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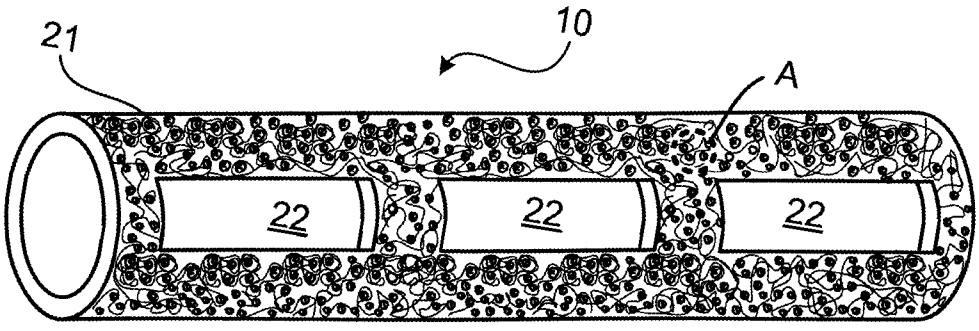
(54) **Title:** ENDOPROSTHESIS WITH ADJUSTABLE SURFACE FEATURES




(57) **Abstract:** Endoprostheses (e.g., stents) containing adjustable surfaces are disclosed.

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# ENDOPROSTHESIS WITH ADJUSTABLE SURFACE FEATURES

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 USC §119(e) to U.S. Provisional Patent Application Serial No. 60/845,047, filed on September 15, 2006, the entire contents of which are hereby incorporated by reference.

## TECHNICAL FIELD

This invention relates to medical devices, such as endoprostheses, and methods of making and using the same.

## BACKGROUND

The body includes various passageways including blood vessels such as arteries, and other body lumens. These passageways sometimes become occluded or weakened. For example, they can be occluded by a tumor, restricted by 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 an artificial implant that is typically placed in a passageway or lumen in the body. Many endoprostheses are tubular members, examples of which include stents, stent-grafts, and covered stents.

Many endoprostheses can be delivered inside the body by a catheter. Typically the catheter supports a reduced-size or compacted form of the endoprosthesis as it is transported to a desired site in the body, for example, the site of weakening or occlusion in a body lumen. Upon reaching the desired site, the endoprosthesis is installed so that it can contact the walls of the lumen.

One method of installation involves expanding the endoprosthesis. The expansion mechanism used to install the endoprosthesis may include forcing it to expand radially. For example, the expansion can be achieved with a catheter that carries a balloon in conjunction with a balloon-expandable endoprosthesis reduced in size relative to its final form in the body. The balloon is inflated to deform and/or expand the endoprosthesis in order to fix it at a predetermined position in contact with the lumen wall. The balloon can then be deflated, and the catheter withdrawn.

## SUMMARY

In one aspect, the invention features an endoprosthesis, e.g., a stent, having a surface or portion thereof that includes a polymer having a morphology of surface features having a substantially uniform periodicity of about 1 to 50 microns (e.g., about 15 to 25 microns).

In another aspect, the invention features a method of forming a stent that includes providing the stent with a polymer morphology having surface features having a substantially uniform periodicity of about 1 to 50 microns (e.g., about 15 to 25 microns), by applying a solution to the polymer.

Embodiments may include one or more of the following features. The endoprosthesis, e.g., stent, has surface features that include a plurality of nodules, e.g., nodules having one or more of the following features: a nodule diameter of about 5 to 50 microns (e.g., about 19 microns); a nodule height of less than 50 microns, e.g., about 1 to 10 microns; a nodule density of about 0.0025 nodules per square micron; and/or nodules defining regions therebetween having a width of about 50 to 2000 nm. In embodiments, the nodules are arranged in substantially parallel rows, e.g., arranged radially in substantially parallel rows. In embodiments, the endoprosthesis, e.g., stent, has surface features that include one or more rib-forms, e.g., rib-forms about 500 to 2500 nm in depth; having a periodicity of less than about 50 microns; and/or rib-forms defining regions therebetween having a width of about 50 to 2000 nm. The endoprosthesis, e.g., stent, can have a combination of surface features that includes nodules and rib-forms. For example, the surface features can be porous, e.g., a porous polymer and/or can include one or more elongated grooves. In embodiments, the polymer further includes a therapeutic agent; is bioerodible; and/or is a layer on the endoprosthesis, e.g., stent, surface (e.g., a metal or a polymer layer on the endoprosthesis, e.g., stent, surface). In other embodiments, the endoprosthesis, e.g., stent, has a polymer body. In yet other embodiments, the morphology is formed by the same polymer as the polymer body.

Further embodiments may include one or more of the following features. The endoprosthesis, e.g., stent, is formed by a method that includes one or more of, e.g., controlling the evaporation rate and/or volatility of the solution (e.g., using a solution mixture of solvents having a boiling point in the range of about 50°C to about 180°C);

applying the solution (e.g., a solution that includes the polymer) to the stent; applying the solution by spraying; controlling the size and/or velocity of the drops in the spray; controlling the surface energy of the solution, e.g., surface energy in the range of about 26 to 34 $mJ/m^2$. In embodiments, the solution further includes a surfactant and/or a therapeutic agent. In embodiments, nodule and/or rib-form surface features are formed. Embodiments may additionally include one or more of the following features: controlling the nodule size, e.g., by controlling the evaporation rate and/or surface energy of the solution; applying the solution by spraying and controlling the nodule size by controlling the size and/or velocity of the drops in the spray; controlling the rib form features by forming micelles in the solution; or masking at least a portion of the endoprosthesis, e.g., stent, to form morphological features.

Endoprostheses, e.g., stents, made by the methods described herein are also within the scope of the invention.

