeutic agent from polymer layer 114 through barrier layer 132 to the external environment.]

[0056] In another embodiment, the swellable material is an oxidizable metal that undergoes volume expansion upon oxidation (e.g., iron). The oxidation can occur upon exposure to an

aqueous environment. As such, the oxidizable metal may be used in a manner similar to that for the water-swellable polymer described above.

[0057] In yet another aspect, the present invention provides a medical device having a multi-layered coating. The multi-layered coating comprises a first reservoir layer over a surface of the medical device, wherein the first reservoir layer comprises a first therapeutic agent. Further, a first barrier layer is disposed over the first reservoir layer, wherein the first barrier layer comprises a first inorganic material. Further, a second reservoir layer is disposed over the first barrier layer, wherein the second reservoir layer comprises a second therapeutic agent. The reservoir layers are formed using a material that is capable of retaining or holding the therapeutic agent, such as polymeric materials.

[0058] The first and second therapeutic agents may be the same or different. For example, one therapeutic agent may be an anti-thrombotic agent and the other therapeutic agent may be an anti-inflammatory agent to provide a combination treatment. Also, various characteristics of the first and second reservoir layers may be the same or different. Such characteristics include, for example, their composition, their density, their thicknesses, and the rate at which the therapeutic agents diffuse through the polymer layers. By independently controlling the characteristics of each reservoir layer, the release rate of the therapeutic agents can be adjusted.

[0059] Further, a second barrier layer is disposed over the second reservoir layer, wherein the second barrier layer comprises a second inorganic material. The composition and structure of the barrier layers, as well as the manner in which they may be formed, are as described above. Each barrier layer may each independently have their own various characteristics, including their composition, density, thickness, and permeability to the therapeutic agents.

[0060] Further, a plurality of excavated regions (as defined above) penetrate through at least a partial thickness of the multi-layered coating. The excavated regions provide a means by which therapeutic agents in the reservoir layers may be released into the external environment.

[0061] For example, referring to the embodiment shown in FIG. 9, a stent strut 20 of a stent has a multi-layered coating 170. The first layer in multi-layered coating 170 is a first reservoir layer 140 containing a first therapeutic agent. First reservoir layer 140 is coated with a first barrier layer 150 which, in this particular embodiment, is impermeable to the first therapeutic agent. First barrier layer 150 is coated with a second reservoir layer 142 which contains a second therapeutic agent which, in this particular embodiment, is different from the first therapeutic

agent. Second reservoir layer 142 is coated with a second barrier layer 152 which, in this particular embodiment, is impermeable to the second therapeutic agent. Multiple slots 160 penetrating through the full thickness of multi-layered coating 170 are created by laser ablation. In this particular embodiment, slots 160 have a width in the range of 100 nm to 1 μm, but other widths are also possible depending upon the particular application. In operation, when the stent is delivered to a body site, the therapeutic agents diffuse out of reservoir layers 140 and 142 through the side aspects (e.g., side aspect 146) of reservoir layers 140 and 142. The therapeutic agents are then released out of slots 160.

[0062] The excavated regions may have various geometries and dimensions, including various sizes, widths, shapes, and degrees of penetration through the multi-layered coating. This feature may be useful in varying the release rate of the therapeutic agents. For example, referring to the embodiment shown in FIG. 10, a stent strut 20 of a stent has a multi-layered coating 172 with slots (162, 164, 166, and 168) having various different dimensions and geometries. Multi-layered coating 172 has a first reservoir layer 140 containing a first therapeutic agent, a first barrier layer 150, a second reservoir layer 142 containing a second therapeutic agent, and a second barrier layer 152. Slot 162 penetrates partially through multi-layered coating 172 such that only reservoir layer 142 is exposed. Because of this geometry, only the first therapeutic agent in reservoir layer 142 would be released from slot 162. Slot 164 also penetrates partially through the multi-layered coating, but both reservoir layer 140 and 142 are exposed. Slot 166 has a slanted geometry with respect to the plane of multi-layered coating 172. A slot having this geometry may be useful in enlarging the side aspect surface (e.g., side aspect 144) of reservoir layers 140 and 142, which would increase the rate at which the therapeutic agents diffuse out of the layers. Slot 168 has a wedge-shaped geometry, which like slot 166, enlarges the side aspect surface of reservoir layers 140 and 142, which would increase the rate at which the therapeutic agents diffuse out of the layers.

[0063] In certain embodiments, the excavated regions on one portion of the medical device have different characteristics than the excavated regions on another portion of the medical device. These different characteristics can involve different geometries or dimensions, or a different arrangement (e.g., pattern, number, or density) of the excavated regions. This feature may be useful in providing different therapeutic agent release rates on different portions of the medical device, or the release of different therapeutic agents on different portions of the medical device.

For example, a vascular stent may have larger or a higher density of excavated regions at the end portions of the stent than at the intermediate portions of the stent to reduce the unwanted "edge-effect" that sometimes occurs with stent implantation.

[0064] The first and second barrier layers may have varying degrees of permeability to the therapeutic agents, or be completely impermeable. In some cases, the first barrier layer and/or second barrier layer are impermeable so that the therapeutic agent is released only though the excavated regions in the multi-layered coating. The permeability of the barrier layers may be controlled in various ways, including selecting the thickness, the density, the deposition process used, and the composition of the barrier layers. By individually adjusting the permeability of the barrier layers, the release rate profiles of the therapeutic agents may be further controlled.

[0065] In certain embodiments, the multi-layered coating comprises a plurality of alternating reservoir layers and barrier layers. For example, there may be a third reservoir layer disposed over the second barrier layer, wherein the third reservoir layer comprises a third therapeutic agent; and a third barrier layer disposed over the third reservoir layer, wherein the third barrier layer comprises a third inorganic material.

[0066] In yet another aspect, the present invention provides a medical device having a polymer layer, which comprises a block copolymer and a therapeutic agent. Further, a barrier layer is disposed over the polymer layer. The barrier layer comprises an inorganic material and has a plurality of discontinuities. The composition and structure of the reservoir, as well as the manner in which it may be formed, are as described above. The composition and structure of the barrier layer, as well as the manner in which it may be formed, are as described above.

[0067] The inventors have discovered that depositing a thin layer of gold (by sputter deposition) onto a film of SIBS block copolymer on a stainless steel coupon unexpectedly resulted in the formation of nanometer-sized (about 20 nm wide) cracks in a reticulated pattern, as shown under 60,000-fold magnification in FIG. 11. It is believed that this pattern of cracks in the gold layer follows the particular surface morphology of the SIBS polymer film. Referring to FIG. 12, an atomic force microscopy image of the SIBS polymer film (deposited by evaporation on a stainless steel stent shows the surface morphology of this film as having features sized from about 30 – 90 nm. These surface features are believed to be caused by microphase-separated domains of the block copolymers in the film.

[0068] Therefore, in this aspect of the present invention, the polymer layer (comprising a block copolymer) and the barrier layer have a synergistic relationship because the resulting formation of discontinuities in the barrier layer allows for the release of therapeutic agent in the polymer layer to the external environment. Also, the polymer layer and the barrier layer have an additional synergistic relationship because the resulting surface morphology of the barrier layer is believed to be capable of promoting endothelial cell attachment and/or growth, which may improve the therapeutic effectiveness of medical devices that are implanted in blood vessels.

[0069] In certain embodiments, the surface morphology of the polymer layer comprises a plurality of microphase-separated domains. In some cases, the surface morphology of the barrier layer follows the surface morphology of the polymer layer. In some cases, the discontinuities in the barrier layer follow the surface morphology of the polymer layer. Various characteristics of the microphase-separated domains (e.g., their size, geometry, and periodicity) on the surface of the polymer layer will depend upon the specific characteristics of the block copolymer, such as the relative chain lengths, positions, and composition of the blocks. As such, the block copolymer can be selected to achieve the desired surface morphology in the polymer layer, which in turn, will influence the formation of discontinuities and/or the surface morphology of the barrier layer.

[0070] In certain embodiments, the surface morphology of the barrier layer comprises a plurality of features elements or feature domains having a size that promotes endothelial cell attachment and/or growth. As used herein, the term “feature element” refers to any feature on a surface that causes the surface to be uneven, non-smooth, or discontinuous. For example, the feature elements may be bumps, nodules, ridges, grains, protrusions, pits, holes, openings, cracks, fracture lines, pores, grooves, channels, etc. As used herein, the term “feature domain” refers to a domain that is defined by one or more feature elements. For example, referring to schematic illustration of FIG. 13, a surface 200 comprises multiple grooves 202 which define a series of pattern domains 204. Grooves 202 would be considered feature elements and pattern domains 204 would be considered feature domains. The size of a feature element or feature domain, as used herein, is intended to be measured along its shortest axis. In some cases, the feature elements or feature domains have an average size of less than 200 nm. In some cases, the feature elements or feature domains have an average size in the range of 10 nm to 200 nm; and in some

cases, in the range of 30 nm to 90 nm. The pattern of the feature elements or feature domains may be regular or irregular, ordered or random, and have varying densities.

