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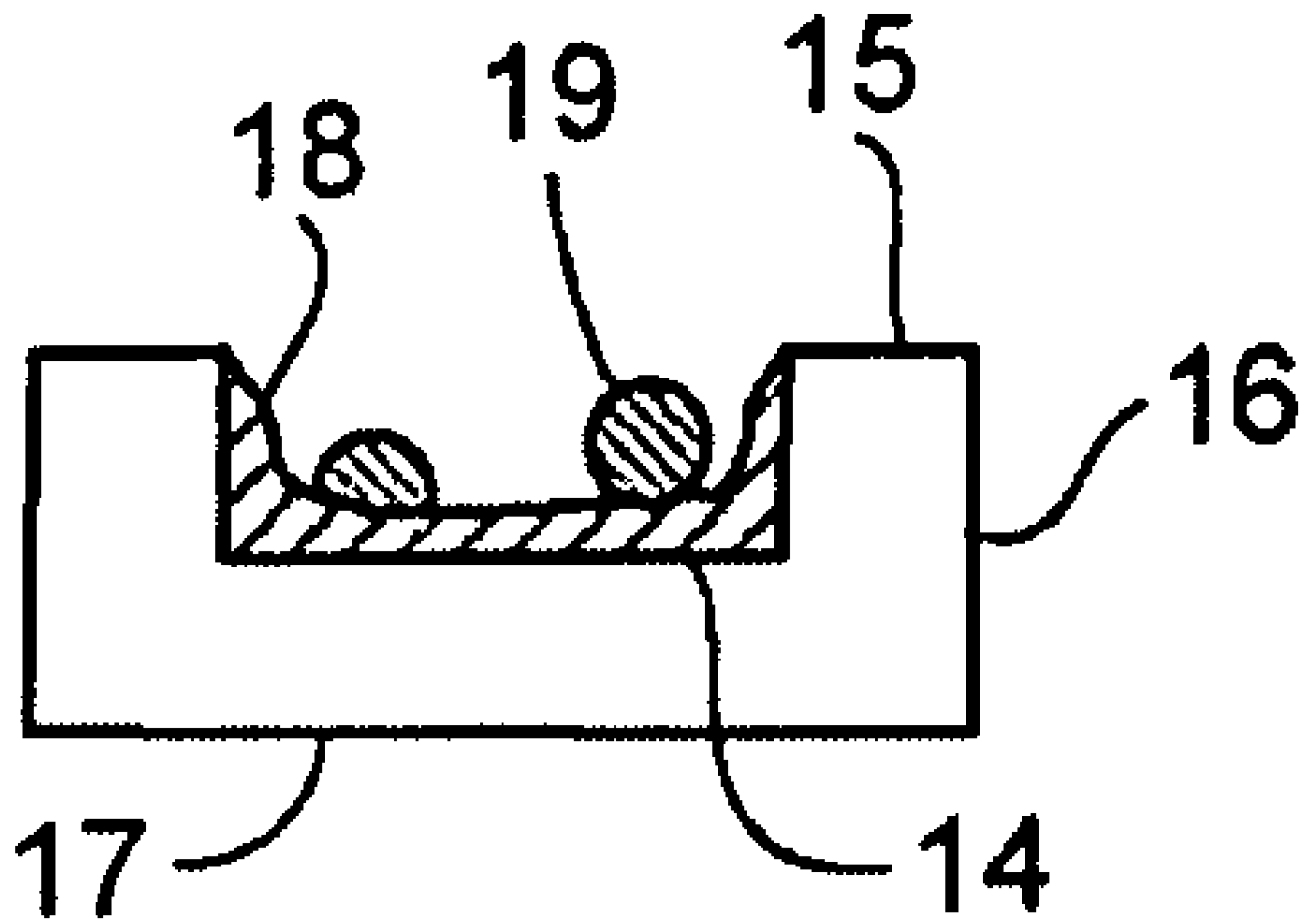

(57) Abrégé/Abstract:
Medical devices, such as endoprostheses, and methods of making the devices are described. In one embodiment, a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure is described. One or more wall surfaces of the tubular structure can bear a coating whose selected regions define at least one depression. The coating can further include at least one biologically active substance.

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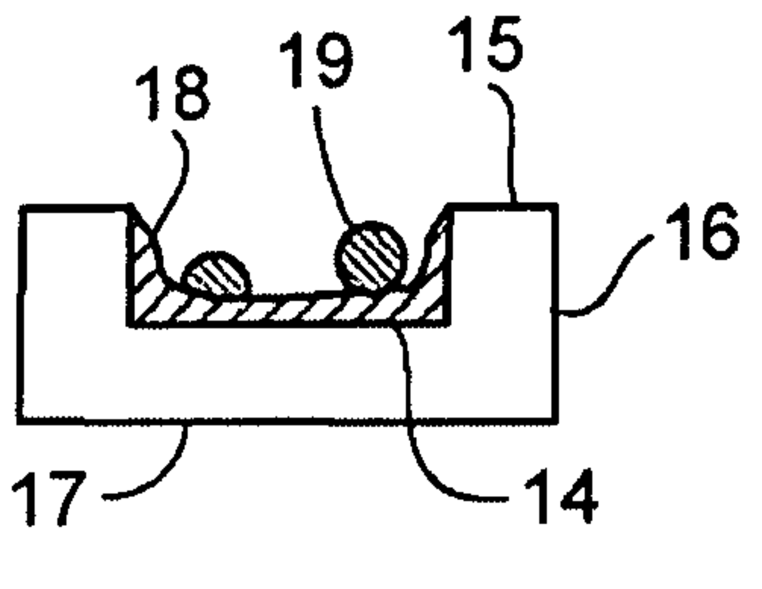


(57) **Abstract:** Medical devices, such as endoprostheses, and methods of making the devices are described. In one embodiment, a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure is described. One or more wall surfaces of the tubular structure can bear a coating whose selected regions define at least one depression. The coating can further include at least one biologically active substance.

MEDICAL DEVICES WITH DRUG-ELUTING COATING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 USC § 119(e) to U.S. Patent Application Serial No. 60/844,471, filed on September 14, 2006, the entire contents of which are hereby incorporated by reference.

TECHNICAL FIELD

This invention relates to medical devices, such as endoprostheses (e.g., stents).

BACKGROUND

The body defines various passageways such as arteries, other blood vessels, and other body lumens. These passageways sometimes become occluded or weakened. For example, the passageways can be occluded by a tumor, restricted by a plaque, or weakened by an aneurysm. When this occurs, the passageway can be reopened or reinforced, or even replaced, with a medical endoprosthesis. An endoprosthesis is typically a tubular member that is placed in a lumen in the body. Examples of endoprostheses include stents, covered stents, and stent-grafts.

Endoprostheses can be delivered inside the body by a catheter that supports the endoprosthesis in a compacted or reduced-size form as the endoprosthesis is transported to a desired site. Upon reaching the site, the endoprosthesis is expanded, for example, or allowed to expand, so that it can contact the walls of the lumen.

Endoprostheses can be coated with biocompatible materials and/or biologically active substances, including active pharmaceutical agents.

SUMMARY

This invention is based, in part, on the discovery that applying biologically active substances (e.g., drugs) to a depression defined in a surface of a medical device (e.g., a stent) protects the substances during delivery of the device into the body. During delivery, e.g., via a catheter, biologically active substances located within such depressions remain generally undisturbed and in place, while substances located on a generally flat surface of currently-available medical devices are exposed and thus subject to shear forces that can strip the substances off the surface. The depression or depressions can be coated with a component that promotes initial adherence and subsequent elution of the biologically active substance.

In one aspect, the disclosure features a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure, and wherein one or more wall surfaces of the tubular structure bears a coating whose selected regions define at least one depression.

Embodiments may include one or more of the following features.

The surface bearing the coating defining at least one depression can be the abluminal wall surface, the luminal wall surface, the side wall surface or a combination thereof.

The coating can include at least one biologically active substance, a polymer, e.g., a biodegradable polymer, a tie layer, e.g., a biodegradable tie layer, or a combination thereof. For example, the coating can include a layer of a first biologically active substance, and a layer of a polymer and a second biologically active substance (the first and second substances can be the same or different). The polymer can be biodegradable, exposing the first substance upon erosion. The polymer, e.g., a porous polymer, can allow the first substance to diffuse through and out of the polymer. The coating can also include a ceramic layer, e.g., silica. The ceramic layer can contain, e.g., titanium (+y) oxide (-x), e.g., titanium dioxide. The coating can include titanium (+y) oxide (-x), e.g., titanium dioxide. The coating can include regions of hydrophilic and/or hydrophobic titanium (+y) oxide (-x). For example, regions of the coating that define the depression can bear a coating of hydrophobic titanium (+y) oxide (-x), e.g., hydrophobic titanium dioxide, while regions of the coating that do not define the depression can bear a coating of hydrophilic titanium (+y) oxide (-x), e.g., hydrophilic titanium dioxide, e.g., superhydrophilic titanium dioxide. In another embodiment, regions of the coating that define the depression can bear a coating of hydrophilic titanium (+y) oxide (-x), e.g., hydrophilic titanium dioxide, e.g., superhydrophilic titanium dioxide, while regions of the coating that do not define the depression can bear a coating of hydrophobic titanium (+y) oxide (-x), e.g., hydrophobic titanium dioxide. The coating can also include titanium (+y) oxide (-x) generally in one state, either hydrophilic or hydrophobic. The coating can be as thick as the depression that the coating defines is deep. The coating can be thinner than the depth of the depression that the coating defines.

The depression can be configured to extend generally along the axis of the band or connector in which the depression is defined, e.g., to extend generally in a parallel orientation to the axis of the band or connector in which the depression is defined. The depression can be configured to extend generally in traverse orientation to the axis of the band or connector in which the depression is defined, e.g., generally in a perpendicular orientation to the axis of the band or connector in which the depression is defined. The coating can define multiple depressions. The width of the depression can constitute up to about 80% of the width of the band or the connector in which the depression is defined. The depth of the depression can constitute on average up to about 50% of the thickness of the band or the connector in which the depression is defined, but locally additional depressions can constitute up to about 90% of the thickness of the band or connector.

In another aspect, the disclosure features a method of producing a medical device that includes: (a) generating a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure, and wherein one or more wall surfaces define at least one depression; and (b) applying a coating upon one or more surfaces of the medical device.

Embodiments may include one or more of the following features.

The surface that defines at least one depression can be the abluminal wall surface, the luminal wall surface, the side wall surface or a combination thereof.

The depression can be generated by laser, e.g., by a laser ablation process and/or laser-assisted chemical etching. The depression can be generated by chemical etching. The depression can be machined or formed into the raw material of the medical device, e.g., a tube, before the interconnected bands and connectors are formed. The depression can be configured to extend generally along the axis of the band or connector in which the depression is defined, e.g., to extend generally in a parallel orientation to the axis of the band or connector in which the depression is defined. The depression can be configured to extend generally in traverse orientation to the axis of the band or connector in which the depression is defined, e.g., generally in a perpendicular orientation to the axis of the band or connector in which the depression is defined. The surface can define multiple depressions. The width of the depression can constitute up to about 80% of the width of the band or the connector in which the depression is defined. The depth of the depression can constitute on average up to about 50% of the thickness of the band or the connector in which the depression is defined, but locally additional depressions can constitute up to 90% of the thickness of the band or connector.

The coating of step (b) can be applied to the depression of the abluminal surface, the luminal surface, the side surface or a combination thereof. The coating of step (b) can be applied in multiple layers.

Applying of the coating of step (b) can be carried out by dipcoating, roll coating, MicroPen® application, electrospraying, gas-assisted spraying, electrospinning or a combination thereof. Applying the coating of step (b) can be carried out by rolling the medical device over the surface of a polymer tube comprising a biologically active substance to direct the polymer and the biologically active substance into the depressions of the medical device. Applying the coating of step (b) can be carried out by forcing a mixture of a biologically active substance and a polymer through a heated nozzle into the depression.

Step (b) can further include activating the surface of the depression by, e.g., plasma treatment, ultraviolet light activation, electrical charging of desired regions of the device and texturizing.

The coating applied in step (b) can include at least one biologically active substance, a polymer, e.g., a biodegradable polymer, a tie layer, e.g., a biodegradable tie layer, or a combination thereof. For example, a first layer of coating comprising a first biologically active substance can be applied, followed by application of a second layer of coating comprising a polymer and a second biologically active substance (the first and second substances can be the same or different). The polymer can be biodegradable, exposing the first substance upon erosion. The polymer, e.g., a porous polymer, can allow the first substance to diffuse through and out of the polymer. The coating applied in step (b) can include titanium (+y) oxide (-x), e.g., titanium dioxide, and step (b) can include exposing the medical device to conditions sufficient to cause desired regions of the surface bearing titanium (+y) oxide (-x) to become hydrophobic or hydrophilic. The desired regions can be surfaces, e.g., abluminal, luminal and/or side wall surfaces, defining the depression. The desired regions can be surfaces, e.g., abluminal, luminal and/or side wall surfaces, that do not define the depression. The coating can be applied at a thickness about equal to the depth of the depression to which the coating is applied, e.g., about 50% to about 90% of the thickness of the band or connector that defines the depression. The coating can be applied at a thickness of less than the depth of the depression to which the coating is applied.

Following step (b), the coating can be removed from desired regions of the device, e.g., from surfaces exterior to the depression. The removal process can include grinding off the coating. The removal process can include rinsing off the coating.