An erodible or bioerodible medical device, e.g., a stent, refers to a device, or a portion thereof, that exhibits substantial mass or density reduction or chemical transformation, after it is introduced into a patient, e.g., a human patient. Mass reduction can occur by, e.g., dissolution of the material that forms the device and/or fragmenting of the device. Chemical transformation can include oxidation/reduction, hydrolysis, substitution, electrochemical reactions, addition reactions, or other chemical reactions of the material from which the device, or a portion thereof, is made. The erosion can be the result of a chemical and/or biological interaction of the device with the body environment, e.g., the body itself or body fluids, into which it is implanted and/or erosion can be triggered by applying a triggering influence, such as a chemical reactant or energy to the device, e.g., to increase a reaction rate. For example, a device, or a portion thereof, can be formed from an active metal, e.g., Mg or Ca or an alloy thereof, and which can erode by reaction with water, producing the corresponding metal oxide and hydrogen gas (a redox reaction). For example, a device, or a portion thereof, can be formed from an erodible or bioerodible polymer, or an alloy or blend erodible or bioerodible polymers which can erode by hydrolysis with water. The erosion occurs to a desirable extent in a time frame that can provide a therapeutic benefit. For example, in embodiments, the device exhibits substantial mass reduction after a period of time which a function of the

device, such as support of the lumen wall or drug delivery is no longer needed or desirable. In particular embodiments, the device exhibits a mass reduction of about 10 percent or more, e.g. about 50 percent or more, after a period of implantation of one day or more, e.g. about 60 days or more, about 180 days or more, about 600 days or more, or 1000 days or less. In embodiments, the device exhibits fragmentation by erosion processes. The fragmentation occurs as, e.g., some regions of the device erode more rapidly than other regions. The faster eroding regions become weakened by more quickly eroding through the body of the endoprosthesis and fragment from the slower eroding regions. The faster eroding and slower eroding regions may be random or predefined. For example, faster eroding regions may be predefined by treating the regions to enhance chemical reactivity of the regions. Alternatively, regions may be treated to reduce erosion rates, e.g., by using coatings. In embodiments, only portions of the device exhibits erodibilty. For example, an exterior layer or coating may be erodible, while an interior layer or body is non-erodible. In embodiments, the endoprosthesis is formed from an erodible material dispersed within a non-erodible material such that after erosion, the device has increased porosity by erosion of the erodible material.

Erosion rates can be measured with a test device suspended in a stream of Ringer's solution flowing at a rate of 0.2 m/second. During testing, all surfaces of the test device can be exposed to the stream. For the purposes of this disclosure, Ringer's solution is a solution of recently boiled distilled water containing 8.6 gram sodium chloride, 0.3 gram potassium chloride, and 0.33 gram calcium chloride per liter.

Aspects and/or embodiments may have one or more of the following advantages. The growth and/or migration of cells, such as endothelial or red blood cells can be controlled, e.g., the migration of the cells can be oriented radially, longitudinally, or in both directions around and/or along the strut. Such increased growth and migration may facilitate endothelial encapsulation of the endoprosthesis, e.g., stent. The endoprosthesis can also have reduced restenosis and/or thrombogenecity *in vivo*. The porosity of the endoprosthesis, can be controlled, e.g., increased, thereby controlling the exposure of the endoprosthesis to fluids, e.g., bodily fluids. Enhanced fluid exposure can increase erosion of an erodible (e.g., bioerodible) portion of the endoprosthesis. Increased porosity of the endoprosthesis can also increase the elution rate of a therapeutic agent

from the endoprosthesis, e.g., a drug-eluting stent. Increased elution of the therapeutic agent can have the additional advantage of reducing the amount of agent used in the endoprosthesis.

Other aspects, features, and advantages will be apparent from the description and drawings, and from the claims.

## DESCRIPTION OF DRAWINGS

FIGS. 1A-1C are longitudinal cross-sectional views, illustrating delivery of a stent in a collapsed state (FIG. 1A), expansion of the stent (FIG. 1B) and deployment of the stent (FIG. 1C).

FIG. 2A is a perspective view of a stent.

FIG. 2B is an enlarged view of region A in FIG. 2A.

FIG. 2C is a cross-sectional view through the stent wall.

FIG. 2D is a cross-sectional view through the stent wall in FIG. 2C with cells interspersed within the polymer layer.

FIG. 3A is a perspective view of a stent.

FIG. 3B is an enlarged view of region A in FIG. 3A.

FIG. 3C is an enlarged three-dimensional view of the ribs in FIGS. 3A-3B.

FIG. 4 is a schematic of a system for applying a controllable morphology to the stent.

FIG. 5A is a perspective schematic of a stent including a mask.

FIG. 5B is a perspective schematic of the stent in 5A after application of a morphology to the stent and removal of the mask.

FIG. 6 is a perspective view of a stent.

FIGS. 7 – 13 are photographs of stents.

Like reference symbols in the various drawings indicate like elements.

## DETAILED DESCRIPTION

Referring to FIGS. 1A-1C, in use stent 10 is placed over a balloon 12 carried near the distal end of a catheter 14, and is directed through a lumen 15 (FIG. 1A) until the portion carrying the balloon and stent reaches the region of an occlusion 18. The stent 10

is then radially expanded by inflating the balloon 12 and pressed against the vessel wall with the result that occlusion 18 is compressed, and the vessel wall surrounding it undergoes a radial expansion (FIG. 1B). The pressure is then released from the balloon and the catheter 14 is withdrawn from the vessel (FIG. 1C).