[0071] In certain embodiments, the polymer layer is exposed to a solvent which dissolves the polymeric material in the polymer layer, but does not dissolve the therapeutic agent. In some cases, the solvent may access the polymer layer through the discontinuities in the barrier layer. For example, referring to the embodiment shown in FIG. 14A, a medical device 15 is coated with a polymer layer 180 formed of a block copolymer. Polymer layer 180 contains particles 182 of a therapeutic agent. A barrier layer 190 is deposited over polymer layer 180, and cracks 192 form in barrier layer 190 due to the surface morphology of polymer layer 180. Medical device 15 is then exposed to a solvent which penetrates through the cracks 192 of barrier layer 190 and dissolves the polymeric material in polymer layer 180. However, the particles 182 of the therapeutic agent are left intact. As shown in FIG. 14B, this results in a coating in which the therapeutic agent is contained in a polymer-free layer 184 under barrier layer 190. This feature may be useful in reducing exposure of body tissue to polymeric materials which may not be fully biocompatible. In some cases, barrier layer 190 may then be augmented by further depositing additional inorganic material (e.g., a biodegradable metal such as a magnesium alloy, iron, or zinc) onto barrier layer 190. Augmenting barrier layer 190 may be useful in reducing the permeability of barrier layer 190, and thereby, reducing the rate at which the therapeutic agent is released.

[0072] In an experimental example, a coating was formed by sputter-depositing a layer of gold onto an SIBS block copolymer film stainless steel coupon containing paclitaxel particles. This coating was then exposed to toluene, which penetrated through the cracks in the gold film and dissolved the SIBS polymer. FIG. 15 shows the surface (under 134,00-fold magnification) of the gold layer, in which the preserved paclitaxel particles are evident as bumps (black arrow) in the layer. Additional gold material was then sputtered-deposited onto this coating to form the coating seen in FIG. 16, which shows the surface under 60,000-fold magnification.

[0073] Non-limiting examples of medical devices that can be used with the present invention include stents, stent grafts, catheters, guide wires, neurovascular aneurysm coils, balloons, filters (*e.g.*, vena cava filters), vascular grafts, intraluminal paving systems, pacemakers, electrodes, leads, defibrillators, joint and bone implants, spinal implants, access ports, intra-aortic balloon pumps, heart valves, sutures, artificial hearts, neurological stimulators, cochlear implants, retinal

implants, and other devices that can be used in connection with therapeutic coatings. Such medical devices are implanted or otherwise used in body structures, cavities, or lumens such as the vasculature, gastrointestinal tract, abdomen, peritoneum, airways, esophagus, trachea, colon, rectum, biliary tract, urinary tract, prostate, brain, spine, lung, liver, heart, skeletal muscle, kidney, bladder, intestines, stomach, pancreas, ovary, uterus, cartilage, eye, bone, joints, and the like.

[0074] The therapeutic agent used in the present invention may be any pharmaceutically acceptable agent such as a non-genetic therapeutic agent, a biomolecule, a small molecule, or cells.

[0075] Exemplary non-genetic therapeutic agents include anti-thrombogenic agents such heparin, heparin derivatives, prostaglandin (including micellar prostaglandin E1), urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone); anti-proliferative agents such as enoxaparin, angiopeptin, sirolimus (rapamycin), tacrolimus, everolimus, zotarolimus, monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, rosiglitazone, prednisolone, corticosterone, budesonide, estrogen, estrodiol, sulfasalazine, acetylsalicylic acid, mycophenolic acid, and mesalamine; anti-neoplastic/anti-proliferative/anti-mitotic agents such as paclitaxel, epothilone, cladribine, 5-fluorouracil, methotrexate, doxorubicin, daunorubicin, cyclosporine, cisplatin, vinblastine, vincristine, epothilones, endostatin, trapidil, halofuginone, and angiostatin; anti-cancer agents such as antisense inhibitors of c-myc oncogene; anti-microbial agents such as triclosan, cephalosporins, aminoglycosides, nitrofurantoin, silver ions, compounds, or salts; biofilm synthesis inhibitors such as non-steroidal anti-inflammatory agents and chelating agents such as ethylenediaminetetraacetic acid, O,O'-bis (2-aminoethyl) ethyleneglycol-N,N,N',N'-tetraacetic acid and mixtures thereof; antibiotics such as gentamycin, rifampin, minocyclin, and ciprofloxacin; antibodies including chimeric antibodies and antibody fragments; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; nitric oxide; nitric oxide (NO) donors such as linsidomine, molsidomine, L-arginine, NO-carbohydrate adducts, polymeric or oligomeric NO adducts; 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, enoxaparin, hirudin, warfarin sodium, Dicumarol, aspirin, prostaglandin inhibitors, platelet aggregation

inhibitors such as cilostazol and tick antiplatelet factors; vascular cell growth promotors such as growth factors, transcriptional activators, and translational promotors; vascular cell growth inhibitors such as 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 vascoactive mechanisms; inhibitors of heat shock proteins such as geldanamycin; angiotensin converting enzyme (ACE) inhibitors; beta-blockers; βAR kinase (βARK) inhibitors; phospholamban inhibitors; protein-bound particle drugs such as ABRAXANE™; structural protein (e.g., collagen) cross-link breakers such as alagebrium (ALT-711); any combinations and prodrugs of the above.

[0076] Exemplary biomolecules include peptides, polypeptides and proteins; oligonucleotides; nucleic acids such as double or single stranded DNA (including naked and cDNA), RNA, antisense nucleic acids such as antisense DNA and RNA, small interfering RNA (siRNA), and ribozymes; genes; carbohydrates; angiogenic factors including growth factors; cell cycle inhibitors; and anti-restenosis agents. Nucleic acids may be incorporated into delivery systems such as, for example, vectors (including viral vectors), plasmids or liposomes.

[0077] Non-limiting examples of proteins include serca-2 protein, monocyte chemoattractant proteins (MCP-1) and bone morphogenic proteins ("BMP's"), such as, for example, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (VGR-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15. Preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, and BMP-7. These BMPs can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively, or in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedghog" proteins, or the DNA's encoding them. Non-limiting examples of genes include survival genes that protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; serca 2 gene; and combinations thereof. Non-limiting examples of angiogenic factors include acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factors α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor, and insulin-like growth factor. A non-limiting example of a cell cycle

inhibitor is a cathespin D (CD) inhibitor. Non-limiting examples of anti-restenosis agents include p15, p16, p18, p19, p21, p27, p53, p57, Rb, nFkB and E2F decoys, thymidine kinase and combinations thereof and other agents useful for interfering with cell proliferation.

[0078] Exemplary small molecules include hormones, nucleotides, amino acids, sugars, and lipids and compounds have a molecular weight of less than 100kD.

[0079] Exemplary cells include stem cells, progenitor cells, endothelial cells, adult cardiomyocytes, and smooth muscle cells. Cells can be of human origin (autologous or allogenic) or from an animal source (xenogenic), or genetically engineered. Non-limiting examples of cells include side population (SP) cells, lineage negative (Lin^-) cells including Lin^-CD34^-, Lin^-CD34^+, Lin^-cKit^+, mesenchymal stem cells including mesenchymal stem cells with 5-aza, cord blood cells, cardiac or other tissue derived stem cells, whole bone marrow, bone marrow mononuclear cells, endothelial progenitor cells, skeletal myoblasts or satellite cells, muscle derived cells, go cells, endothelial cells, adult cardiomyocytes, fibroblasts, smooth muscle cells, adult cardiac fibroblasts + 5-aza, genetically modified cells, tissue engineered grafts, MyoD scar fibroblasts, pacing cells, embryonic stem cell clones, embryonic stem cells, fetal or neonatal cells, immunologically masked cells, and teratoma derived cells. Any of the therapeutic agents may be combined to the extent such combination is biologically compatible.