In another aspect, the disclosure features a method of producing a medical device, including: (a) generating a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure, and wherein one or more wall surfaces bear a coating defining at least one depression; and

(b) further applying at least one desired substance to the device.

Embodiments may include one or more of the following features.

The surface that bears the coating can be abluminal, luminal, side wall surface or a combination thereof.

The coating of step (a) can be applied by a sol-gel process. The process can include use of a nonsurfactant template, e.g., glucose or urea. The coating can include titanium (+y) oxide (-x), e.g., titanium dioxide. Between steps (a) and (b), the device can be exposed to conditions selected to cause the titanium (+y) oxide (-x) coating to become hydrophobic and/or hydrophilic, e.g., exposure to UV light (to cause the coating to become superhydrophilic) and/or long-term exposure to darkness (to cause the coating to become hydrophobic). The coating can define multiple depressions. The substance can be applied in step (b) preferentially to the depression. The substance applied in step (b) can be a biologically active substance. The substance applied in step (b) can be a polymer, e.g., a biodegradable polymer.

In another aspect, the disclosure features a method of producing a medical device, the method comprising: (a) generating a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure; (b) applying a first coating comprising a biologically active substance upon one or more surfaces of the medical device; and (c) applying a second coating to define at least one depression upon one or more surfaces of the medical device.

Embodiments can include one or more of the following features.

The first coating of step (b) can be applied to the abluminal wall surface, luminal wall surface, side wall surface or a combination thereof. The first coating can be applied by dipcoating, roll coating, MicroPen® application, electrospraying, gas-assisted spraying, electrospinning or a combination thereof. The first coating can include at least one biologically active substance, a polymer, e.g., a biodegradable polymer, a tie layer, e.g., a biodegradable tie layer, or a combination thereof.

The second coating of step (c) can be applied by a sol-gel method. The method can include using a nonsurfactant template, e.g., glucose or urea. The second coating can include titanium (+y) oxide (-x), e.g., titanium dioxide. Following application of the second coating comprising titanium (+y) oxide (-x), the device can be exposed to conditions selected to cause the titanium (+y) oxide (-x) coating to become hydrophobic and/or hydrophilic, e.g., exposure to UV light (to cause the coating to become superhydrophilic) and/or long-term exposure to darkness (to cause the coating to become hydrophobic). The second coating can be applied upon a region(s) of the medical device distinct from a region(s) upon which the first coating had been applied. The second coating can be applied upon the first coating, and the second coating can be configured to allow diffusion of the biological substance of the first coating through the second coating.

Between steps (a) and (b) the desired surface(s) of the medical device can be activated by, e.g., plasma treatment, ultraviolet light activation, electrical charging of desired regions of the device and texturizing. The activated surface(s) can include the abluminal wall surface, the luminal wall surface, the side wall surface or a combination thereof.

In another aspect, the disclosure features a medical device comprising a stent, having the form of an elongated tubular structure with an outer wall surface, side wall surface and an inner wall surface defining a central lumen or flow passageway, and one or more depressions defined by one or more surfaces of the stent containing a substance positioned, in use, for a delivery into a fluid flow passage of a living body.

The term "biologically active substance" as used herein refers to chemical compounds, therapeutic agents, drugs, pharmaceutical compositions and similar substances that exert biological effects.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Other features and advantages of the disclosure will be apparent from the following detailed description, and from the claims.

DESCRIPTION OF DRAWINGS

Fig. 1A is a perspective view of a stent. Fig. 1B is a top view of an embodiment of a section of a stent band. Fig. 1C is a cross-section of an embodiment of a stent band. Fig. 1D is a top view of an embodiment of a section of a stent band. Fig. 1E is a cross-section of an embodiment of a stent band. Fig. 1F is a top view of an embodiment of a section of a stent band. Fig. 1G is a cross-section of an embodiment of a stent band.

Fig. 2A is a perspective view of a stent. Fig. 2B is a top view of an embodiment of a section of a stent band. Fig. 2C is a cross section of an embodiment of stent band. Fig. 2D is a cross section of an embodiment of a stent band. Fig. 2E is a cross-section of an embodiment of a stent band.

Fig. 3 is a flow chart of an embodiment of a method of making a stent.

Fig. 4 is a flow chart of an embodiment of a method of making a stent.

Fig. 5 is a flow chart of an embodiment of a method of making a stent.

Fig. 6 is a flow chart of an embodiment of a method of making a stent.

Fig. 7 is a flow chart of an embodiment of a method of making a stent.

Fig. 8 is a scanning electron microscope image of a hollow ceramic sphere on top of steel.

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

Medical devices, such as endoprostheses or stents, often need to be delivered into a vessel of a living body with biologically active substances, e.g., drugs, that can subsequently be eluted from such devices. Medical devices are generally coated with such substances on their outer, or abluminal, surface. The substances can be embedded, e.g., in a soft, biodegradable, polymeric matrix coating. During delivery, e.g., via a catheter, however, the coating can be torn off due to shear forces. The coating can be stripped off as the stent is expelled from a catheter. For example, shear forces between a self-expanding stent and an enclosing delivery tube can cause damage to the coating of the stent, as the stent is being pushed outward, while the tube is being withdrawn, allowing the stent to expand. Coatings of balloon-expandable stents can also be damaged during passage of the devices through calcified lesions or through other devices used in stent procedures. Self-expanding and balloon-expandable stents are also prone to damage by shear forces generated as the stents expand and contact, e.g., walls of the target vessel. For example, expansion of a balloon-expandable stent inside a calcified lesion can damage stent coating. It would be advantageous to develop medical devices coated with biologically active substances that are protected during delivery of the device. This disclosure features such medical devices and methods of making such devices.

Fig. 1A shows stent 10 having a body of interconnected bands 12 and connectors 11 forming an elongated tubular structure. A top view of section 13 of one band 12 shown in Fig. 1B demonstrates that depression 14 extends generally along the axis of the band. Cross-section of section 13 taken along line B1-B1 is shown in Fig. 1C. The band has an abluminal (outer) wall surface 15, a side wall surface 16 and a luminal (inner) surface 17. Abluminal surface 15 bears a coating 18 defining depression 14. Coating 18 can include a polymer, e.g., a biodegradable polymer. The coating also includes a biologically active substance 19. Depression 14 can also extend generally along the axis of any of the connectors 11 (not shown). Depression 14 can extend generally in parallel to the axis of any of the bands 12 or connectors 11 (not shown). Fig. 1D and Fig. 1E show that multiple depressions 14 can be defined by coating 18 and extend generally along the axis of the band. Multiple depressions 14 can also extend generally in traverse, e.g., perpendicularly, to the axis of the band, as shown in Fig. 1F. The shape of the depression 14 can vary from the one shown in Fig. 1C and Fig. 1E. For example, the shape can include angles other than 90°, as shown in Fig. 1G, which is a cross section of band 12, taken along line B1-B1 of Fig. 1B. Undercutting sides of the depression shown in the embodiment of Fig. 1G, can further facilitate mechanical retention of the coating applied to the stent.

Depression 14 can constitute up to about 80% of the width of the band or the connector in which it is defined., The depth of depression 14 can constitute on average up to about 50% of the thickness of the band or the connector in which the depression is defined, but local depressions (analogous to potholes) can also constitute up to about 90% of the thickness of the band or connector.

Fig. 2A through Fig. 2E show that various regions of the stent can bear depressions and various types of coating. Fig. 2A shows stent 10 having a body of interconnected bands 12 and connectors 11 forming an elongated tubular structure. In one embodiment, shown in Fig. 2B, depression 14 extends generally along the axis of band 12. Fig. 2C (which is a cross section of band 12 taken along line B1-B1 of Fig. 2B) shows that in one embodiment, coating 18 of the abluminal surface 15 can include a region 20 that defines depression 14 and a region 21 that does not define the depression. The properties of the coating in these two regions can vary, e.g., region 20 can include hydrophilic coating, e.g., hydrophilic titanium (+y) oxide (-x), e.g., hydrophilic titanium dioxide, e.g., superhydrophilic titanium dioxide, while region 21 can include hydrophobic coating, e.g., hydrophobic titanium (+y) oxide (-x), e.g., hydrophobic titanium dioxide (or vice versa). Such properties allow these regions to further include biologically active substances with different characteristics, e.g., a hydrophilic substance 22 in region 20 and a hydrophobic substance 23 in region 21.

Referring to Fig. 2D, in another embodiment, abluminal wall surface 15 includes coating 18 that defines depression 14, while the luminal and side wall surfaces 17 and 16, respectively, include coating 18 that does not define a depression. Again, the properties of coating of the abluminal surface and of the luminal and side surfaces can vary. For example, the coating of the abluminal surface can be hydrophilic, e.g., hydrophilic titanium (+y) oxide (-x), e.g., hydrophilic titanium dioxide, e.g., superhydrophilic titanium dioxide, while the coating of the luminal and side surfaces can be hydrophobic, e.g., hydrophobic titanium (+y) oxide (-x), e.g., hydrophobic titanium dioxide (or vice versa). These properties allow for the coating of the abluminal surface to include biologically active substances, e.g., hydrophilic substances 22, with properties differing from the biologically active substances of the luminal and side surface coating, e.g., hydrophobic substances 23.

Referring to Fig. 2E, in yet another embodiment, the coating of both abluminal wall surface 15 and luminal surface 17 defines a depression. In another embodiment, the coating of side wall surface 16 can define a depression (not shown). The combinations of the regions of the coating that can define depressions are numerous. The combinations of the properties of various regions of the coating are also many.

As discussed above, coating 18 can include at least one releasable biologically active substance, e.g., a therapeutic agent, a drug, or a pharmaceutically active compound, such as described in U.S. Patent No. 5,674,242, U.S. Application No. 09/895,415, filed July 2, 2001, and U.S. Application No. 10/232,265, filed August 30, 2002. The therapeutic agents, drugs, or pharmaceutically active compounds can include, for example, anti-proliferative agents, anti-thrombogenic agents, antioxidants, antiinflammatory agents, immunosuppressive compounds, anesthetic agents, anti-coagulants, and antibiotics. Specific examples of such biomolecules include paclitaxel, sirolimus, everolimus, zotarolimus, picrolimus and dexamethasone. The coating can also include a polymer, e.g., a biodegradable polymer, that releases the biologically active substance as it degrades. Coating 18 can also include a tie layer that promotes its adhesion to the underlying stent 10. The tie layer can be biodegradable or non-biodegradable. Coating 18 can be a combination of biologically active substance(s), tie layer(s) and/or polymers. For example, the coating can include a layer of a first biologically active substance, and a layer of a polymer and a second biologically active substance (the first and second substances can be the same or different). The polymer can be biodegradable, exposing the first substance upon erosion. The polymer, e.g., a porous polymer, can allow the first substance to diffuse through and out of the polymer.

As discussed, coating 18 can include titanium (+y) oxide (-x) (Ti_xO_y), e.g., titanium dioxide (TiO_2). Titanium dioxide, also known as titanium (IV) oxide or titania is the naturally occurring oxide of titanium, chemical formula TiO_2. TiO_2 occurs in a number of forms: rutile, anatase, brookite, titanium dioxide (B) (monoclinic), titanium dioxide (II), and titanium dioxide (H). Carp *et al.*, *Prog. Solid State Chem.* 32:33-177, 2004. One interesting property of Ti_xO_y, e.g., TiO_2, is that it can be either hydrophobic or hydrophilic, e.g., superhydrophilic. Stents coated with Ti_xO_y and methods of coating stents with Ti_xO_y are described in the U.S. Patent Application No. 60/818,101, filed June 29, 2006, and U.S. Patent Application No. 11/763,770, filed on June 15, 2007. As described therein, coating stent 10 with various combination of hydrophobic and/or hydrophilic Ti_xO_y allows for placing various biologically active substances on selected regions of stent 10. The term "biomolecule" used in that application is equivalent to the term "biologically active substance" used herein.

Stent 10 can be used, e.g., delivered, using a catheter delivery system. Catheter systems are described, e.g., in Wang U.S. Patent No. 5,195,969, Hamlin U.S. Patent No. 5,270,086, and Raeder-Devens U.S. Patent No. 6,726,712. Stents and stent delivery are also exemplified by the Radius® or Symbiot® systems, available from Boston Scientific Scimed, Maple Grove, MN.

In use, stent 10, bearing at least one type of a biologically active substance, can deliver the substance to, e.g., a blood vessel. Biologically active substances can target various cells of the blood vessels, e.g., endothelial cells or smooth muscle cells. As discussed, currently available stents deliver biologically active substances, e.g., drugs, that are directly exposed to the delivery catheter and/or to the target vessel. During expulsion of the stent from the catheter, some of the biologically active substances and polymers that bear them can be torn off and thus lost before their delivery to a target. For example, shear forces between a self-expanding stent and an enclosing delivery tube can cause damage to the coating of the stent, as the stent is being pushed outward, while the tube is being withdrawn, allowing the stent to expand. Coating of balloon-expandable stents can also be damaged during passage of the devices through calcified lesions or through other devices used in stent procedures. Self-expanding and balloon-expandable stents are also prone to damage by shear forces generated as the stents expand and contact, e.g., walls of the target vessel. For example, expansion of a balloon-expandable stent inside a calcified lesion can damage stent coating.