Referring to FIG. 2A, the stent 10 is a generally tubular device defined by a stent wall 21 including fenestrations 22 separated by struts. Referring to FIG. 2B, an enlarged view of the region A in FIG. 2A, the surface of the stent wall is composed of polymer that has a controlled morphology characterized by bumps or nodules 24 that facilitates endothelization. Referring to FIG. 2C, a cross-section through the stent wall, the nodules 24 are formed in a polymer layer 25 provided on the outside surface of a body 26 of the stent. The layer 25 defines within its thickness a porous structure characterized by tortuous channels 28. Referring to FIG. 2D, a cross-sectional view through the stent wall, cells 29 (e.g., endothelial cells) migrate on the outside surface of the polymer 25 and/or through tortuous channels 28 within the polymer.

Referring particularly to FIG. 2B, in embodiments, the nodules 24 have a substantially uniform periodicity, P, of about 5 microns to about 50 microns, e.g., typically about 15 to 25 microns, e.g., about 20 microns. The nodule diameter, d, is about 5 to 50 microns, e.g., typically about 10 to 30 microns, e.g., about 19 microns or more in diameter (e.g., a radius of 9.5 microns that equals to an area of about 283 square microns). The nodule height, h, is less than 50 microns, e.g., typically less than 25 microns, e.g., about 1 to 10 microns (e.g., about 6 microns). The density of nodules is about 0.0010 to 0.1 nodules per square micron, typically about 0.002 to 0.0050 nodules per square micron, e.g., about 0.0025 nodules per square micron. The morphology defines spaces 28 between the features having a width and depth of about 50 to 2000 nm or more, e.g., about 1000 nm, or about the size of a typical endothelial cell. The thickness of the polymer morphology layer can vary as needed, but is typically in the range of less than 100 microns, typically less than 50 microns; and more typically about 0.5 to 20 microns.

Referring to FIGS. 3A-3C, a stent 30 with a radially ribbed morphology is illustrated. Referring to FIG. 3B, an enlarged view of the region A in FIG. 3A, the surface of the stent wall is composed of ribs 32 that are arranged radially around the stent

in generally parallel rows. Referring to FIG. 3C, an enlarged three-dimensional view of the ribs in FIG. 3B, a plurality of ribs 32 having a wave-like morphology is shown. The ribs can have a wave-like morphology as shown in FIG. 3C, or have a more linear configuration. In embodiments, the ribs provide a surface to facilitate the migration of cells, e.g., endothelial cells. Typically, the radial ribs are about 100 to 5000 nm, about 500 to 2500 nm, more typically about 800 to 1500 nm in depth, and have a periodicity of less than 50 μm, typically less than 20 μm, more typically less than 13 μm. In one exemplary embodiment, a plurality of ribs extends radially around the strut, e.g., overlaying the stent wall. The ribs can extend radially in any desired configuration, e.g., a spiral configuration.

The size, period and pattern of the morphology, as well as the porosity can be controlled to facilitate the growth and/or migration of endothelial cells, and/or the delivery of a therapeutic agent from the cavity. In some embodiments, the morphology provides a tortuous interstitial path that facilitates cell, e.g., endothelial cell, in-growth and migration (e.g., randomly disposed within a porous surface). In embodiments, cell migration can be guided, e.g., proceeding radially, longitudinally, or both, along the surface of the stent. The width and depth of the morphology, as well as the porosity can be adapted to provide different topographical cues to the cells, thus influencing their migration. In some embodiments, the morphology includes one or more agents that stimulate endothelial cell growth and/or attachment (e.g., placental growth factors, such as PIGF-1 and PIGF-2, and vascular endothelial growth factor (VEGF)).

Increasing the porosity of the stent can increase its exposure to fluids, e.g., bodily fluids, thus, increasing the rate of drug elution from a drug-eluting stent, or increasing erosion rate of an erodible stent (e.g., a bioerodible stent). An erodible stent may contain a therapeutic agent, the release of which can be further increased as the stent erodes. In one embodiment, a plurality of nodules formed in an outer layer of the stent can be used as wells for immediate release of a therapeutic agent, e.g., heparin. In other embodiments, the therapeutic agent can be embedded within the morphology layer or one or more layers located beneath or over the morphology layer. The release of the therapeutic agent will depend on factors, such as the solubility of the therapeutic agent being released and the porosity of the outer layer of the stent.

Referring to FIG. 4, the morphology can be controlled by altering the parameters of a spray system 40 used to form the morphology layer. The system 40 includes a nozzle 47 which sprays a solution onto a stent 43. The nozzle pressurizes the solution with gas from a supply 45. The temperature of the solution is controlled using a temperature controller 46. The solution is held in a reservoir 48 and can include selected aliquots of polymer material 41, solvent 42, and additive 44.

In particular, the morphology can be controlled by modifying the droplet speed and size, the evaporation rate or volatility of the solution and/or the surface energy of the solvent. Larger droplets and slower drop velocity increase the size of morphological features such as nodules. A more rapid evaporation rate increases the nodular nature of the morphology, and reduces the size and periodicity of the nodules. A higher surface energy, relative to the surface energy of the stent surface, promotes nodular formation by promoting a beading of the solution on the stent surface. The evaporation rate or volatility and the surface energy can be controlled by the selection of the solvent and/or use of additives.

In particular embodiments, the drop velocity is about 5 – 35 meter/second. For example, to increase the droplet size, the velocity of the sprayed formulation can be decreased to about 10-15 meter/second. The spraying distance can also be adjusted depending on the volatility of the formulation. The evaporation rate and/or volatility of the solvent can be controlled by controlling the temperature of the spray solution, the stent and/or the composition of the solution.