[0080] The polymeric materials used in the present invention may comprise polymers that are biodegradable or non-biodegradable. Non-limiting examples of suitable non-biodegradable polymers include polystyrene; polystyrene maleic anhydride; block copolymers such as styrene-isobutylene-styrene block copolymers (SIBS) and styrene-ethylene/butylene-styrene (SEBS) block copolymers; polyvinylpyrrolidone including cross-linked polyvinylpyrrolidone; polyvinyl alcohols, copolymers of vinyl monomers such as EVA; polyvinyl ethers; polyvinyl aromatics; polyethylene oxides; polyesters including polyethylene terephthalate; polyamides; polyacrylamides including poly(methylmethacrylate-butylacetate-methylmethacrylate) block copolymers; polyethers including polyether sulfone; polyalkylenes including polypropylene, polyethylene and high molecular weight polyethylene; polyurethanes; polycarbonates, silicones; siloxane polymers; cellulosic polymers such as cellulose acetate; polymer dispersions such as polyurethane dispersions (BAYHYDROL®); squalene emulsions; and mixtures and copolymers of any of the foregoing.

[0081] Non-limiting examples of suitable biodegradable polymers include polycarboxylic acid, polyanhydrides including maleic anhydride polymers; polyorthoesters; poly-amino acids; polyethylene oxide; polyphosphazenes; polylactic acid, polyglycolic acid and copolymers and mixtures thereof such as poly(L-lactic acid) (PLLA), poly(D,L-lactide), poly(lactic acid-co-glycolic acid), 50/50 (DL-lactide-co-glycolide); polydioxanone; polypropylene fumarate; polydepsipeptides; polycaprolactone and co-polymers and mixtures thereof such as poly(D,L-lactide-co-caprolactone) and polycaprolactone co-butyl acrylate; polyhydroxybutyrate valerate and blends; polycarbonates such as tyrosine-derived polycarbonates and acrylates, polyiminocarbonates, and polydimethyltrimethylcarbonates; cyanoacrylate; calcium phosphates; polyglycosaminoglycans; macromolecules such as polysaccharides (including hyaluronic acid; cellulose, and hydroxypropyl methyl cellulose; gelatin; starches; dextrans; alginates and derivatives thereof), proteins and polypeptides; and mixtures and copolymers of any of the foregoing. The biodegradable polymer may also be a surface erodable polymer such as polyhydroxybutyrate and its copolymers, polycaprolactone, polyanhydrides (both crystalline and amorphous), maleic anhydride copolymers, and zinc calcium phosphate.

[0082] The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Each of the disclosed aspects and embodiments of the present invention may be considered individually or in combination with other aspects, embodiments, and variations of the invention. Modifications of the disclosed embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art and such modifications are within the scope of the present invention.

CLAIMS

We claim:

1. A medical device having a first configuration and a second configuration, wherein the medical device comprises:

a reservoir containing a therapeutic agent; and

a barrier layer disposed over the reservoir, wherein the barrier layer comprises an inorganic material;

wherein the barrier layer has a first permeability to the therapeutic agent when the medical device is in the first configuration and a second permeability to the therapeutic agent when the medical device is in the second configuration, and wherein the second permeability is greater than the first permeability.

2. The medical device of claim 1, wherein the medical device is an expandable medical device, and wherein the first configuration is an unexpanded configuration and the second configuration is an expanded configuration.

3. The medical device of claim 2, wherein the barrier layer has a plurality of regions of structural weakness.

4. The medical device of claim 3, wherein the regions of structural weakness are regions where the barrier layer has reduced thickness.

5. The medical device of claim 3, wherein the regions of structural weakness form a pre-determined fracture pattern for the barrier layer.

6. The medical device of claim 3, wherein discontinuities are formed in the regions of structural weakness when the configuration of the medical device changes from the unexpanded configuration to the expanded configuration.

7. The medical device of claim 4, wherein the regions of reduced thickness are excavated regions in which material has been removed from the barrier layer.

8. The medical device of claim 7, wherein the excavated regions contain a biodegradable filler material.

9. The medical device of claim 8, wherein the filler material is released from the excavated regions when the configuration of the medical device changes from the unexpanded configuration to the expanded configuration in an aqueous environment.

10. The medical device of claim 4, wherein the barrier layer is disposed on a textured surface, and wherein the regions of reduced thickness are located over the protruding features of the textured surface.

11. The medical device of claim 4, wherein the barrier layer is formed by a layer deposition process, and wherein the regions of reduced thickness are formed during the layer deposition process.

12. The medical device of claim 3, wherein the regions of structural weakness in a first portion of the medical device have a different characteristic than the regions of structural weakness in a second portion of the medical device.

13. The medical device of claim 12, wherein the second portion has a greater density of regions of structural weakness than the first portion.

14. The medical device of claim 12, wherein the regions of structural weakness are regions where the barrier layer has reduced thickness, and wherein the regions of reduced thickness are thinner in the second portion than in the first portion.

15. The medical device of claim 1, wherein the reservoir containing the therapeutic agent is a polymer layer.

16. The medical device of claim 1, wherein the inorganic material is a metal or metal oxide.

17. The medical device of claim 1, wherein the first permeability is negligible or zero.

18. The medical device of claim 1, wherein the first permeability does not provide a therapeutically effective release profile of the therapeutic agent, and wherein the second permeability provides a therapeutically effective release profile of the therapeutic agent.

19. A method of forming a coating on a medical device, comprising:
providing a medical device;
disposing a therapeutic agent over a surface of the medical device;
disposing a barrier layer over the therapeutic agent, wherein the barrier layer comprises an inorganic material; and
removing portions of the barrier layer to form regions of structural weakness in the barrier layer.

20. The method of claim 19, wherein the step of removing is performed using an energetic beam.

21. The method of claim 20, wherein the step of removing is performed by laser ablation.

22. The method of claim 19, wherein the step of disposing the barrier layer comprises depositing the inorganic material over the therapeutic agent by a layer deposition process.

23. The method of claim 22, wherein the layer deposition process is a nanoparticle deposition process.

24. The method of claim 19, wherein more material is removed from the barrier layer at a first portion of the medical device than at a second portion of the medical device.

25. A medical device comprising:

a reservoir containing a therapeutic agent;

a barrier layer disposed over the reservoir, wherein the barrier layer comprises an inorganic material; and

a swellable material disposed between the barrier layer and a surface of the medical device, wherein the swellable material is a material that swells upon exposure to an aqueous environment.

26. The medical device of claim 25, wherein the barrier layer has a first permeability to the therapeutic agent prior to swelling of the swellable material and a second permeability to the therapeutic agent after swelling of the swellable material, and wherein the second permeability is greater than the first permeability.

27. The medical device of claim 26, wherein the first permeability is provided by one or more discontinuities in the barrier layer.

28. The medical device of claim 27, wherein the swelling of the swellable material causes the formation of further discontinuities in the barrier layer.

29. The medical device of claim 25, wherein the medical device further comprises an intermediate layer disposed between the medical device and the barrier layer, wherein the intermediate layer comprises a polymeric material.

30. The medical device of claim 29, wherein the intermediate layer contains the reservoir containing the therapeutic agent.

31. The medical device of claim 30, wherein the medical device further comprises a swellable layer disposed between the medical device and the barrier layer, and wherein the swellable layer contains the swellable material.

32. The medical device of claim 30, wherein the intermediate layer further comprises the swellable material.

33. The medical device of claim 32, wherein the swellable material is contained in capsules.

34. The medical device of claim 25, wherein the barrier layer has a plurality of regions of structural weakness.

35. The medical device of claim 25, wherein the swellable material is a water-swellable polymer.

36. The medical device of claim 25, wherein the swellable material is an oxidizable metal that swells upon oxidation.

37. The medical device of claim 27, wherein the one or more discontinuities are created by cooling the barrier layer.

38. The medical device of claim 37, wherein the barrier layer is cooled by exposure to a cryogenic liquid.

39. The medical device of claim 27, wherein the one or more discontinuities are created by at least one cycle of heating and then cooling the barrier layer, or at least one cycle of cooling and then heating the barrier layer.

40. A medical device having a multi-layered coating, wherein the multi-layered coating comprises:

a first reservoir layer over a surface of the medical device, wherein the first reservoir layer comprises a first therapeutic agent;

a first barrier layer over the first reservoir layer, wherein the first barrier layer comprises a first inorganic material;

a second reservoir layer over the first barrier layer, wherein the second reservoir layer comprises a second therapeutic agent;

a second barrier layer over the second reservoir layer, wherein the second barrier layer comprises a second inorganic material; and

a plurality of excavated regions penetrating through at least a partial thickness of the multi-layered coating.

41. The medical device of claim 40, wherein at least one of the plurality of excavated regions penetrates through the full thickness of the multi-layered coating.

42. The medical device of claim 40, wherein at least one of the plurality of excavated regions penetrates through only a partial thickness of the multi-layered coating.