The medical devices described herein, e.g., stents, protect biologically active substances, which are located in depressions defined by the coating of the stents. These protected substances are delivered to their targets and allowed to gradually elute from the stents, e.g., as the polymer portion of the coating biodegrades. Because the devices described herein can minimize loss of biologically active substances, relatively lower amounts of the substances need to be provided in the stent coating, and the coating itself can be thinner than currently used coatings. For example, some currently-used coatings are about 10 μm thick and loaded with about 8.8% by weight paclitaxel. Such coatings release only about 10% of available paclitaxel. The stents described herein can include coating as thin as 3 μm, containing biodegradable polymers, and having up to a 100% release rate of a biologically active substance, as such coating is now protected during delivery.

Stent 10 can be made by a variety of methods, e.g., by laser ablation process, laser-assisted chemical etching, or chemical etching. An example of one method is outlined in Fig. 3. In method 30, a medical device, e.g., stent 10 having a body of interconnected bands 12 and connectors 11 forming an elongated tubular structure, is generated (step 31). The stent has an inner luminal wall surface 17, a side wall surface 16 and an outer abluminal surface 15, as described above, e.g., in Fig. 1C. At least one depression 14 is generated in one or more of the surfaces of the stent (step 32). The depression can be generated by laser, e.g., ultra-short pulsed laser, e.g., a laser system delivering femtosecond pulses in the ultraviolet range (about 248 nm), e.g., short-pulse dye excimer hybrid laser delivering about 500-fs pulses at 248 nm. Bekesi *et al.*, *Appl. Phys. A* 76:355-57, 2003. The depression can also be generated by a UV laser, e.g., 248 nm or 193 nm laser, having pulse length in the nanosecond range. The depression can be generated with an ultra-short laser having pulse length of sub pico, femto, or even attosecond length, operating at various wavelengths, e.g., visible, infrared, or near infrared. The depression can be generated by, e.g., laser ablation process, laser-assisted chemical etching, or chemical etching. For example, femtosecond lasers that can be used with the featured stents and methods are available from Del Mar Photonics, see, e.g., http://www.femtosecondsystems.com/products/category.php/1/.

In one embodiment, multiple depressions 14 can be generated in any band or connector of stent 10. The depression or depressions can be configured to extend generally along the axis of any band or connector in which the depression(s) is defined, e.g., generally in a parallel orientation to the axis. The depression or depressions can also be configured to extend generally in a traverse orientation, e.g., generally perpendicularly, to the axis of the band or connector in which the depression(s) is defined. The depression can be further undercut or etched, generating angles other than 90°, as shown in Fig. 1G. Undercutting the depressions in such configurations can facilitate mechanical retention of coating applied to the depressions. The depression(s) can constitute up to about 80% of the width of the band or connected in which the depression(s) is defined The depth of the depression(s) can constitute on average up to about 50% of the thickness of the band or connector in which the depression(s) is defined, but local depressions (analogous to potholes) can constitute up to about 90% of the thickness of the band or connector.

Further referring to Fig. 3, after generating at least one depression, in some embodiments, the surface of the depression can be activated (step 33). The surface can be activated by, e.g., plasma treatment, texturizing and/or electrical charging the desired regions of the device. A coating including at least one desired substance is then applied to the stent (step 34). Activation of the surface in step 33 can increase adhesion of the coating in step 34. Applying the coating can be carried out by dipcoating, roll coating, MicroPen® application, electrospraying, gas-assisted spraying, electrospinning or a combination thereof. An example of applying a coating to a stent by electrospraying is described in, e.g., Weber *et al.* U.S. Pat. No. 6,861,088. Applying the coating can also be carried out by rolling the stent over a surface of a polymer tube that contains a biologically active substance. Such rolling directs or pushes the polymer and the substance into the depression(s) of the stent. The coating can also be applied by generating a rod of a polymer and a biologically active substance, e.g., a drug, which is inserted into a delivery device with a heated nozzle. The heated nozzle can be guided over the depressions and can melt the polymer/drug mixture as it expels and deposits the mixture into the depressions.

After the coating is applied in step 34, it may be localized to the surfaces inside the depression(s) and to the surfaces outside the depression(s). In one embodiment, it may be desirable to remove the coating from the surfaces outside the depression, leaving the coating mainly inside the depression (step 35). Removal of the coating from desired regions can be accomplished by grinding it off the desired surfaces or rinsing it off the desired surfaces.

The coating applied in step 34 can include Ti_xO_y, e.g., TiO_2. Following application of Ti_xO_y coating, the medical device, e.g., a stent, can be exposed to conditions sufficient to cause desired regions of the device bearing Ti_xO_y coating to become hydrophilic or hydrophobic. See, e.g., U.S. Application No. 60/818,101, filed June 29, 2006, and U.S. Patent Application No. 11,763,770, filed June 15, 2007. The desired regions can include a surface that defines a depression, e.g., an abluminal, luminal and/or side wall surface that defines a depression. The desired regions can include a surface that does not define a depressions, e.g., an abluminal, luminal and/or side wall surface that does not define a depression.

The coating applied in step 34 can include at least one biologically active substance and/or a polymer. The biologically active substance can be hydrophobic or hydrophilic and preferentially bind to a hydrophobic or a hydrophilic coating, e.g., Ti_xO_y

coating described above. The coating can also include a tie layer to bind the coating to the underlying stent surface. The coating can include a combination of biologically active substance(s), polymers, and/or tie layer(s). For example, a coating of a first biologically active substance can be applied, followed by application of another layer of coating comprising a polymer and a second biologically active substance (the first and second substances can be the same or different). The polymer can be biodegradable, exposing the first substance upon erosion. The polymer, e.g., a porous polymer, can allow the first substance to diffuse through and out of the polymer.

Another example of generating the medical device is presented in Fig. 4. In method 40, raw material for a medical device is formed (step 41). The raw material can be, e.g., a tube. In step 42, at least one depression 14 is machined or formed into the desired region(s) of the raw material. In step 43, a stent is generated by, e.g., forming a pattern of bands and connectors into the raw material. The bands and connector define at least one depression 14. Steps 44-46 are analogous to steps 33-35 of Fig. 3 described above. Briefly, in step 44, the surface of the depression(s) can be, optionally, activated. The stent is coated in at least one desired substance (step 45). The coating can be, optionally, removed from desired region(s) of the stent (step 46).

Yet another example of generating the medical device is presented in Fig. 5. In method 50, a medical device, e.g., stent 10, is generated (step 51). Next, an *in situ* sol-gel process within a polyelectrolyte coating template is used to generate a coating upon the desired surface(s) of the stent (step 52). The coating is a ceramic coating bearing at least one depression, and preferably multiple depressions. The coating can be generated on abluminal, luminal and/or side wall surfaces of the device. The initial layer-by layer (LBL) self assembly polyelectrolyte coating can utilize various organic polyelectrolyte materials, e.g., polyacrylic acid (PAA), polycyclic aromatic hydrocarbons (PAH), polyethylene imide (PEI) and polystyrene sulfonate (PSS), deposited in a layer-by-layer method. In one embodiment, PEI is used as a first layer, followed by PAA/PAH or PSS/PAH layers. Macrosized polyelectrolyte materials, e.g., polystyrene, can be deposited in round ball-like structures or as fibers within this LBL structure. After the LBL coating has been deposited on the stent surface (or just within the depression) an *in-situ* sol-gel reaction is performed. The inorganic precursor in the process can be titanium-based, e.g., titanium (IV) bis(ammonium lactate) dihydroxide (TALH) or titanium (IV) butoxide ($Ti(OBu)_4$). Titanium oxide-based surfaces promote endothelial cell adhesion, which, in turn, may prevent thrombogenicity of stents delivered to blood vessels. Chen *et al.*, *Surf. Coat. Tech.* 186:270-76, 2004. Within the *in-situ* sol-gel reaction, the precursor is mixed with an organic solvent , i.e. ethanol, and the sol-gel precursor therefore only hydrolizes within the polyelectrolyte layers by the presence of entrapped water molecules from previous steps. After the *in situ* sol-gel reaction, the organic template (polyelectrolyte materials) is removed by calcination at a high temperature. Removal of the organic template leaves depressions or pores in the overall structure where the organic template had been. In general, sol-gel-derived ceramic porous layers are generated with use of a surfactant (polymer) as a template, which needs to be removed at high temperatures. *See, e.g.,* Cernigoj *et al.*, Thin Solid Films 495:327-332, 2006. To avoid the use of high temperatures, in method 50, a nonsurfactant, e.g., glucose or urea, can be used to generate the ceramic layer. Zheng *et al.*, J. Sol-Gel Science and Tech. 24:81-88, 2002. Glucose or urea can be removed with use of water at room temperature and leave behind a pure porous layer, e.g., nanoporous Titania layer. Changing template contents can generate materials with different pore sizes, thus allowing generation of a required drug release profile. For example, urea leaves larger pores than glucose. Because many nonsurfactants are biocompatible, they can also be allowed to remain in the sol-gel layer until they bioerode in the body after delivery of the stent.

Examples of sol-gel process are provided, e.g., in Maehara *et al.*, *Thin Solid Films* 438-39:65-69, 2003; Kim *et al.*, *Thin Solid Films* 499:83-89, 2003; and Bu *et al.*, *J. Europ. Cer. Soc.* 25:673-79, 2005. To obtain selective coating, e.g., coating of the abluminal surface only, instead of using a layer-by-layer process within a solution, alternative layers of cationic and anionic molecules are micro-contact printed on the desired surface of the stent. One embodiment of depositing ceramic coating with depressions is described in an Example below.

Further referring to Fig. 5, the device is next coated in at least one desired substance (step 53). The substance can adhere to the depressions generated by the sol-gel process and be protected during delivery of the device, e.g., via a catheter. The substance is a biologically active substance and, optionally, includes a polymer. The substance can adhere to the surface of the depressions.

Another example of generating a medical device is depicted in Fig. 6. In method 60, a stent is generated (step 61). Desired surface(s) of the stent can be optionally activated (step 62), as described above. Desired surface(s) of the stent can then be coated with desired substances, e.g., drugs and/or polymers as described *supra* (step 63). Hard walls can be deposited on at least one side of coated region(s), thereby generating depressions (step 64). The walls can be deposited by, e.g., a sol-gel process, e.g., by drawing a line on a desired surface(s), annealing and heat-treating to create hard walls. Steps 63 and 64 can be carried out simultaneously as one step. Alternatively, depressions can be generated in step 64 by applying a top layer of sol-gel derived, porous ceramic layer, e.g., nanonporous Titania or silica-Titania layer, onto the coating of step 63. As discussed *supra*, sol-gel-derived ceramic porous layers are often generated with use of a surfactant (polymer), which needs to be removed at high temperatures. *See, e.g.*, Cernigoj *et al.* To avoid damaging the underlying biologically active substance, in method 60, a non-surfactant, e.g., glucose or urea, can be used to generate the ceramic layer. Zheng *et al.* Glucose or urea can be removed with use of water at room temperature and leave behind a pure porous layer, e.g., nanoporous Titania layer. The underlying biologically active substance can then diffuse through the top ceramic layer. The size of the pores in the ceramic layer can be adjusted (by changing template contents) to generate a required drug release profile. For example, urea leaves larger pores than glucose. In addition, because many nonsurfactants are biocompatible, they can also be allowed to remain in the sol-gel layer until they bioerode in the body after delivery of the stent.

Stent 10 can include (e.g., be manufactured from) metallic materials, such as stainless steel (e.g., 316L, BioDur® 108 (UNS S29108), and 304L stainless steel, and an alloy including stainless steel and 5-60% by weight of one or more radiopaque elements (e.g., Pt, Ir, Au, W) (PERSS®) as described in US-2003-0018380-A1, US-2002-0144757-A1, and US-2003-0077200-A1), Nitinol (a nickel-titanium alloy), cobalt alloys such as Elgiloy, L605 alloys, MP35N, titanium, titanium alloys (e.g., Ti-6Al-4V, Ti-50Ta, Ti-10Ir), platinum, platinum alloys, niobium, niobium alloys (e.g., Nb-1Zr) Co-

28Cr-6Mo, tantalum, and tantalum alloys. Other examples of materials are described in commonly assigned U.S. Application No. 10/672,891, filed September 26, 2003; and U.S. Application No. 11/035,316, filed January 3, 2005. Other materials include elastic biocompatible metal such as a superelastic or pseudo-elastic metal alloy, as described, for example, in Schetsky, L. McDonald, "Shape Memory Alloys", Encyclopedia of Chemical Technology (3rd ed.), John Wiley & Sons, 1982, vol. 20. pp. 726-736; and commonly assigned U.S. Application No. 10/346,487, filed January 17, 2003.

In some embodiments, materials for manufacturing stent 10 include one or more materials that enhance visibility by MRI. Examples of MRI materials include non-ferrous metals (e.g., copper, silver, platinum, titanium, niobium, or gold) and non-ferrous metal-alloys containing superparamagnetic elements (e.g., dysprosium or gadolinium) such as terbium-dysprosium, dysprosium, and gadolinium. Alternatively or additionally, stent 10 can include one or more materials having low magnetic susceptibility to reduce magnetic susceptibility artifacts, which during imaging can interfere with imaging of tissue, e.g., adjacent to and/or surrounding the stent. Low magnetic susceptibility materials include those described above, such as tantalum, platinum, titanium, niobium, copper, and alloys containing these elements.