In particular embodiments, the formulation (also referred to herein as "solution") includes a blend of solvents of different boiling points. For example, the blend can include solvents with a boiling point in the range of about 50 to about 180°C. In particular embodiments, the solvent is a blend of higher boiling point solvents, with boiling points in the range of 100 to 150°C, and lower boiling point solvents such as boiling point in the range of 50 to 90°C. In one embodiment, the higher boiling point solvent is present in an amount of about 40% or more, e.g., about 50 – 90%. In embodiments, the porosity can be increased, for example, by coating the stent with a formulation that includes a higher proportion of a solvent having a lower boiling point and/or higher volatility. For example, the formulation can include a solvent with a

boiling point in the range of 50 to 90°C, typically 55 to 85°C (e.g., tetrahydrofluran (THF), acetone 56°C, isopropyl alcohol 82.2°C, and methanol 64.5°C) mixed with a solvent having a higher boiling point in the range of 110 to 140°C (e.g., toluene or xylene). The proportion of the more volatile solvent (e.g., THF) in the formulation can be 20%, 30%, 40%, and more typically, 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99% relative to the less volatile solvent (e.g., toluene or xylene). Additional solvents having similar volatile properties as THF, toluene or xylene can be used instead of, or in addition to, the solvents described herein. The less volatile solvent, e.g., toluene, may, optionally, increase the wettability of the formulation.

The surface energy of the stent material or solution can be selected to cause the solution to bead on the stent surface. In embodiments, the surface energy of the solution is lower than the surface energy of the stent surface onto which the solution is applied. In embodiments, the surface energy of the stent material is about 26 to 34 $mJ/m^2$, e.g., about 30 $mJ/m^2$. The formulation can optionally, include one or more other components, including a polymer, a surfactant, and/or a therapeutic agent, as described below. The solvent typically solubilizes about 0.05 to 30% (by weight), e.g., about 0.1 to 1% polymer. Suitable polymers include styrene-isobutylene-styrene (SIBs), polyether block amide (PEBA, PEBAX®), nylon, and polyurethanes. Polymers suitable for incorporation of a therapeutic agent are described in Schwarz *et al.* U.S. 6,368,658. The solution can include the polymer or a pre-polymer (e.g. monomers), which are polymerized on the stent.

The ribbed morphology can be formed using a formulation that includes one or more surfactants as an additive. Suitable surfactants include polymeric dispersants, such as polymeric fatty acids, including polymeric dispersants having a polyakoxylate head group and a polyester tail group, e.g., Zephrym; polymeric dispersants having a fatty acid head group and a polyester tail group, e.g., Hypermer KD-3 and Hypermer KD-4; as well as polymeric dispersants having a polyamine head group and a polyester tail group, e.g., Atlox LP6 (manufactured by Uniqema, Imperial Chemical Industries). In embodiments, the surfactant (e.g., one or more of Zephrym, Hypermer KD-3, Hypermer KD-4 and Atlox LP6) is at least 10%, 15%, 20%, 25% or 30% of the formulation coating. Without being bound by theory, the surfactant is believed to form micelles about the polymer

material, which inhibits polymer agglomeration. As the solvent dries, the coating contracts to form grooves. The transition between the ribbed structure and a nodular pocketed morphology structure can be controlled by controlling the amount of high boiling point additive relative to the surfactant. The ribs need not cover the entire radial surface of the stent, e.g., ribs can extend only on the outer diameter, the inner diameter, or a side wall, or portion thereof.

Referring as well to FIGS. 5A and 5B, in embodiments, the stent 60 can be provided with a mask 62 so that the solution is applied in a desired pattern. In the embodiment of FIG. 5A, the mask is provided in the form of a plurality of wires longitudinally arranged onto the stent; when the wires are removed after spraying, the polymer layer is interrupted by a series of axial grooves 64 that encourage endothelial growth along the length of the stent. Referring to FIG. 6, a stent 70 illustrated includes a surface morphology 72 interrupted by a spiral groove or gap 72. The spiral groove 74 is formed utilizing a wire mask wrapped around the stent during application of the morphology layer. One or more longitudinal grooves can be alternatively created by laser ablation and/or mechanical means (e.g., using blades or by expanding a cutting balloon inside the stent). Typically, the longitudinal grooves are about 100 to 5000 nm, about 500 to 2500 nm, more typically about 800 to 1500 nm in depth; have a periodicity of less than 50 microns, typically less than 20 microns, more typically less than 13 microns, and have a length of about 50 microns to 3mm, typically about 75 microns to 500 microns, more typically about 100 microns. The grooves can extend to the entire surface of the stent (e.g., an outer or inner surface), or a portion of the coating (e.g., 25%, 50%, or 75% of the length of the stent).

In embodiments, any of the morphologies described above can be applied over the entire stent or over only portions of the stent (e.g. over the inner or outer portions). Different morphologies can be provided in different portions (e.g., the inner and the outer surface). The morphology can be applied by incorporating the polymer in the solution which is applied to the stent to form a coating, or the solvent can be applied to a stent already including a polymer. The coating can be applied to a previously applied coating, e.g., a drug-eluting coating, to provide a multilayer system including an inner drug-eluting coating and an outer morphology coating. The drug-eluting coating can also be

applied over a previously applied morphology coating. The stent body itself can be formed of a polymer, which is processed to form a particular morphology and/or include a drug. The solution can be applied by techniques other than spraying, e.g., by dipping the stent into the solution. The components of the solution can be applied sequentially to the stent surface, rather than simultaneously.