43. The medical device of claim 40, wherein at least one of the plurality of excavated regions has a slanted geometry with respect to the plane of the multi-layered coating.

44. The medical device of claim 40, wherein the first therapeutic agent is different from the second therapeutic agent.

45. The medical device of claim 40, wherein the first reservoir layer or the second reservoir layer is formed of a polymeric material.

46. The medical device of claim 40, wherein the thickness of the first reservoir layer is different from the thickness of the second reservoir layer.

47. The medical device of claim 40, further comprising a third reservoir layer disposed over the second barrier layer, wherein the third reservoir layer comprises a third therapeutic agent, and a third barrier layer disposed over the third reservoir layer, wherein the third barrier layer comprises a third inorganic material.

48. The medical device of claim 47, wherein the multi-layered coating comprises a plurality of alternating reservoir layers and barrier layers.

49. The medical device of claim 40, wherein at least one characteristic of the excavated regions on one portion of the medical device is different from that of the excavated regions on another portion of the medical device.

50. The medical device of claim 49, wherein the size of the excavated regions on one portion of the medical device is different from the size of the excavated regions on another portion of the medical device.

51. The medical device of claim 49, wherein the geometry of the excavated regions on one portion of the medical device is different from the geometry of the excavated regions on another portion of the medical device.

52. The medical device of claim 40, wherein the excavated regions are created using an energetic beam.

53. A medical device comprising:

a polymer layer comprising a block co-polymer, wherein the polymer layer contains a therapeutic agent; and

a barrier layer disposed over the polymer layer, wherein the barrier layer comprises an inorganic material, and wherein the barrier layer has a plurality of discontinuities.

54. The medical device of claim 53, wherein the polymer layer has a surface morphology comprising a plurality of microphase-separated domain structures.

55. The medical device of claim 54, wherein the discontinuities in the barrier layer follow the surface morphology of the polymer layer.

56. The medical device of claim 54, wherein the surface morphology of the barrier layer follows the surface morphology of the polymer layer.

57. The medical device of claim 53, wherein the surface morphology of the barrier layer is adapted to promote endothelial cell attachment and/or growth.

58. The medical device of claim 53, wherein the surface morphology of the barrier layer comprises a plurality of feature elements or feature domains that promote endothelial cell attachment and/or growth.

59. The medical device of claim 58, wherein the feature elements or feature domains have an average size of less than 200 nm.

60. The medical device of claim 59, wherein the feature elements or feature domains have an average size in the range of 30 nm to 90 nm.

61. A method of forming a coating in a medical device, comprising:

providing a medical device;

disposing a polymer layer over a surface of the medical device, wherein the polymer layer comprises a polymeric material and a therapeutic agent, wherein the polymeric material comprises a block copolymer, and wherein the polymer layer has a surface morphology comprising a plurality of microphase-separated domain structures; and

disposing a barrier layer over the polymer layer, wherein the barrier layer comprises an inorganic material, and wherein the barrier layer has a plurality of discontinuities that follow the surface morphology of the polymer layer.

62. The method of claim 61, further comprising removing the polymeric material from the polymer layer.

63. The method of claim 62, wherein the step of removing the polymeric material comprises exposing the polymer layer to a solvent.

64. The method of claim 62, further comprising depositing additional inorganic material over the barrier layer after the step of removing the polymeric material.

65. The method of claim 61, wherein the step of disposing a barrier layer comprises depositing the inorganic material over the polymer layer.