Stent 10 can be of a desired shape and size (e.g., coronary stents, aortic stents, peripheral vascular stents, gastrointestinal stents, urology stents, tracheal/bronchial stents, and neurology stents). Depending on the application, stent 10 can have a diameter of between, e.g., about 1 mm to about 46 mm. In certain embodiments, a coronary stent can have an expanded diameter of from about 2 mm to about 6 mm. In some embodiments, a peripheral stent can have an expanded diameter of from about 4 mm to about 24 mm. In certain embodiments, a gastrointestinal and/or urology stent can have an expanded diameter of from about 6 mm to about 30 mm. In some embodiments, a neurology stent can have an expanded diameter of from about 1 mm to about 12 mm. An abdominal aortic aneurysm (AAA) stent and a thoracic aortic aneurysm (TAA) stent can have a diameter from about 20 mm to about 46 mm. Stent 10 can be balloon-expandable, self-expandable, or a combination of both (e.g., U.S. Patent No. 5,366,504).

While a number of embodiments have been described above, the invention is not so limited.

For example, Fig. 7 depicts another method that can be utilized to generate a medical device. In method 70, a stent is generated (step 71). Next, hard walls are formed on the desired surface(s) of the stent, thereby generating depressions (step 72). The hard walls can be formed by, e.g., a sol-gel process, e.g., by drawing a line on a desired surface(s), annealing and heat-treating to create hard walls. The desired surface(s) of the stent can be optionally activated, as described above (step 73). Desired regions(s) of the stent, e.g., regions between the generated walls, can then be coated with desired substance(s), e.g., drugs and/or polymers as described above. Optionally, the coating can be removed from the desired region(s) of the stent (step 74).

In addition, various combinations of coating techniques can be used to generate medical devices whose surfaces define at least one depression. In one embodiment, stent 10 can first be coated in a desired non-conductive ceramic layer of a substance, e.g., Ti_xO_y, e.g., TiO_2. The coating can be carried out by a sol-gel process or conventional plasma immersion process. At least one depression can then be created by an ablating laser, e.g., femtosecond laser, in desired surfaces of the stent, exposing the underlying metal stent. In this embodiment, the metal regions of the stent define at least one depression. The resulting metal regions can then be charged and electrosprayed with desired substances, see, e.g., Weber *et al.*, U.S. Pat. No. 6,861,088.

Example. Generation of Hollow Ceramic Capsules on Stainless Steel

As Fig. 8 shows, hollow ceramic (silica) capsules were generated on stainless steel. Anionic and cationic layers of poly-styrene-sulfonate (PSS) and poly-ethylene-imine (PEI), respectively, along with 1000 nanometer polystyrene balls (obtained from Microparticles \ Forschungs- und Entwicklungslaboratorium, Volmerstr. 9A, UTZ, Geb.3.5.1, D-12489 Berlin) were deposited using a layer-by-layer process. Next, an *in situ* reaction of a sol-gel solution was carried out in pure ethanol with 15% water in the layers of tetraethyl orthosilicate (TEOS). The polyelectrolyte layers attract water because of their ionic charge, and their water content increases above 15%, thus activating the sol-gel reaction. This method is very controlled and stops automatically once the layers are saturated and charge density decreases. There is a direct correlation between the amount of polyelectrolyte layers and the depth of the final sol-gel layer. After the sol-gel layer was generated, the sol-gel and polystyrene construction was calcinated at 600°C. An example of the resulting 50 nm diameter hollow ceramic (silica) capsule is show in Fig. 8.

A number of embodiments have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the disclosure. Accordingly, other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure, and wherein one or more wall surfaces of the tubular structure bears a coating whose selected regions define at least one depression.

2. The medical device of claim 1, wherein the abluminal wall surface bears the coating defining at least one depression.

3. The medical device of claim 1, wherein the coating comprises at least one biologically active substance.

4. The medical device of claim 3, wherein the coating further comprises a polymer.

5. The medical device of claim 1, wherein the coating comprises a tie layer.

6. The medical device of claim 1, wherein the coating comprises a ceramic layer.

7. The medical device of claim 1, wherein the coating comprises titanium (+y) oxide (-x).

8. The medical device of claim 1, wherein the depression is configured to extend generally along the axis of the band or connector in which the depression is defined.

9. The medical device of claim 1, wherein the depression is configured to extend generally in a traverse orientation to the axis of the band or connector in which the depression is defined.

10. The medical device of claim 1 comprising multiple depressions defined in the selected regions of the coating of one or more wall surfaces.

11. The medical device of claim 1, wherein the width of the depression constitutes up to about 80% of the width of the band or the connector in which the depression is defined.

12. The medical device of claim 1, wherein the depth of the depression constitutes up to about 50% of the thickness of the band or the connector in which the depression is defined.

13. A method of producing a medical device, the method comprising:

(a) generating a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure, and wherein one or more wall surfaces define at least one depression; and

(b) applying a coating upon one or more surfaces of the medical device.

14. The method of claim 13, wherein the abluminal surface defines at least one depression.

15. The method of claim 14, comprising, in step (b), applying the coating to the depression of the abluminal surface.

16. The method of claim 13, comprising applying the coating of step (b) by a process selected from an array consisting of dipcoating, roll coating, MicroPen® application, electrospraying, gas-assisted spraying, and electrospinning, or a combination thereof.

17. The method of claim 13, comprising applying the coating of step (b) by rolling the medical device over the surface of a polymer tube comprising a biologically active substance to direct the polymer and the biologically active substance into the depressions of the medical device.

18. The method of claim 13, wherein step (b) further comprises activating the surface of the depression.

19. The method of claim 18, wherein the activating process is selected from the group consisting of plasma treatment, ultraviolet light activation, electrical charging of desired regions of the device and texturizing, or a combination thereof.

20. The method of claim 13, wherein the coating applied in step (b) comprises a biologically active substance.

21. The method of claim 20, wherein the coating further comprises a polymer.

22. The method of claim 13, wherein the coating applied in step (b) comprises a tie layer.

23. The method of claim 13, wherein the coating applied in step (b) comprises titanium (+y) oxide (-x).

24. The method of claim 23, wherein step (b) further comprises exposing the medical device to conditions sufficient to cause desired regions of the surface bearing titanium (+y) oxide (-x) to become hydrophobic.

25. The method of claim 23, wherein step (b) further comprises exposing the medical device to conditions sufficient to cause desired regions of the surface bearing titanium (+y) oxide (-x) to become hydrophilic.

26. The method of claim 13, comprising, following step (b), removing the coating from desired regions of the device.

27. The method of claim 26, wherein the desired regions are surfaces outside the depression.

28. The method of claim 13, comprising, in step (a), generating the depression by laser.

29. A method of producing a medical device, the method comprising:

(a) generating a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure, and wherein one or more wall surfaces bear a coating defining at least one depression; and

(b) further applying at least one desired substance to the device.

30. The method of claim 29, wherein the abluminal wall surface bears the coating.

31. The method of claim 29, comprising applying the coating of step (a) by a sol-gel process.

32. The method of claim 31, wherein the coating comprises titanium (+y) oxide (-x).

33. The method of claim 29, wherein the coating defines multiple depressions.

34. A method of producing a medical device, the method comprising:

(a) generating a medical device having a body of interconnected bands and connectors forming an elongated tubular structure having an inner luminal wall surface, an outer abluminal wall surface and a side wall surface, and defining a central lumen or passageway, wherein said inner luminal wall surface and side wall surface of the bands and connectors form transverse passageways through the elongated tubular structure;

(b) applying a first coating comprising a biologically active substance upon one or more surfaces of the medical device; and

(c) applying a second coating to define at least one depression upon one or more surfaces of the medical device.

35. The method of claim 34, comprising applying the second coating by a sol-gel method.

36. The method of claim 35, wherein the second coating comprises titanium (+y) oxide (-x).

37. A medical device comprising a stent, having the form of an elongated tubular structure with an outer wall surface, side wall surface and an inner wall surface defining a central lumen or flow passageway, and one or more depressions defined by one or more surfaces of the stent containing a substance positioned, in use, for a delivery into a fluid flow passage of a living body.