The stent body can be formed of metal, polymer or ceramic that is bioerodible or biostable. The morphology layer can be a contiguous outer portion of a polymer stent body. Suitable bioerodible materials include one or more of a metallic component (e.g., a metal or alloy), a non-metallic component (e.g., a biodegradable polymer), or any combination thereof. Bioerodible materials are described, for example, in U.S. Patent No. 6,287,332 to Bolz; U.S. Patent Application Publication No. US 2002/0004060 A1 to Heublein; U.S. Patent Nos. 5,587,507 and 6,475,477 to Kohn *et al.* Examples of bioerodible metals include alkali metals, alkaline earth metals (*e.g.*, magnesium), iron, zinc, and aluminum. Examples of bioerodible metal alloys include alkali metal alloys, alkaline earth metal alloys (e.g., magnesium alloys), iron alloys (e.g., alloys including iron and up to seven percent carbon), zinc alloys, and aluminum alloys. Examples of bioerodible non-metals include bioerodible polymers, such as, e.g., polyanhydrides, polyorthoesters, polylactides, polyglycolides, polysiloxanes, cellulose derivatives and blends or copolymers of any of these. Bioerodible polymers are disclosed in U.S. Published Patent Application No. 2005/0010275, filed October 10, 2003; U.S. Published Patent Application No. 2005/0216074, filed October 5, 2004; and U.S. Patent No. 6,720,402, the entire contents of each of which is hereby incorporated by reference herein.

Other examples of bioerodible materials include polyelectrolytes. Polyelectrolytes are polymers having charged (e.g., ionically dissociable) groups. The number of these groups in the polyelectrolytes can be so large that the polymers are soluble in polar solvents (including water) when in ionically dissociated form (also called polyions). Depending on the type of dissociable groups, polyelectrolytes can be classified as polyacids and polybases. When dissociated, polyacids form polyanions, with protons being split off. Polyacids include inorganic, organic and biopolymers. Examples of polyelectrolytes and methods of forming polyelectrolyte-containing stents

are described in WO 2005/115496 and commonly assigned USSN 10/985,242 entitled "Medical Devices and Methods of Making the Same" by Atanasoska. L. *et al.* filed on November 10, 2004, the contents of both of which are incorporated by reference. Examples of polyacids include polyphosphoric acids, polyvinylsulfuric acids, polyvinylsulfonic acids, polyvinylphosphonic acids and polyacrylic acids. Examples of the corresponding salts, which are called polysalts, include polyphosphates, polyvinylsulfates, polyvinylsulfonates, polyvinylphosphonates and polyacrylates. Polybases contain groups that are capable of accepting protons, e.g., by reaction with acids, with a salt being formed. Examples of polybases having dissociable groups within their backbone and/or side groups are polyallylamine, polyethylimine, polyvinylamine and polyvinylpyridine. By accepting protons, polybases form polycations. Some polyelectrolytes have both anionic and cationic groups, but nonetheless have a net positive or negative charge.

The polyelectrolytes can include those based on biopolymers. Examples include alginic acid, gum arabicum, nucleic acids, pectins and proteins, chemically modified biopolymers such as carboxymethyl cellulose and lignin sulfonates, and synthetic polymers such as polymethacrylic acid, polyvinylsulfonic acid, polyvinylphosphonic acid and polyethylenimine. Linear or branched polyelectrolytes can be used. Using branched polyelectrolytes can lead to less compact polyelectrolyte multilayers having a higher degree of wall porosity. In some embodiments, polyelectrolyte molecules can be crosslinked within or/and between the individual layers, to enhance stability, e.g., by crosslinking amino groups with aldehydes. Furthermore, amphiphilic polyelectrolytes, e.g., amphiphilic block or random copolymers having partial polyelectrolyte character, can be used in some embodiments to affect permeability towards polar small molecules. Other examples of polyelectrolytes include low-molecular weight polyelectrolytes (e.g., polyelectrolytes having molecular weights of a few hundred Daltons up to macromolecular polyelectrolytes (e.g., polyelectrolytes of synthetic or biological origin, which commonly have molecular weights of several million Daltons). Still other examples of polyelectrolyte cations (polycations) include protamine sulfate polycations, poly(allylamine) polycations (e.g., poly(allylamine hydrochloride) (PAH)), polydiallyldimethylammonium polycations, polyethyleneimine polycations, chitosan

polycations, gelatin polycations, spermidine polycations and albumin polycations. Examples of polyelectrolyte anions (polyanions) include poly(styrenesulfonate) polyanions (e.g., poly(sodium styrene sulfonate) (PSS)), polyacrylic acid polyanions, sodium alginate polyanions, eudragit polyanions, gelatin polyanions, hyaluronic acid polyanions, carrageenan polyanions, chondroitin sulfate polyanions, and carboxymethylcellulose polyanions.

In other embodiments, the stent can include one or more nonerodible or biostable materials in addition to one or more bioerodible materials. For example, the bioerodible material may be provided as a coating in a biostable stent body. Examples of biostable materials include stainless steel, tantalum, nickel-chrome, cobalt-chromium alloys such as Elgiloy® and Phynox®, Nitinol (*e.g.*, 55% nickel, 45% titanium), and other alloys based on titanium, including nickel titanium alloys, thermo-memory alloy materials. Stents including biostable and bioerodible regions are described, for example, in U.S. Patent Application Serial No. 11/004,009, filed on December 3, 2004, and entitled "Medical Devices and Methods of Making the Same." The material can be suitable for use in, for example, a balloon-expandable stent, a self-expandable stent, or a combination of both (see *e.g.*, U.S. Patent No. 5,366,504).

The stent can be manufactured, or the starting stent can be obtained commercially. Methods of making stents are described, for example, in U.S. Patent No. 5,780,807 and U.S. Application Publication US-2004-0000046-A1. Stents are also available, for example, from Boston Scientific Corporation, Natick, MA, USA, and Maple Grove, MN, USA. The stent can be formed of any biocompatible material, e.g., a metal or an alloy, as described herein. The biocompatible material can be suitable for use in a self-expandable stent, a balloon-expandable stent, or both. Examples of other materials that can be used for a balloon-expandable stent include noble metals, radiopaque materials, stainless steel, and alloys including stainless steel and one or more radiopaque materials.