66. The medical device of claim 2, wherein the medical device is a balloon.

67. The medical device of claim 2, wherein the medical device is a stent.

68. The method of claim 19, wherein the medical device is a balloon.

69. The method of claim 19, wherein the medical device is a stent.

70. The medical device of claim 25, wherein the medical device is a balloon.

71. The medical device of claim 25, wherein the medical device is a stent.

72. The medical device of claim 40, wherein the medical device is a balloon.

73. The medical device of claim 40, wherein the medical device is a stent.

74. The medical device of claim 53, wherein the medical device is a balloon.

75. The medical device of claim 53, wherein the medical device is a stent.

76. The medical device of claim 60, wherein the medical device is a balloon.

77. The medical device of claim 60, wherein the medical device is a stent.

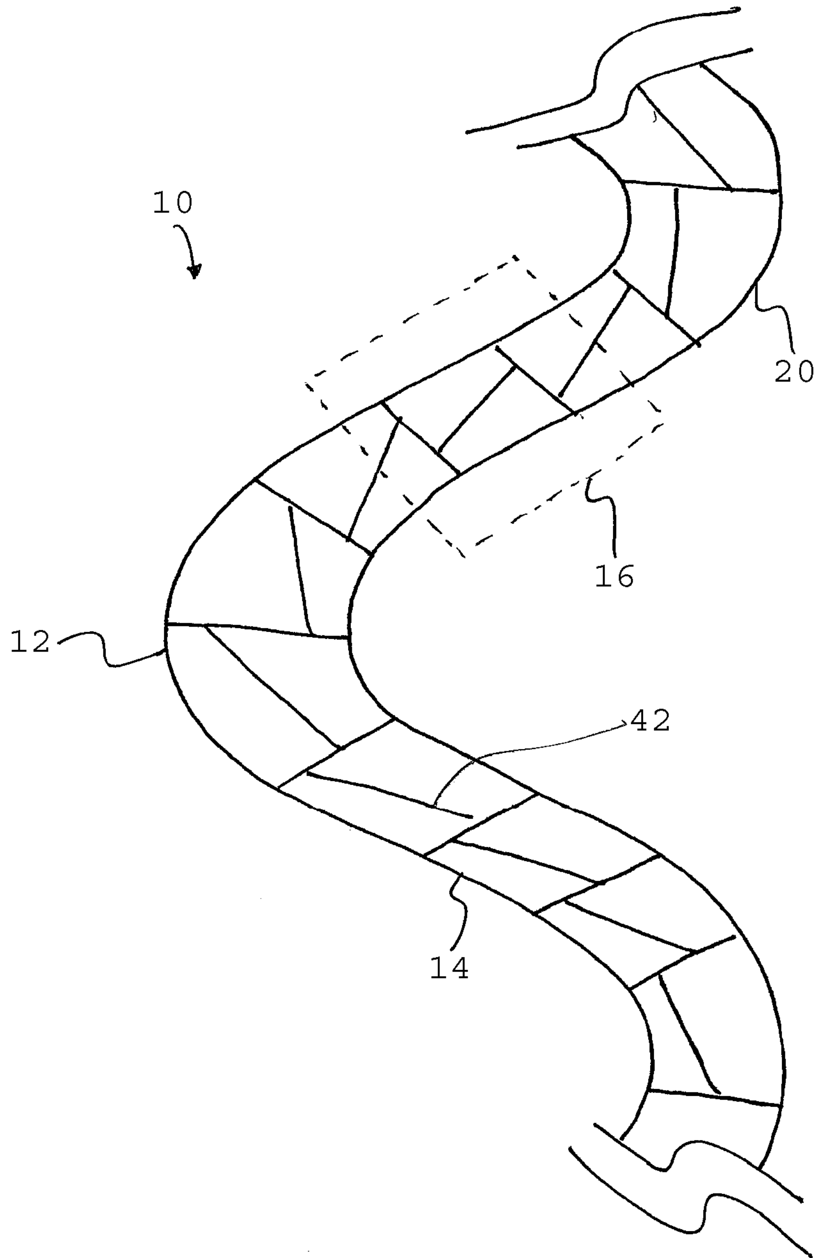

FIG. 1A

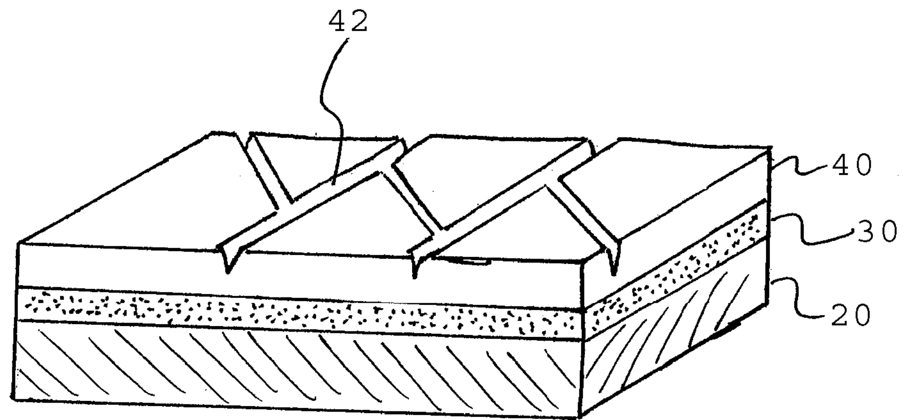

FIG. 1B

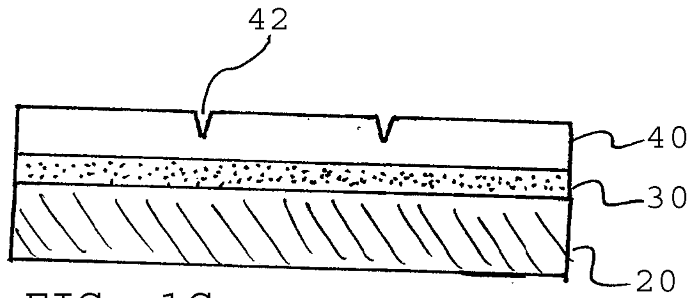

FIG. 1C

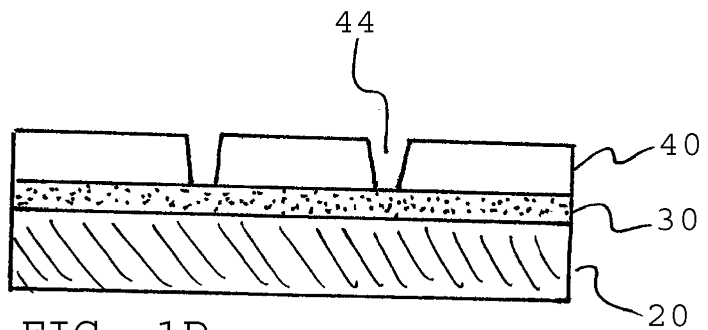

FIG. 1D

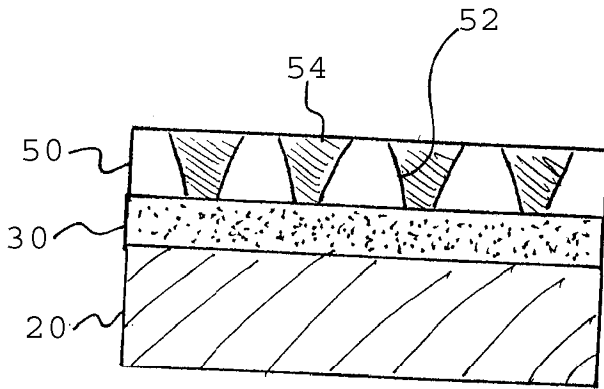