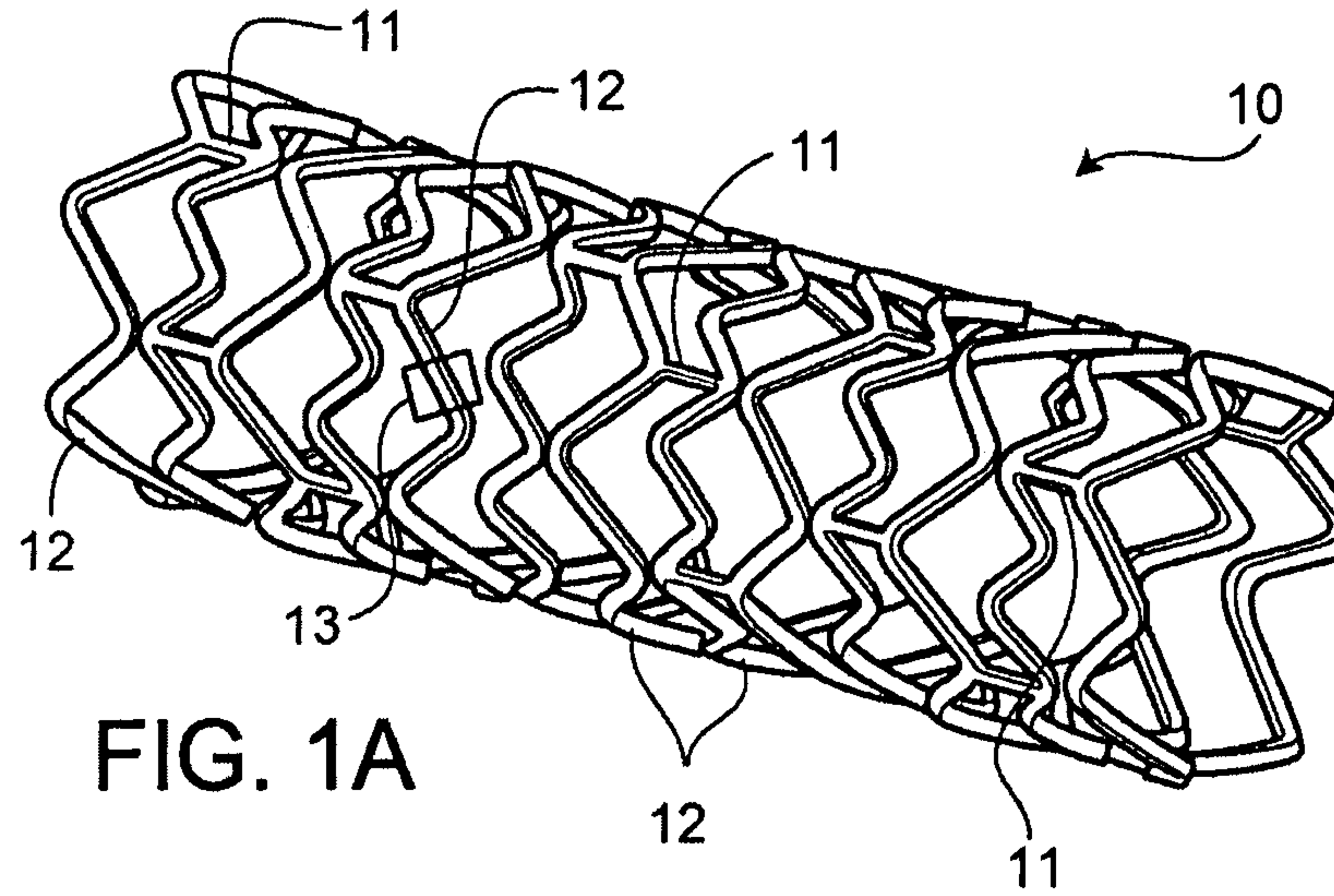


FIG. 1A

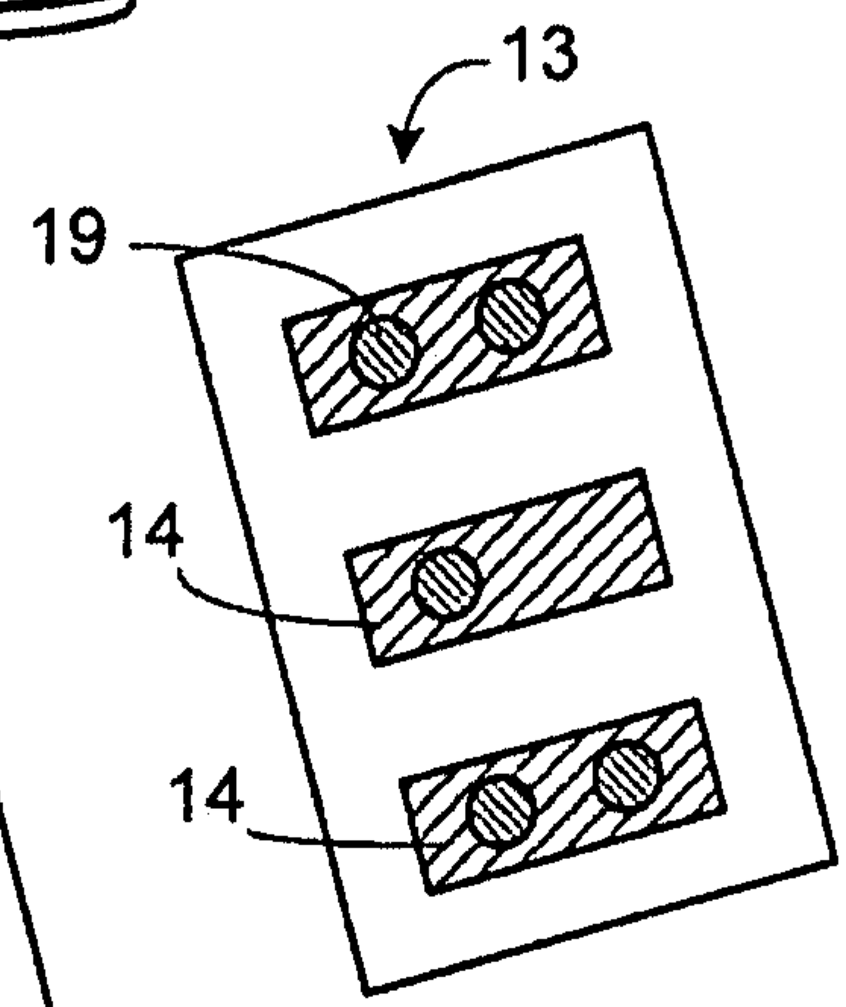


FIG. 1F

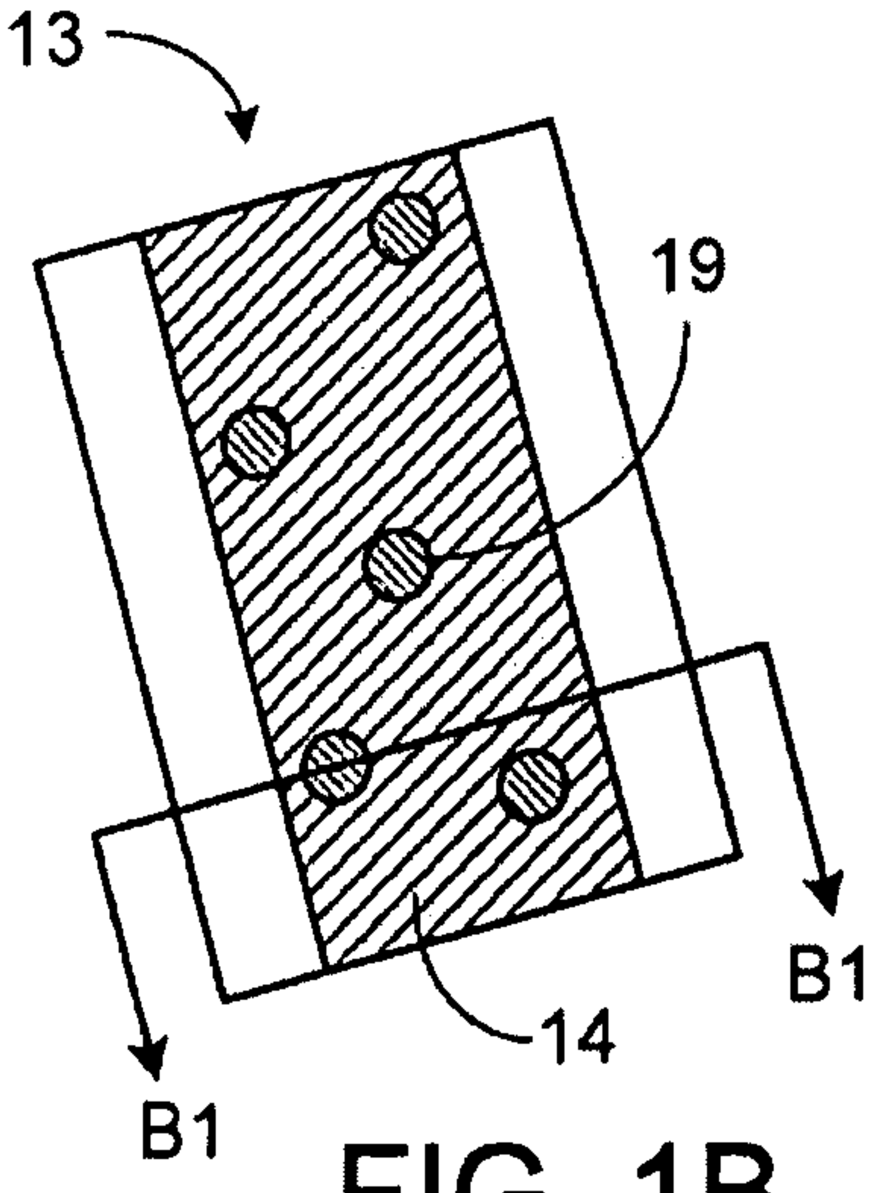


FIG. 1B

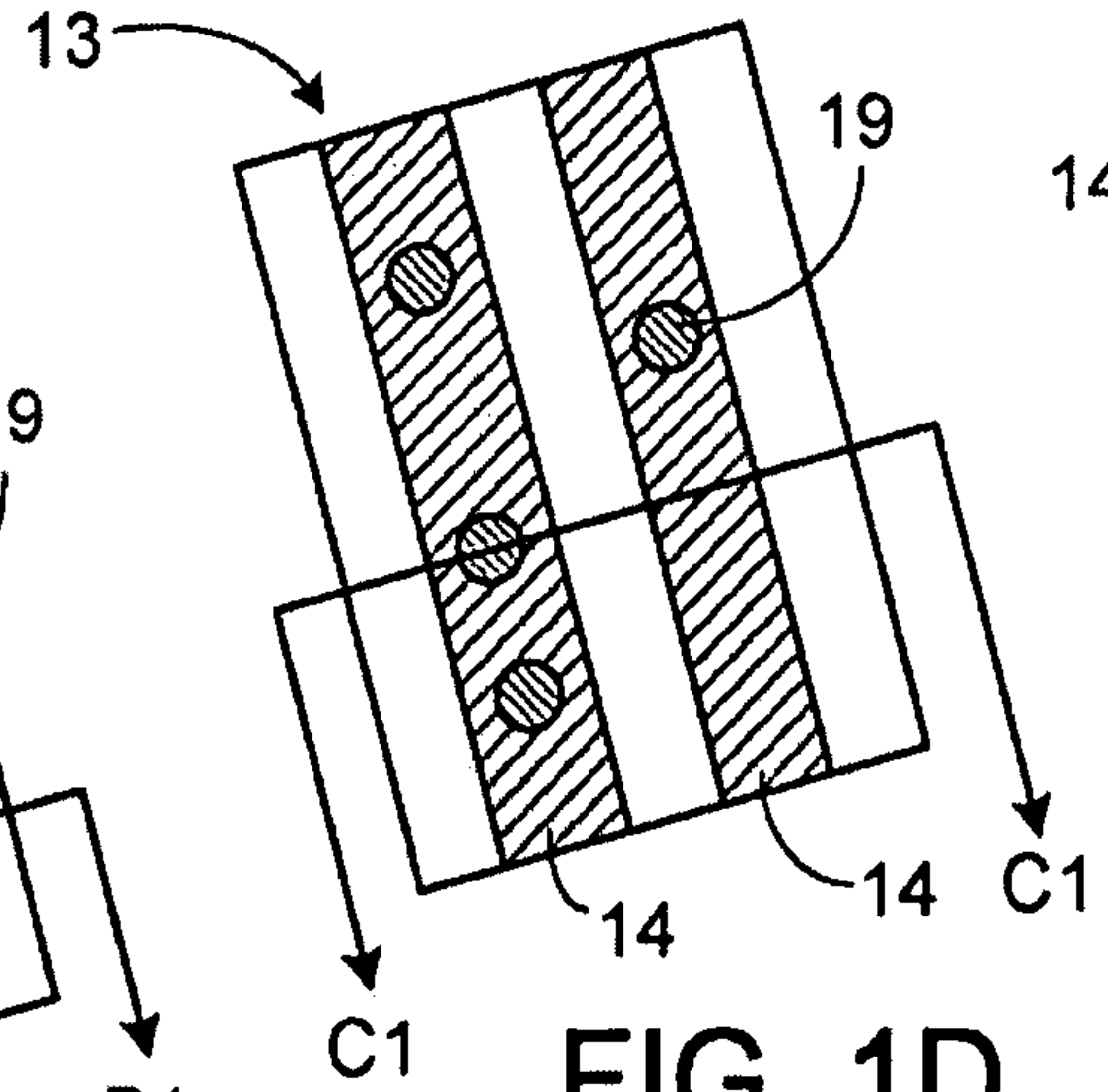


FIG. 1D

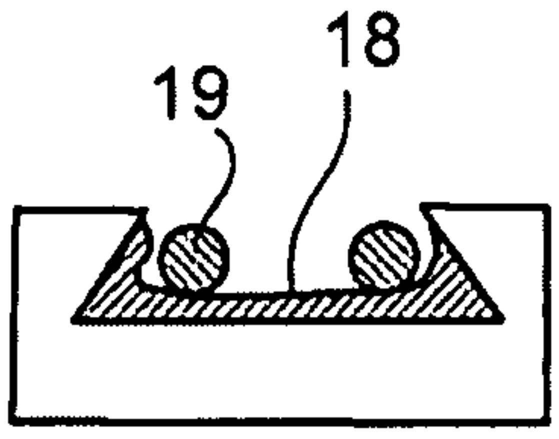


FIG. 1G

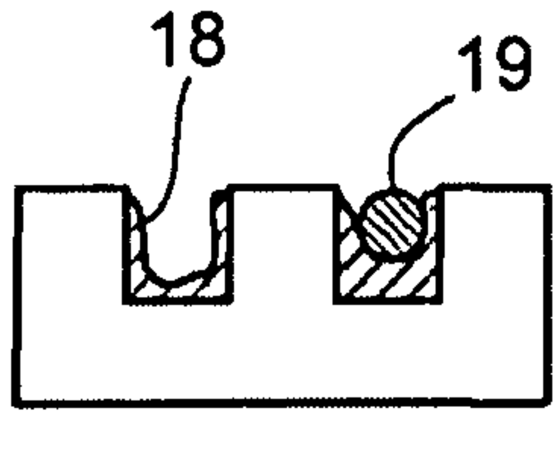


FIG. 1E

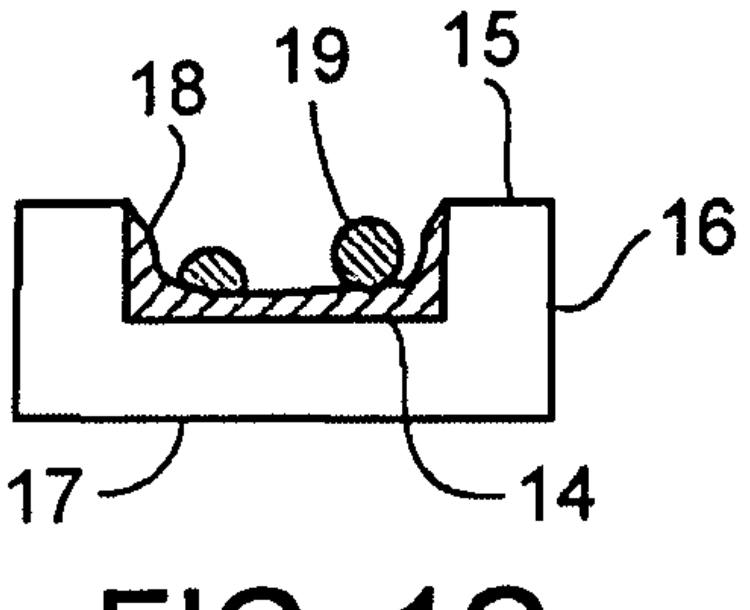


FIG. 1C

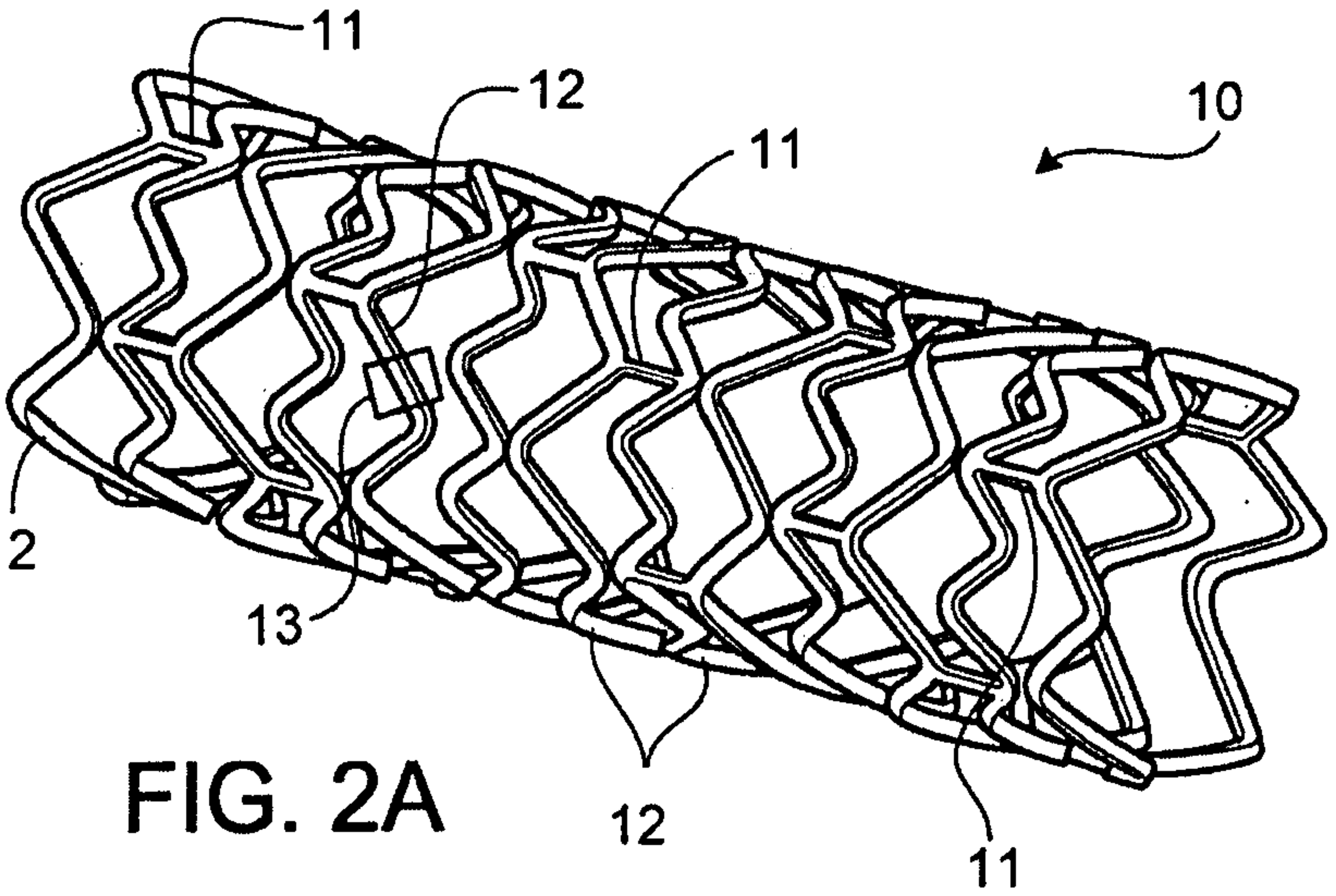


FIG. 2A

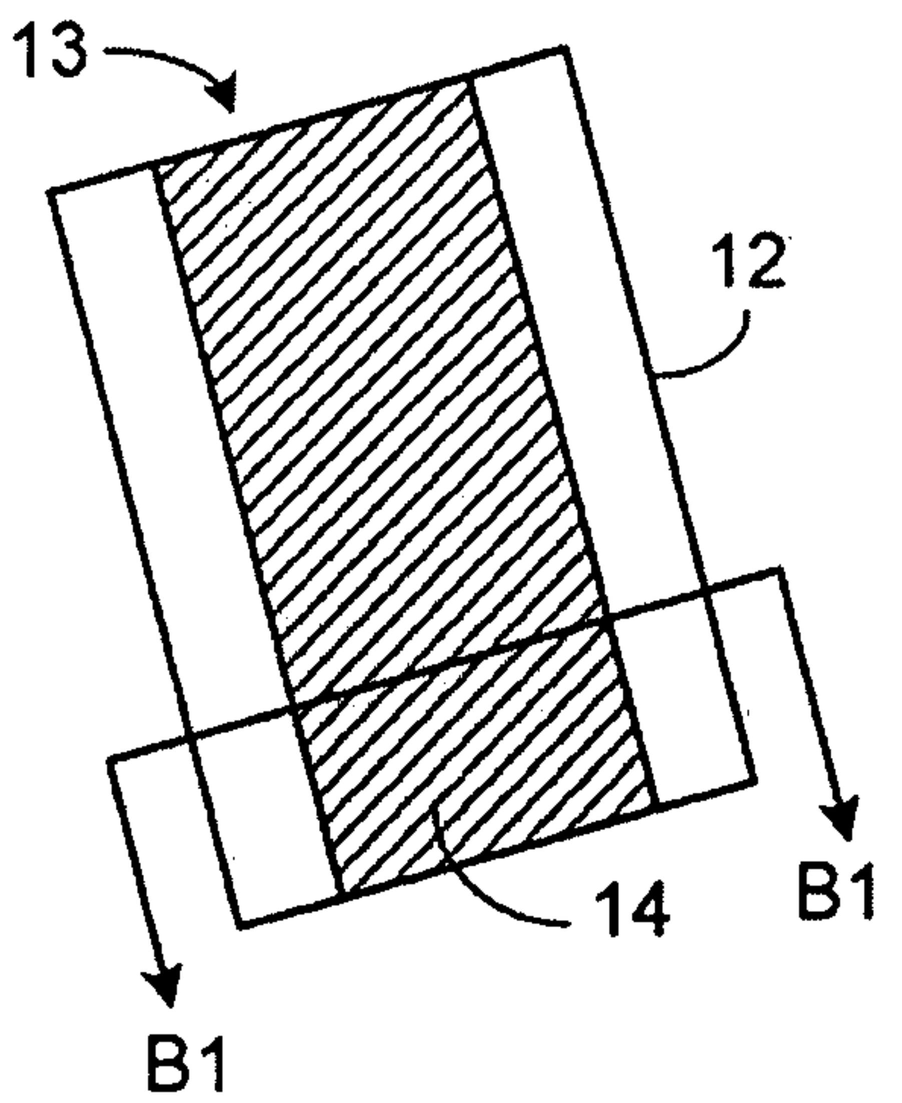


FIG. 2B

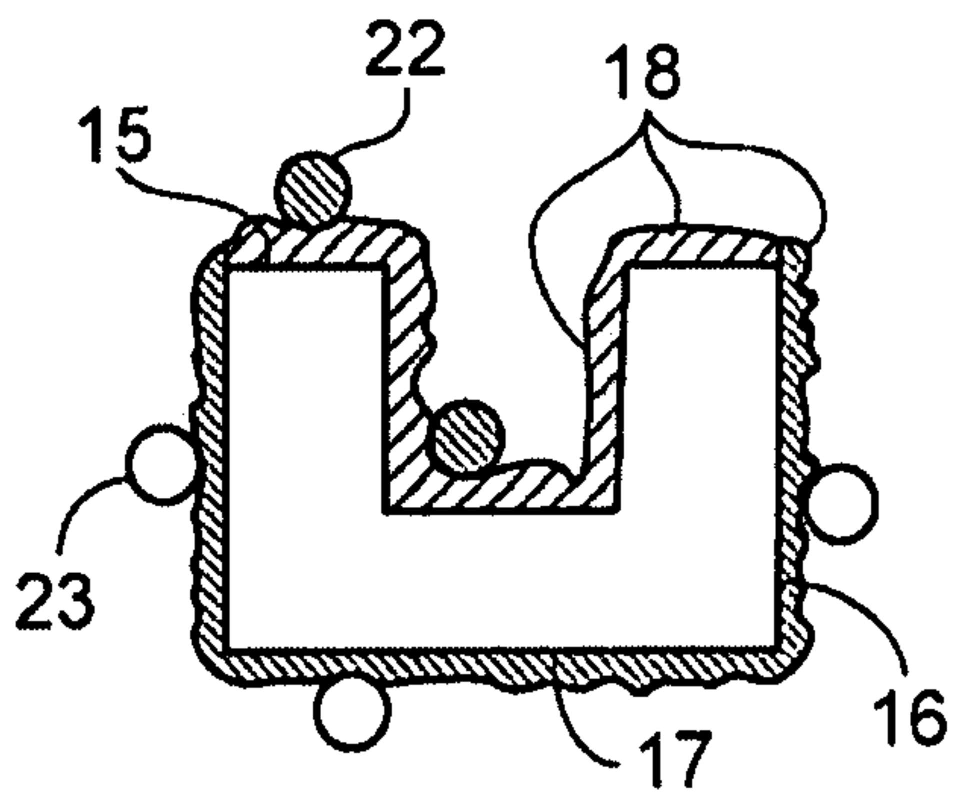


FIG. 2D

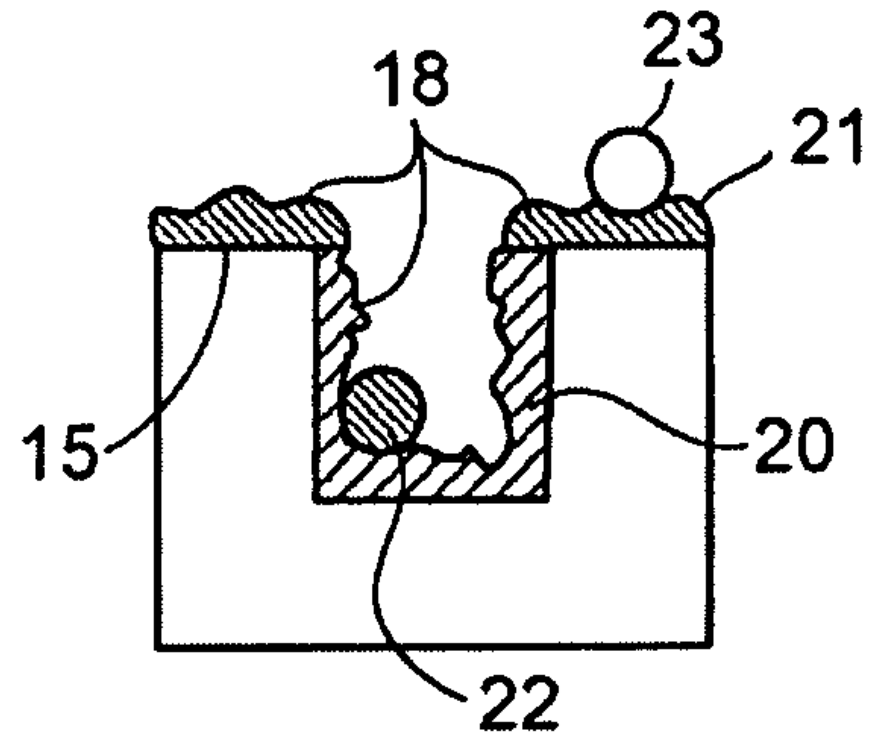


FIG. 2C