The terms "therapeutic agent", "pharmaceutically active agent", "pharmaceutically active material", "pharmaceutically active ingredient", "drug" and other related terms may be used interchangeably herein and include, but are not limited to, small organic molecules, peptides, oligopeptides, proteins, nucleic acids, oligonucleotides, genetic therapeutic agents, non-genetic therapeutic agents, vectors for

delivery of genetic therapeutic agents, cells, and therapeutic agents identified as candidates for vascular treatment regimens, for example, as agents that reduce or inhibit restenosis. By small organic molecule is meant an organic molecule having 50 or fewer carbon atoms, and fewer than 100 non-hydrogen atoms in total. Suitable therapeutic agents are described in U.S. Published Application No. 2005/0216074, entitled "Implantable Medical Devices" by Sahatjian, R. *et al.*, the contents of which are incorporated by reference.

Medical devices, in particular endoprostheses, as described above include implantable or insertable medical devices, including catheters (for example, urinary catheters or vascular catheters such as balloon catheters), guide wires, balloons, filters (*e.g.*, vena cava filters), stents of any desired shape and size (including coronary vascular stents, aortic stents, cerebral stents, urology stents such as urethral stents and ureteral stents, biliary stents, tracheal stents, gastrointestinal stents, peripheral vascular stents, neurology stents and esophageal stents), grafts such as stent grafts and vascular grafts, cerebral aneurysm filler coils (including GDC-Guglilmi detachable coils-and metal coils), filters, myocardial plugs, patches, pacemakers and pacemaker leads, heart valves, and biopsy devices. In one embodiment, the medical device includes a catheter having an expandable member, e.g., an inflatable balloon, at its distal end, and a stent or other endoprosthesis (e.g., an endoprosthesis or stent as described herein). The stent is typically an apertured tubular member (e.g., a substantially cylindrical uniform structure or a mesh) that can be assembled about the balloon. The stent typically has an initial diameter for delivery into the body that can be expanded to a larger diameter by inflating the balloon. The medical devices may further include drug delivery medical devices for systemic treatment, or for treatment of any mammalian tissue or organ.

The medical device, e.g., endoprosthesis, can be generally tubular in shape and can be a part of a stent. Simple tubular structures having a single tube, or with complex structures, such as branched tubular structures, can be used. Depending on specific application, stents can have a diameter of between, for example, 1 mm and 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. Stents can also be preferably bioerodible, such as a bioerodible abdominal aortic aneurysm (AAA) stent, or a bioerodible vessel graft.

In some embodiments, the medical device, e.g., endoprosthesis, is used to temporarily treat a subject without permanently remaining in the body of the subject. For example, in some embodiments, the medical device can be used for a certain period of time (*e.g.*, to support a lumen of a subject), and then can disintegrate after that period of time. Subjects can be mammalian subjects, such as human subjects (e.g., an adult or a child). Non-limiting examples of tissues and organs for treatment include the heart, coronary or peripheral vascular system, lungs, trachea, esophagus, brain, liver, kidney, bladder, urethra and ureters, eye, intestines, stomach, colon, pancreas, ovary, prostate, gastrointestinal tract, biliary tract, urinary tract, skeletal muscle, smooth muscle, breast, cartilage, and bone.

Examples

Stents are spray-coated with SIBs using a concentric nozzle-type gas pressurized nebulizer. The nozzle is pressurized with $N_2$ gas at about 5 psi. The flow of solvent solution is about 20 ml/hr per hour (although solvent flow rates in the range of 10 to 40 ml/hr can be used). The flow rate of the gas in the nozzle is about 15 liter/min (although gas flow rates ranging from 5 to 20 liter/min can be used). The diameter of the nozzle orifice is about 1 mm. Suitable nozzle designs are commercially available as the Microcoat 800 series through EFD Inc., a Nordson Company (East Providence, RI USA). The solution and stent temperature for spray-coating is about 20°C. The spraying distance is about 50 mm. Magnified images of the stent are obtained by scanning electron microscopy (SEM) and optical microscopy as indicated below.

Referring to FIG. 7, which shows a SEM image of a stainless steel body after spraying with a solution consisting of about 94% toluene, about 5% THF and a polymer (SIBs). SIBs is present at about 1% (by weight). The coating exhibits a smooth morphology as shown in FIG. 7 (scale bar corresponds to about 100 microns).

Referring to the Table, to form outer layers of various porosities and morphologies, a coating solution is used that includes toluene and varying amounts of low boiling point solvent THF, with varying amounts of surfactant Zephrym (manufactured by Uniqema), with or without a drug (paclitaxel).

Table

| Solvent | Low Boiling Pt. Solvent | Surfactant | Drug | Morphology | Photo |
|---|---|---|---|---|---|
| Toluene | 99% THF | y(0.3%) | Y | Nodules | FIG. 8, 9 |
| Toluene | 99% THF | y(0.3%) | N | Nodules | FIG. 10 |
| Toluene | 5% THF | y(30%) | N | Ribs | FIG. 11 |
| Toluene | ~50% THF | y(30%) | N | Broken ribs | FIG. 12 |
| Toluene | ~90% THF | y(10%) | N | Broken ribs | FIG. 13 |

Referring to FIG. 8, a stent having a porous surface resembling small spheres packed together is made by increasing the proportion of THF in the solvent sprayed onto the stainless steel body (magnification is about 68X SEM picture; a scale bar corresponding to about 100 μm is shown in FIG. 8). The formulation sprayed contained 99% THF, 0.05% paclitaxel and a low amount of Zephrym (0.3%). A cross-section through the coating shown in FIG. 8 exposing the porous structure is shown in FIG. 9 (optical microscope image; scale bar corresponds to about 100 microns). Referring to FIG. 10, an optical microscope image shows a similar porous structure as in FIG. 8 formed after applying the THF formulation in the absence of paclitaxel. The scale bar shown in FIG. 10 corresponds to about 100 microns.