FIG. 2A

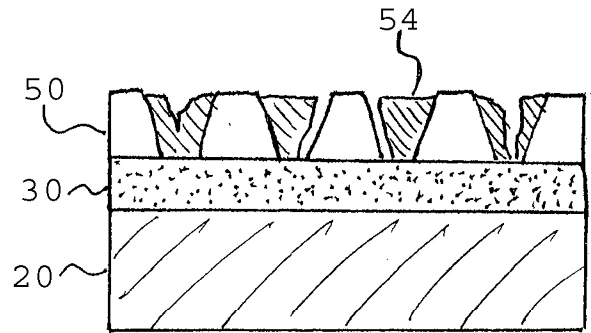

FIG. 2B

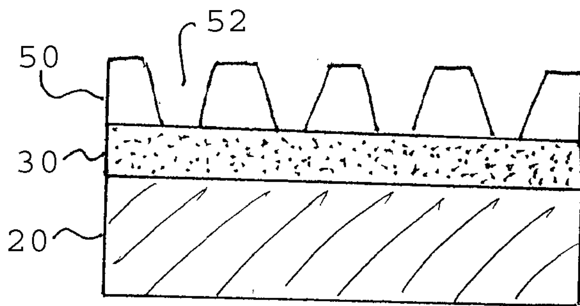

FIG. 2C

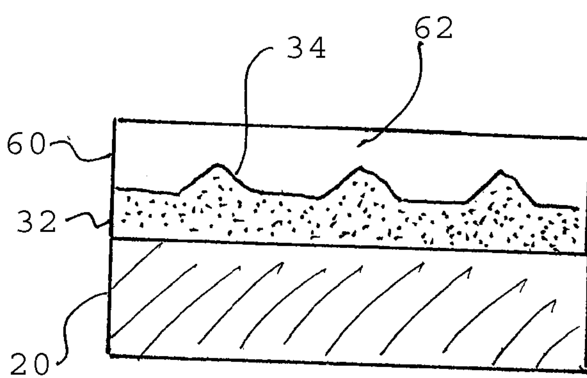

FIG. 3A

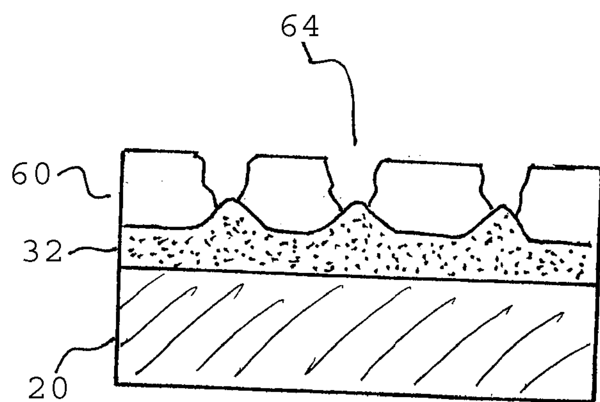

FIG. 3B

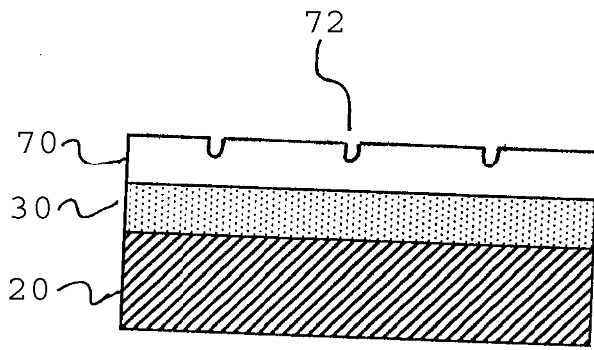

FIG. 4A

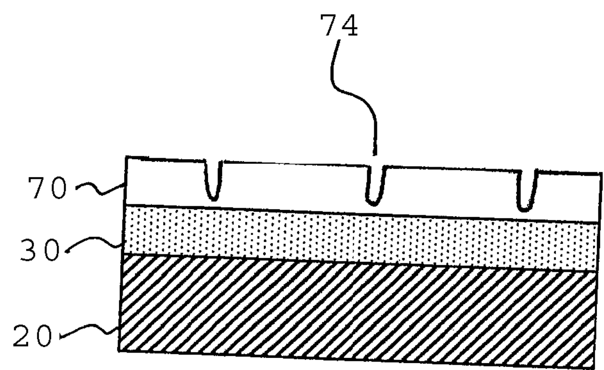

FIG. 4B

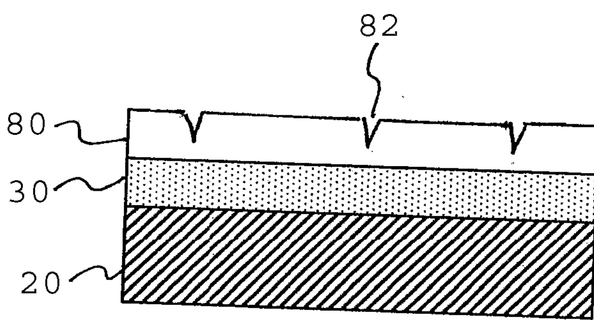

FIG. 5A

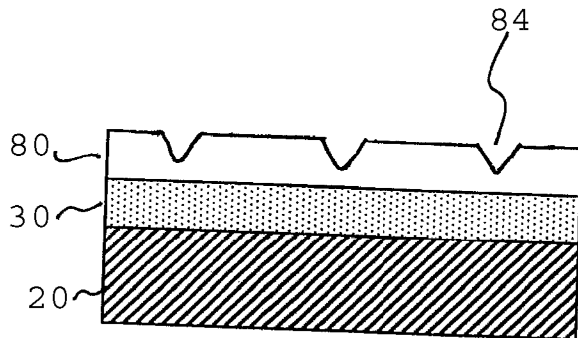

FIG. 5B

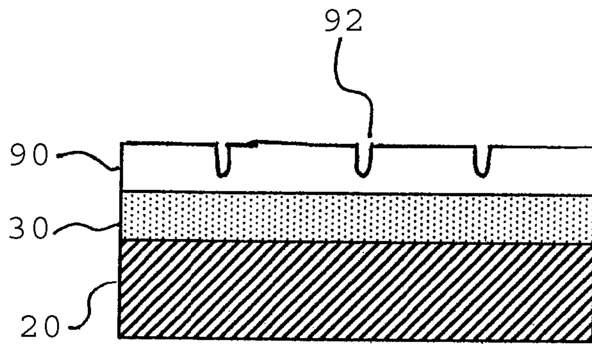

FIG. 6A

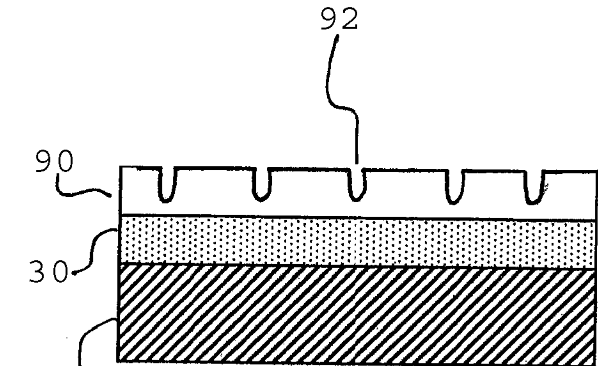

FIG. 6B

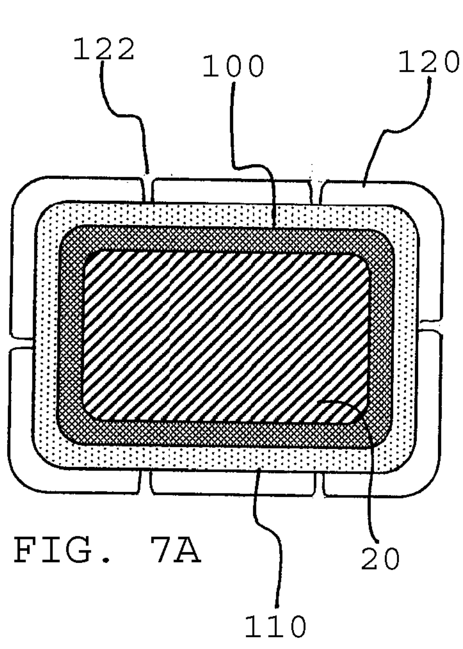

FIG. 7A