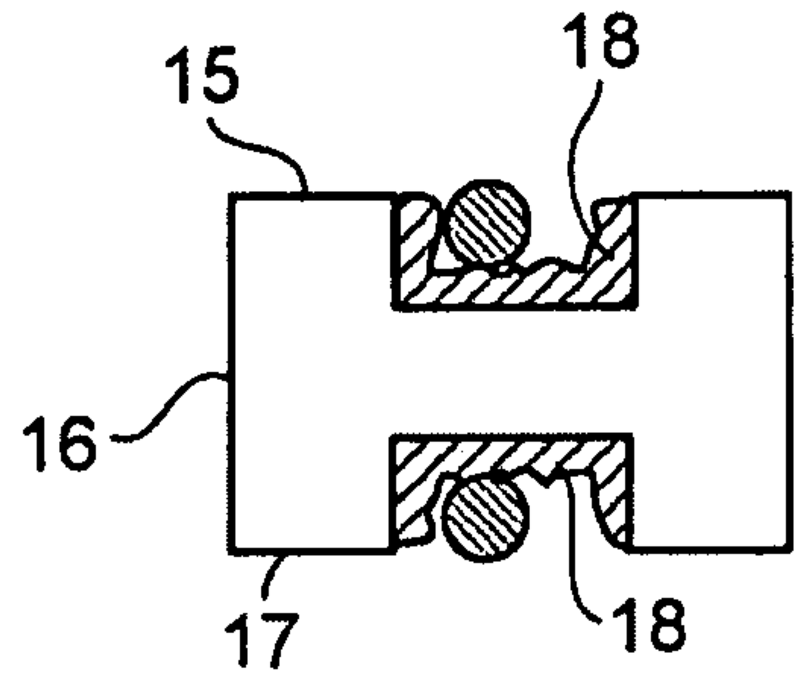


FIG. 2E

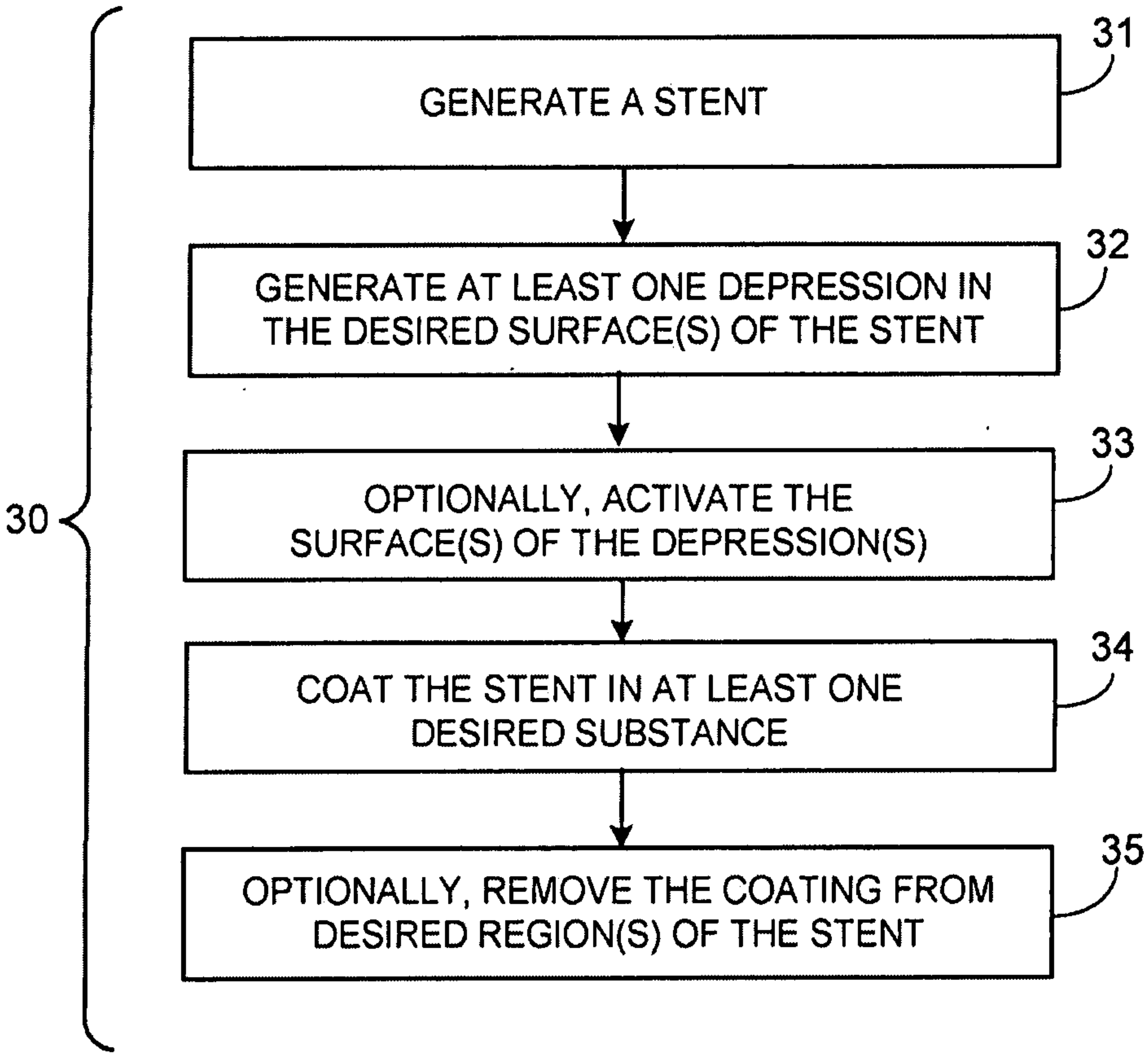

GENERATE A STENT
31
GENERATE AT LEAST ONE DEPRESSION IN THE DESIRED SURFACE(S) OF THE STENT
32
OPTIONALLY, ACTIVATE THE SURFACE(S) OF THE DEPRESSION(S)
33
COAT THE STENT IN AT LEAST ONE DESIRED SUBSTANCE
34
OPTIONALLY, REMOVE THE COATING FROM DESIRED REGION(S) OF THE STENT
35
30

FIG. 3

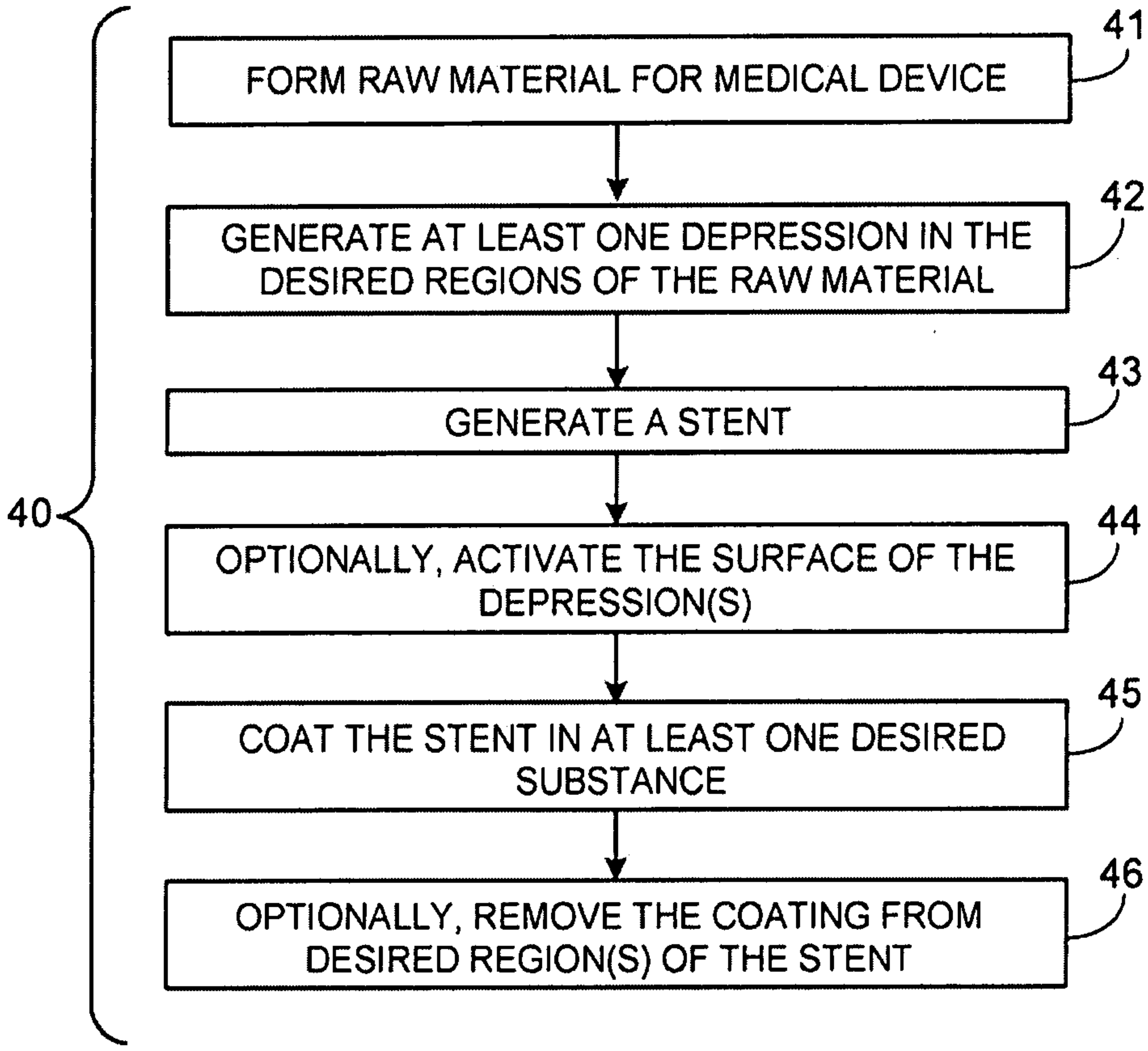

FORM RAW MATERIAL FOR MEDICAL DEVICE
41
GENERATE AT LEAST ONE DEPRESSION IN THE DESIRED REGIONS OF THE RAW MATERIAL
42
GENERATE A STENT
43
OPTIONALLY, ACTIVATE THE SURFACE OF THE DEPRESSION(S)