Referring to FIG. 11, a radially ribbed morphology is formed by increasing the concentration of surfactant to about 30% Zephrym in toluene and 5%THF in the coating formulation (magnification is about 33X SEM picture; a scale bar corresponding to about 100 μm is shown in FIG. 11). A stent surface that includes numerous grooves of about 1.5 microns (depth) with a periodicity of about 12.5 microns extending in a radial direction is formed.

Porous, rib-like morphologies are formed by increasing the concentration of the surfactant and THF in the coating formulation (FIGS. 12-13). Referring to FIG. 12, increasing the concentration of Zephrym to about 30%, and THF to about 50%, in toluene forms the porous ribbed stent surface shown, which has a porosity of about 0.0035 pores per square micron, and further includes numerous grooves extending in a radial direction of about 2 microns (depth) with a periodicity of about 11.5 microns (magnification is about 32X SEM; a scale bar corresponding to about 200 μm is shown in FIG. 12). Referring to FIG. 13, a higher degree of porosity, while preserving the radially ribbed morphology, is obtained by increasing the THF concentration in the coating formulation to greater than 90% in about 10% Zephrym (magnification is about 34X SEM; a scale bar corresponding to about 100 μm is shown in FIG. 13). A stent surface with a high degree of porosity (about 0.0035 pores per square micron) that further includes numerous grooves of about 1 micron (depth) with a periodicity of about 12 microns extending in a radial direction is shown in FIG. 13.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference herein in their entirety.

Other embodiments are within the scope of the following claims.

**WHAT IS CLAIMED IS:**

1. A stent having a surface or portion thereof comprising a polymer having a morphology of surface features having a substantially uniform periodicity of about 1 to 50 microns.

2. The stent of claim 1, wherein the surface features comprise nodules.

3. The stent of claim 2, wherein the nodules have a diameter of about 5 to 50 microns and a height of about 1 to 10 microns, and wherein the nodules define regions therebetween having a width of about 50 to 2000 nm.

4. The stent of claim 2, wherein the nodules are in substantially parallel rows arranged radially.

5. The stent of claim 1, wherein the surface features are rib-forms.

6. The stent of claim 5, wherein the rib-forms are about 500 to 2500 nm in depth, and wherein the rib-forms define regions therebetween having a width of about 50 to 2000 nm.

7. The stent of claim 1, wherein the surface features include elongated grooves.

8. The stent of claim 1, wherein the polymer is porous.

9. The stent of claim 1, wherein the polymer includes a therapeutic agent.

10. The stent of claim 1, wherein the polymer is bioerodible.

11. The stent of claim 1, wherein the polymer is a layer on the stent surface.

12. A method of forming the stent of claim 1, comprising:

providing the stent with a polymer morphology having surface features having a substantially uniform periodicity of about 1 to 50 microns, by applying to the stent a solution and a polymer.

13. The method of claim 12, wherein the solution includes the polymer, and the solution is applied to the stent.

14. The method of claim 12, comprising applying the solution by spraying.

15. The method of claim 12, wherein the solution is a mixture of solvents having a boiling point in the range of about 50 to about 180°C.

16. The method of claim 12, wherein the solution further includes a surfactant.

17. The method of claim 12, wherein the polymer includes a therapeutic agent.

18. The method of claim 12, wherein providing the stent with the polymer morphology having surface features having the substantially uniform periodicity of about 1 to 50 nm includes forming nodule surface features, rib-form surface features, or a combination thereof.