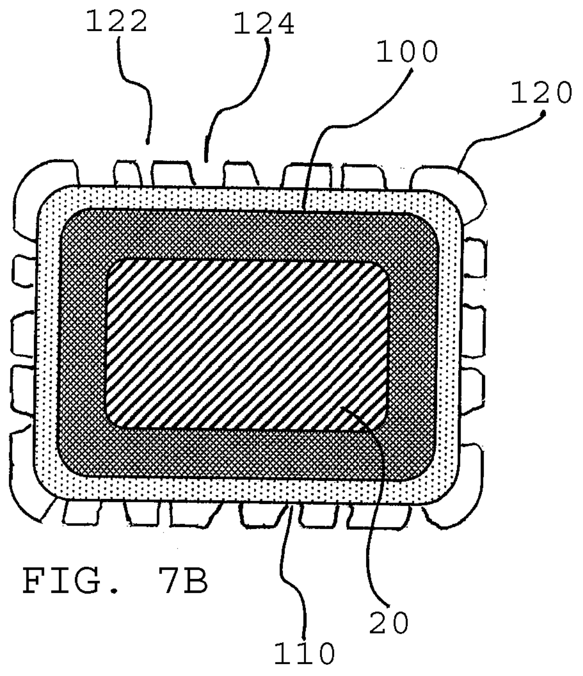

FIG. 7B

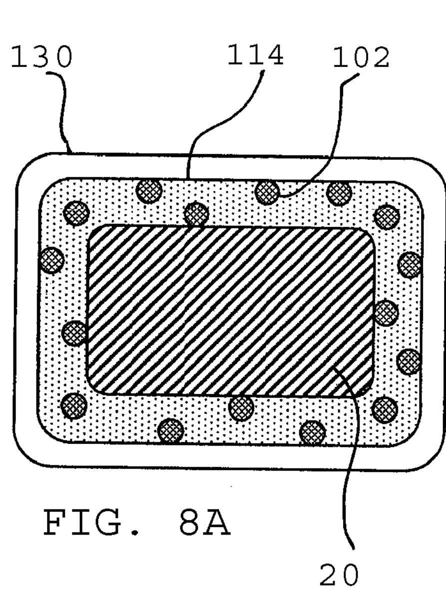

FIG. 8A

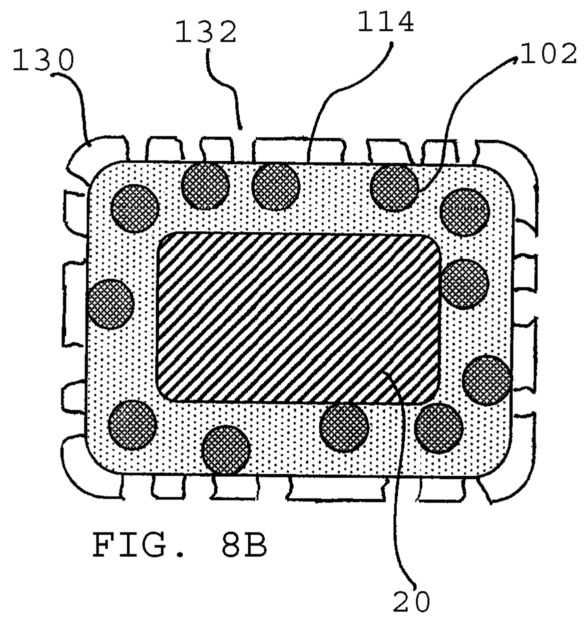

FIG. 8B

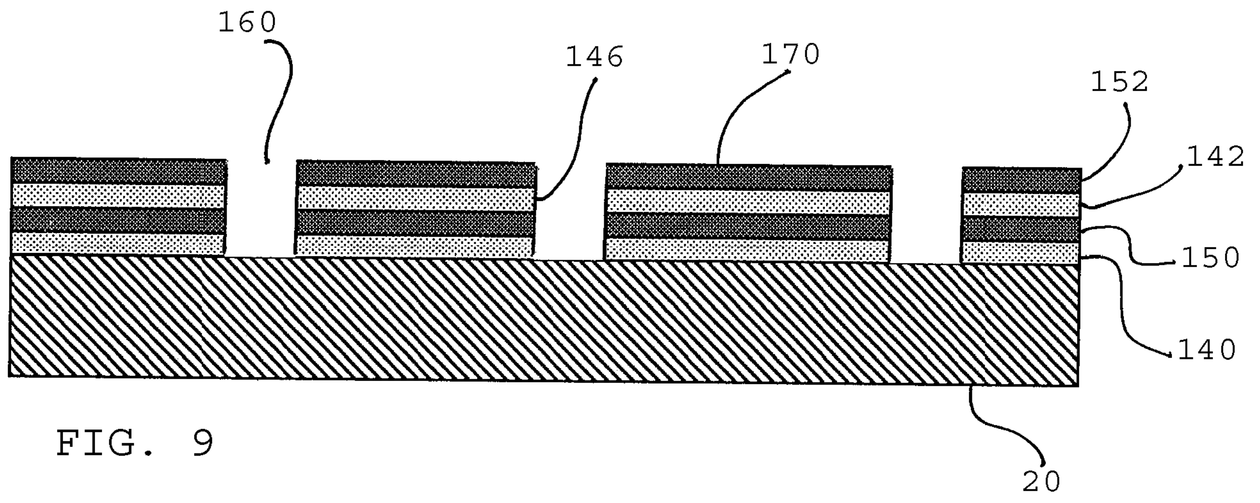

FIG. 9

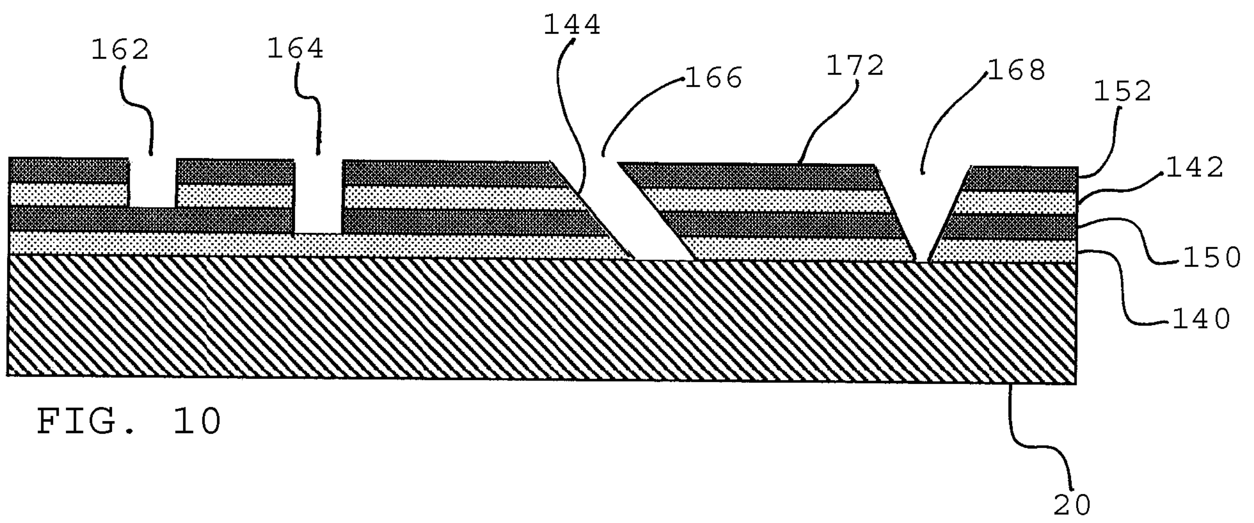

FIG. 10

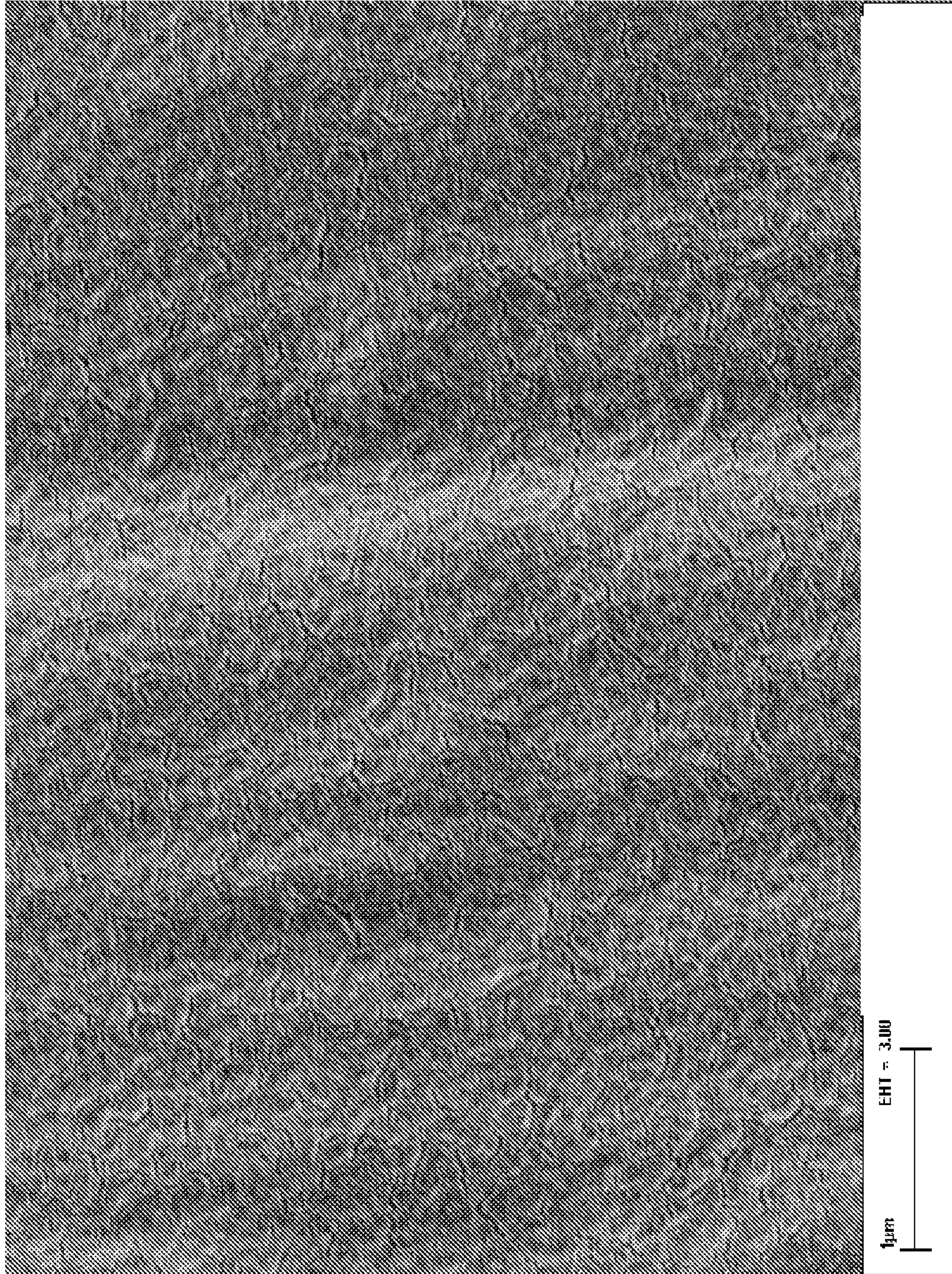

FIG. 11

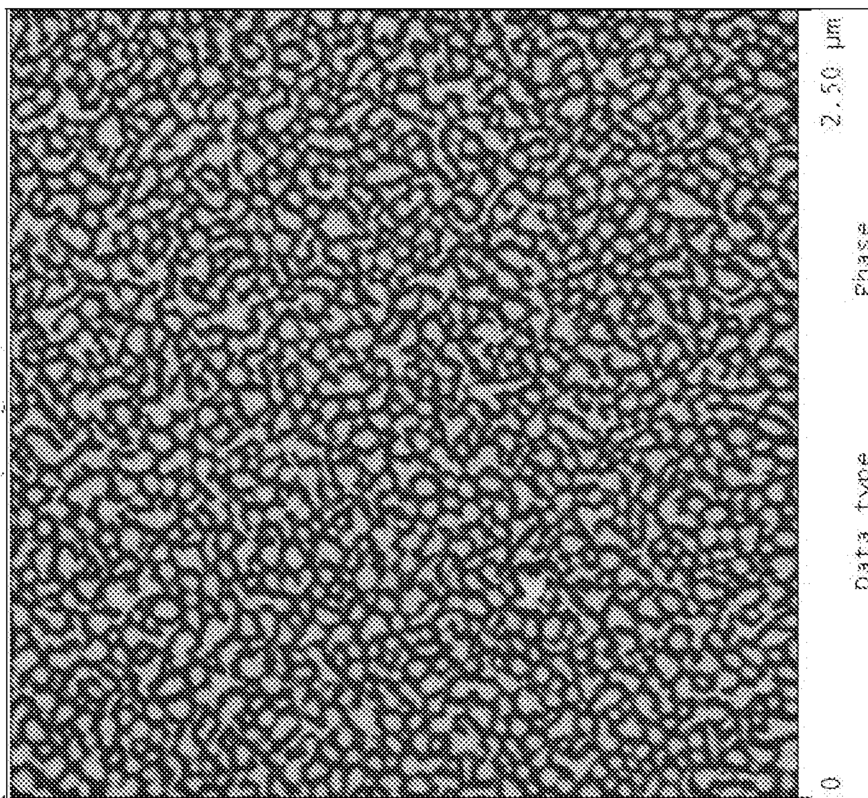

FIG. 12

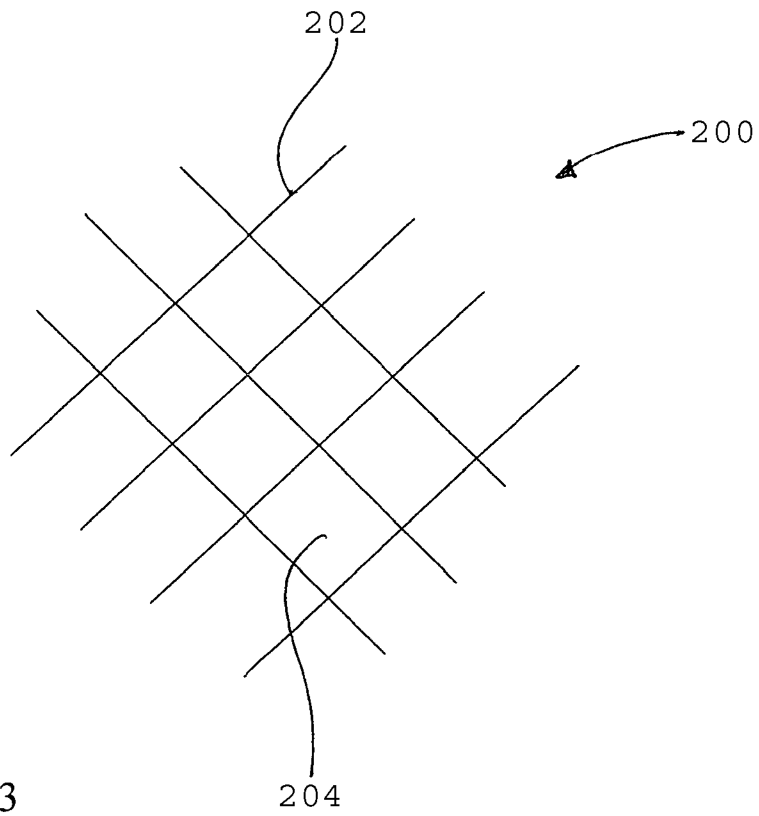

FIG. 13

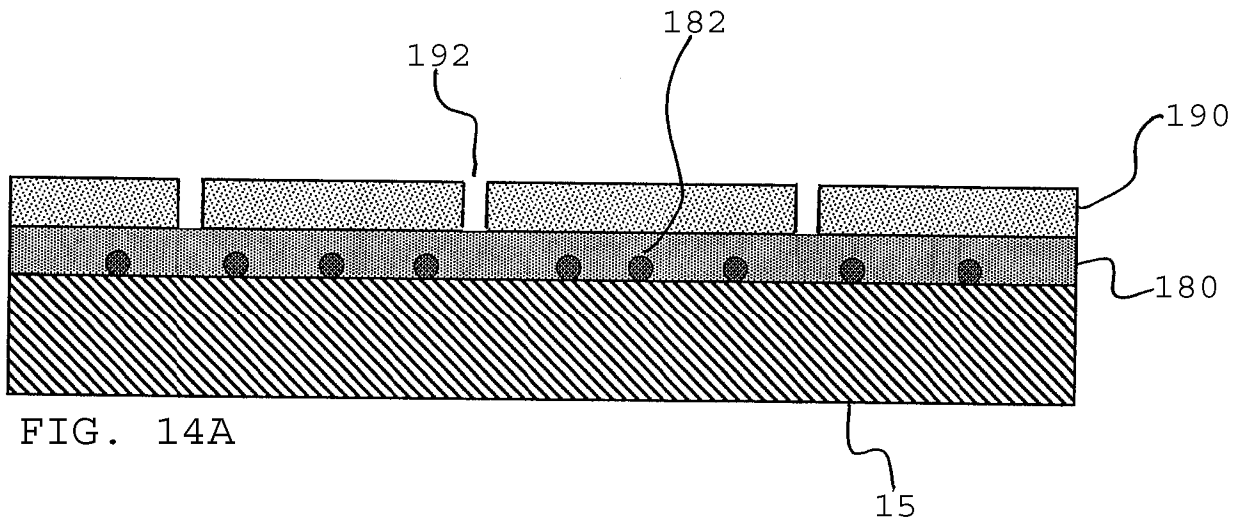

FIG. 14A

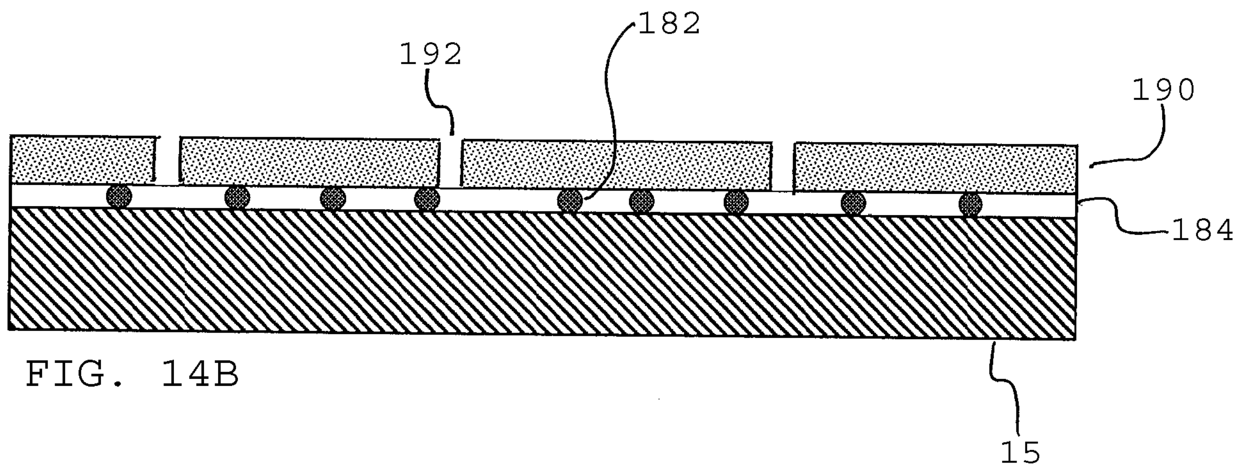

FIG. 14B

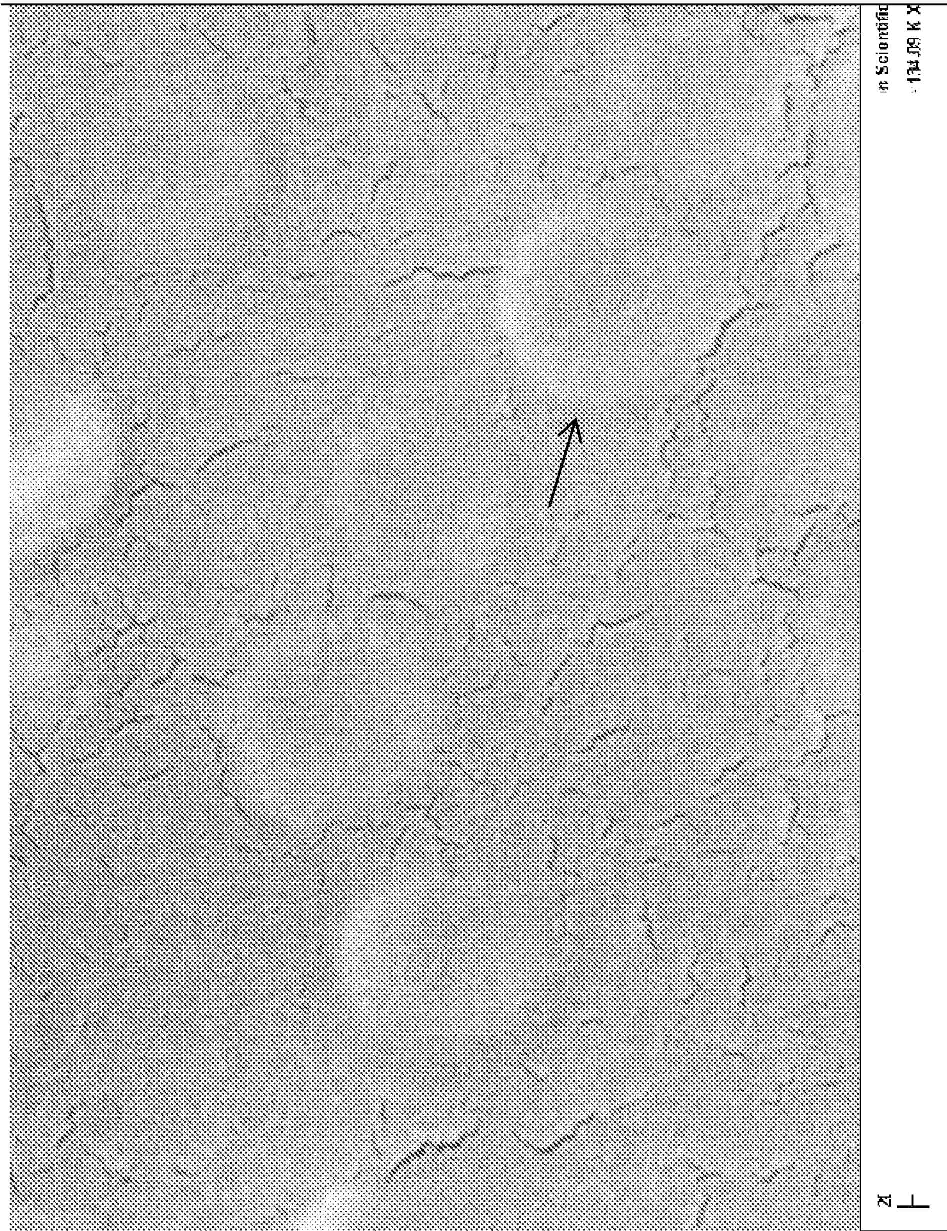

FIG. 15

FIG. 16