44
COAT THE STENT IN AT LEAST ONE DESIRED SUBSTANCE
45
OPTIONALLY, REMOVE THE COATING FROM DESIRED REGION(S) OF THE STENT
46
40

FIG. 4

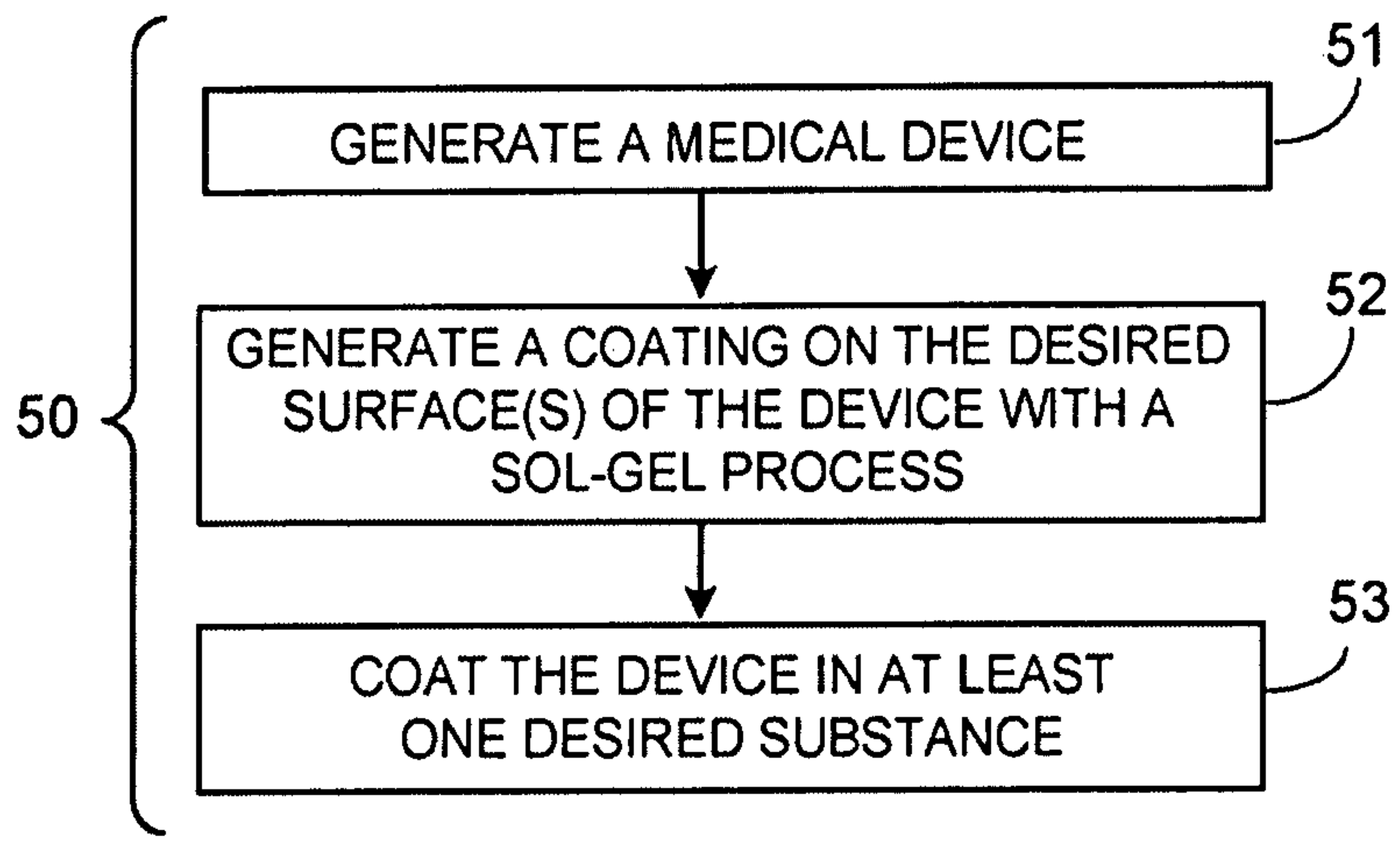

GENERATE A MEDICAL DEVICE
51
GENERATE A COATING ON THE DESIRED SURFACE(S) OF THE DEVICE WITH A SOL-GEL PROCESS
52
COAT THE DEVICE IN AT LEAST ONE DESIRED SUBSTANCE
53
50

FIG. 5

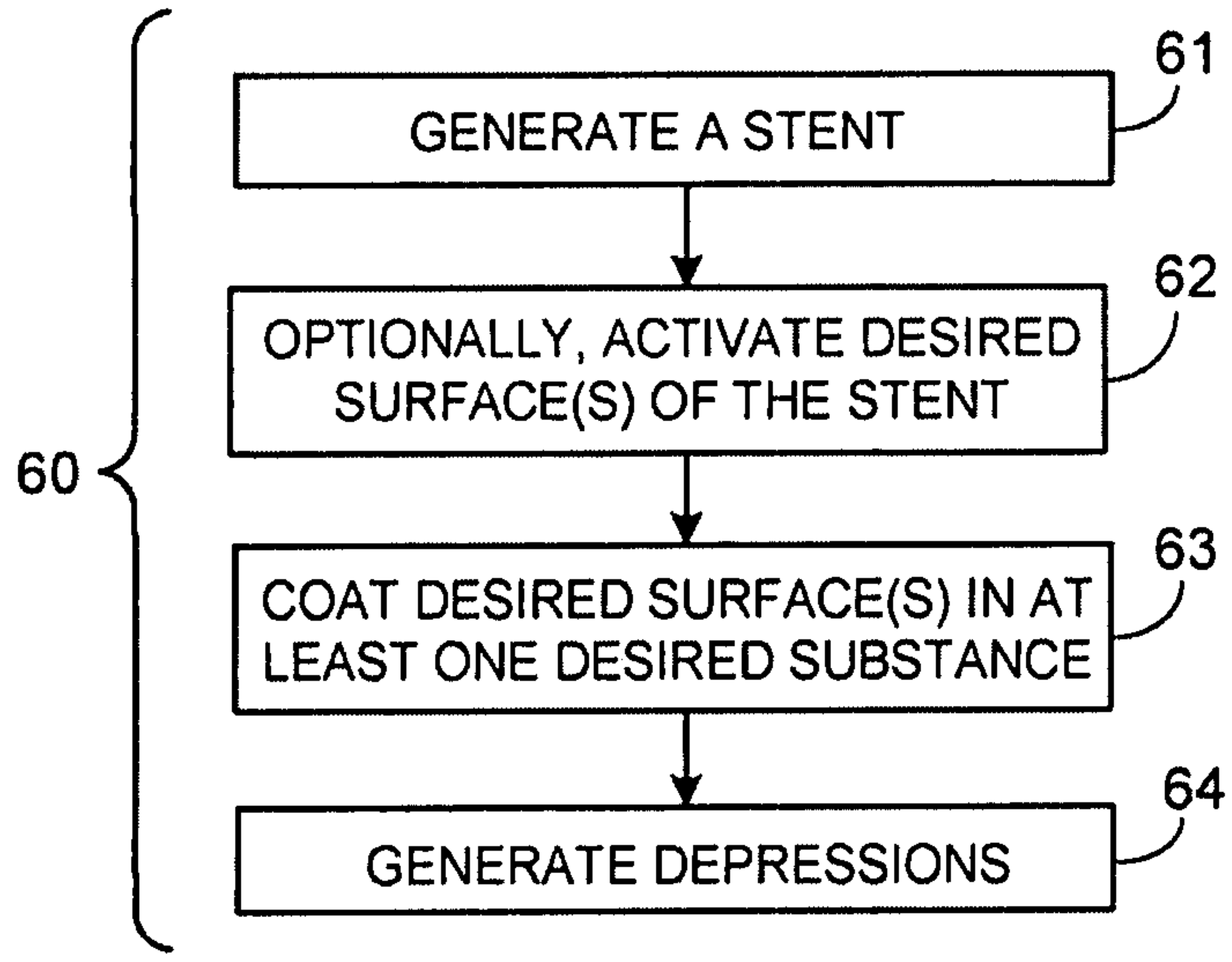

GENERATE A STENT
61
OPTIONALLY, ACTIVATE DESIRED SURFACE(S) OF THE STENT
62
COAT DESIRED SURFACE(S) IN AT LEAST ONE DESIRED SUBSTANCE
63
GENERATE DEPRESSIONS
64
60

FIG. 6

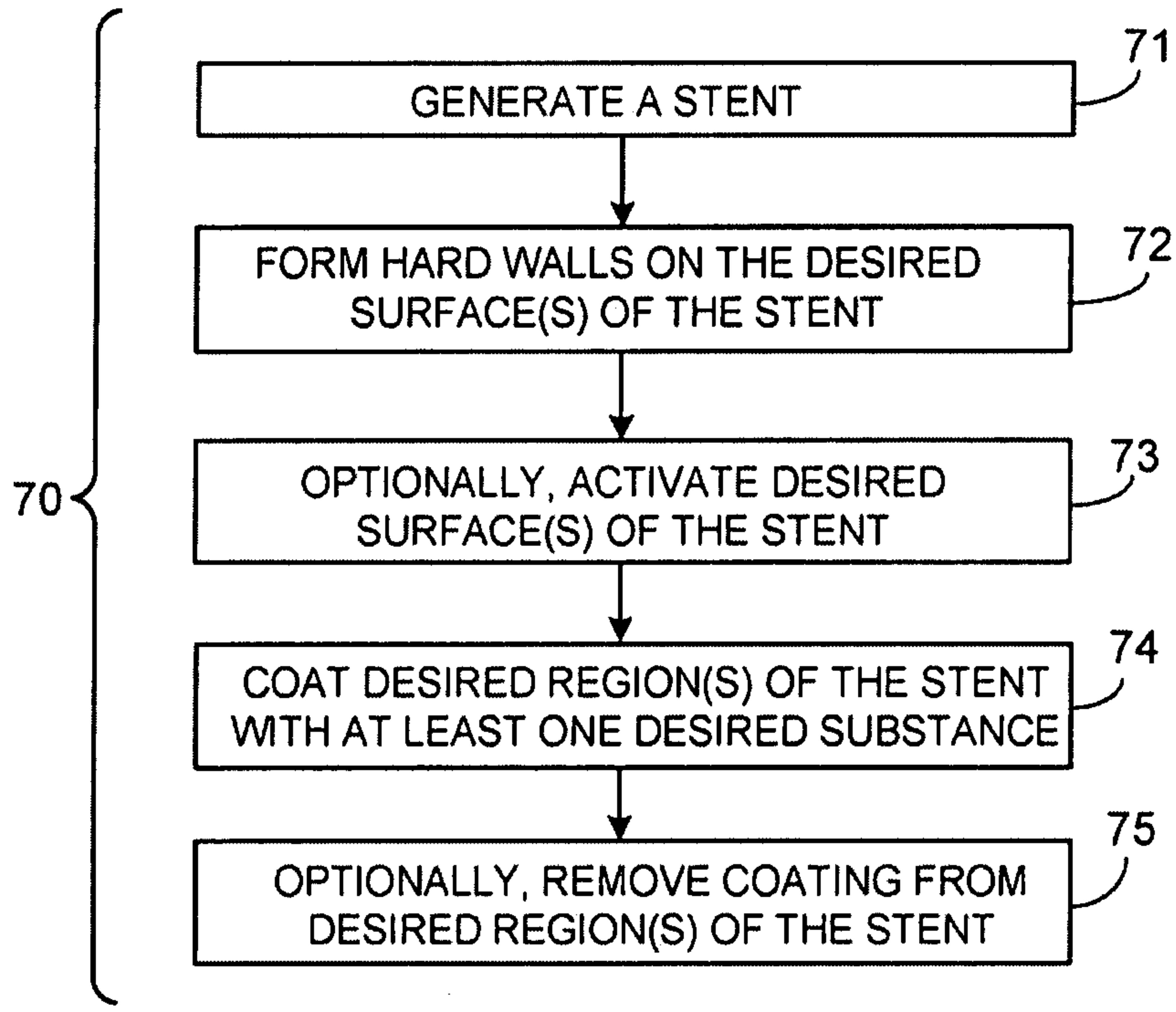

70
71
GENERATE A STENT
72
FORM HARD WALLS ON THE DESIRED SURFACE(S) OF THE STENT
73
OPTIONALLY, ACTIVATE DESIRED SURFACE(S) OF THE STENT
74
COAT DESIRED REGION(S) OF THE STENT WITH AT LEAST ONE DESIRED SUBSTANCE
75
OPTIONALLY, REMOVE COATING FROM DESIRED REGION(S) OF THE STENT

FIG. 7

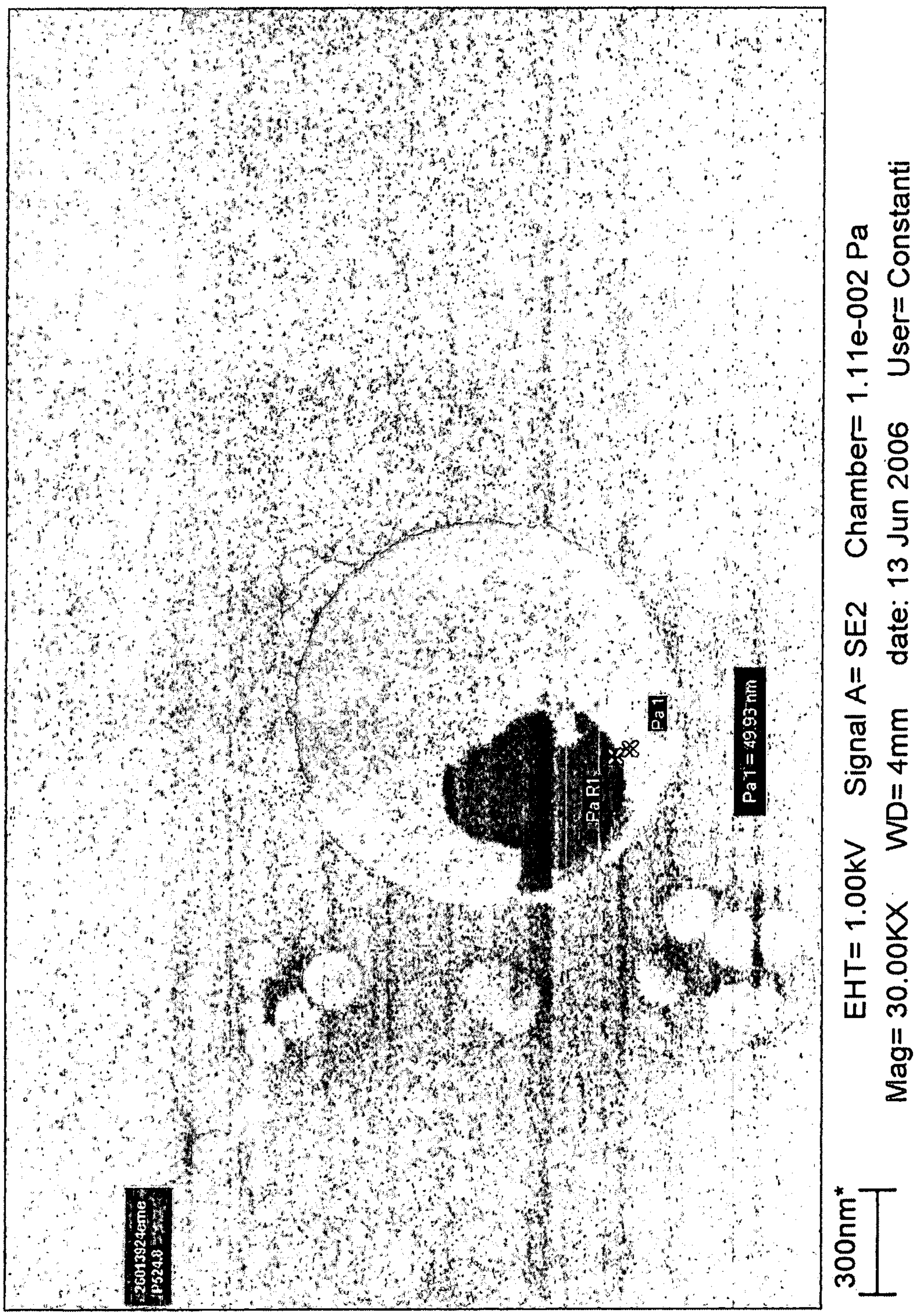
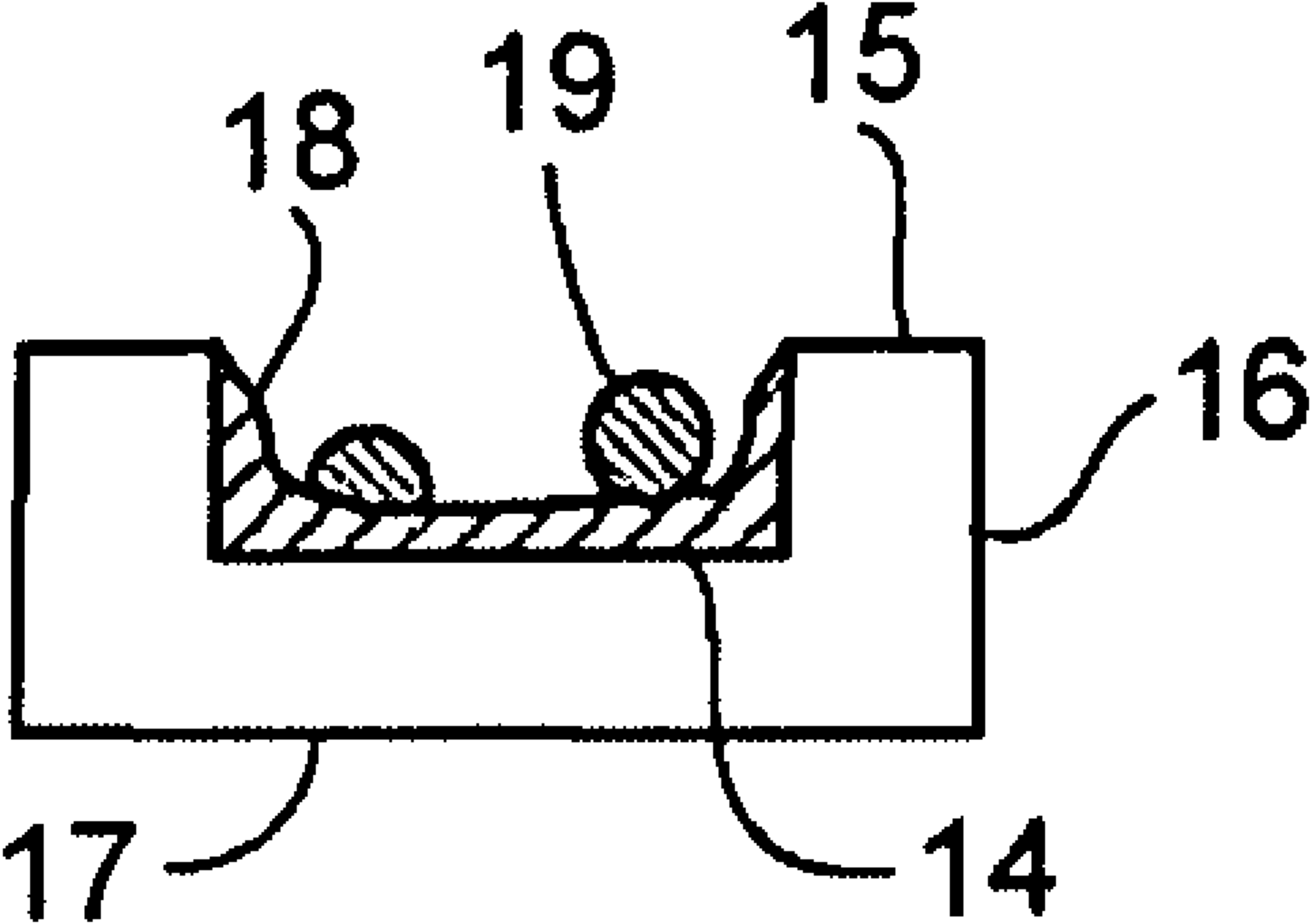

Pa R1
Pa 1
Pa 1 = 49.93 nm
300nm*
EHT= 1.00kV Signal A= SE2 Chamber= 1.11e-002 Pa
Mag= 30.00KX WD= 4mm date: 13 Jun 2006 User= Constanti

FIG. 8


18
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