19. The method of claim 18, wherein forming the rib-form features includes forming micelles in the solution.

20. The method of claim 12, further comprising masking at least a portion of the stent to form morphology features.

FIG. 1A

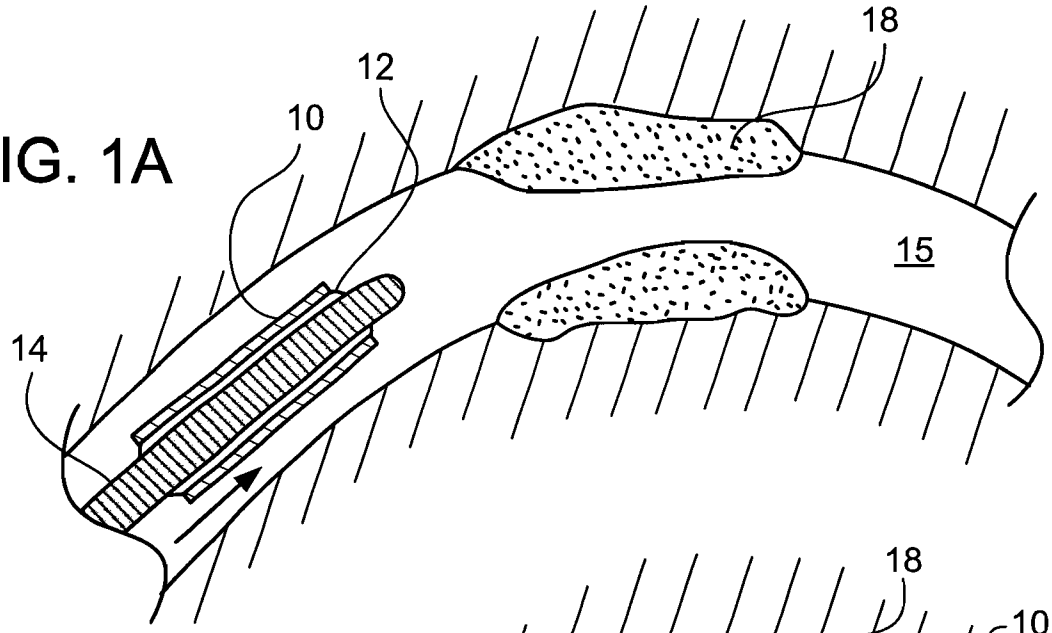



FIG. 1B

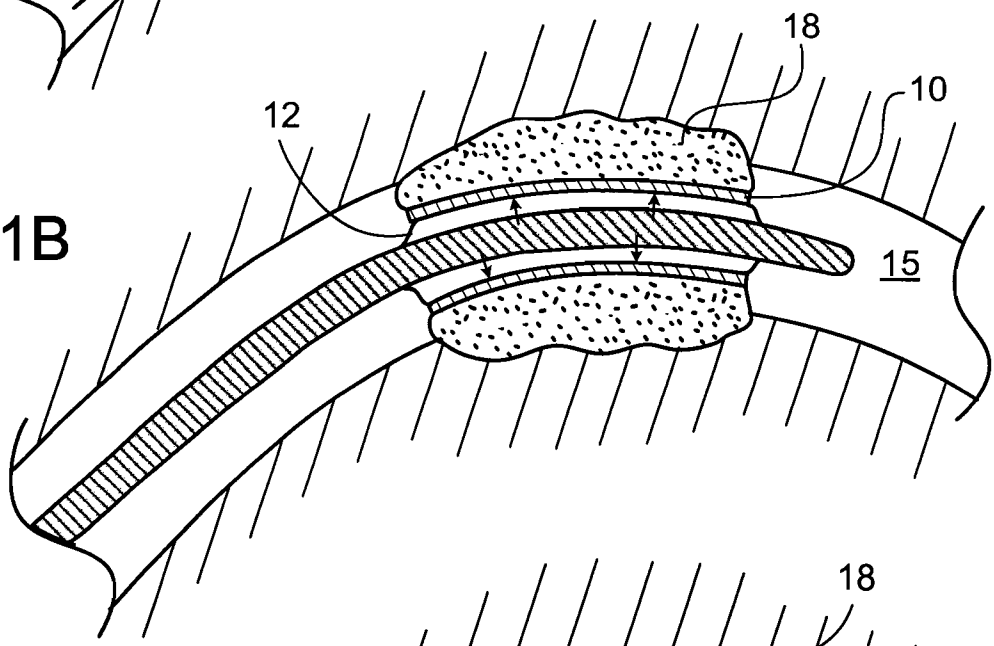
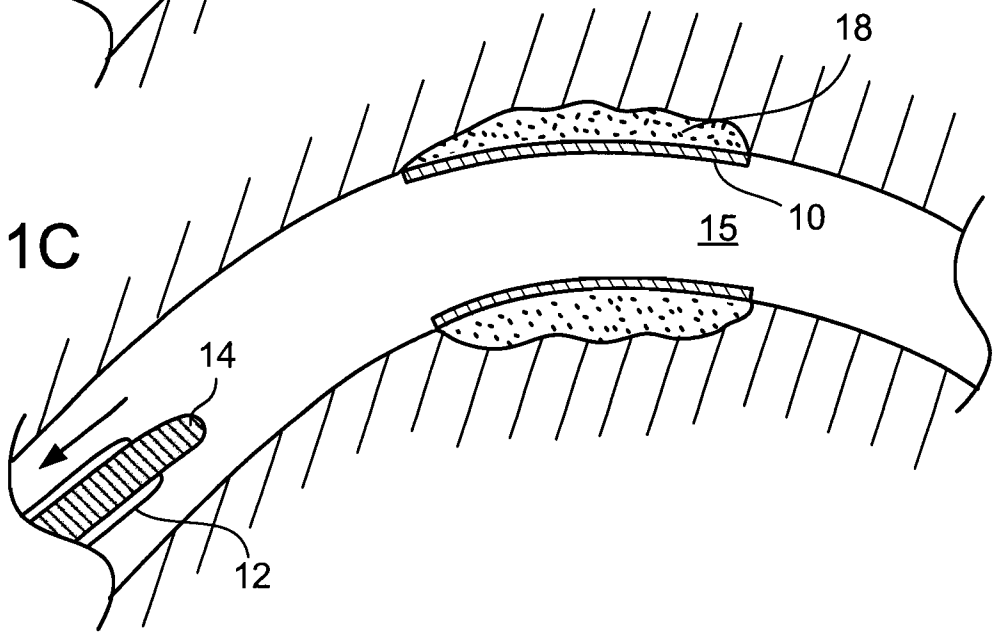



FIG. 1C



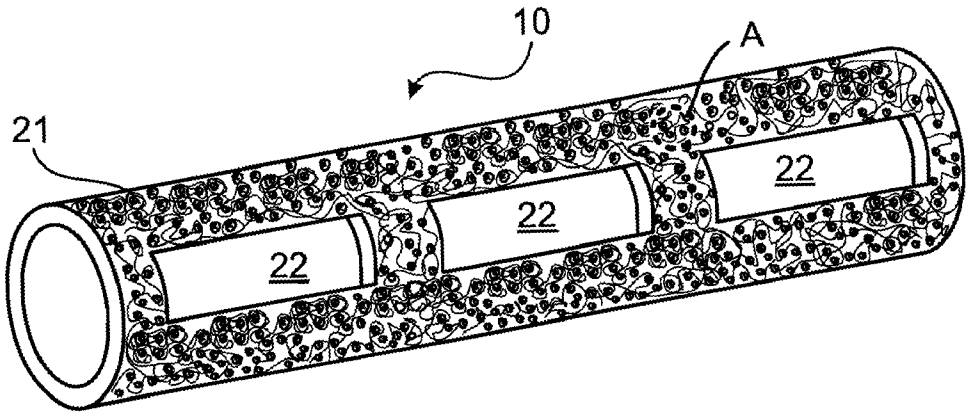



FIG. 2A

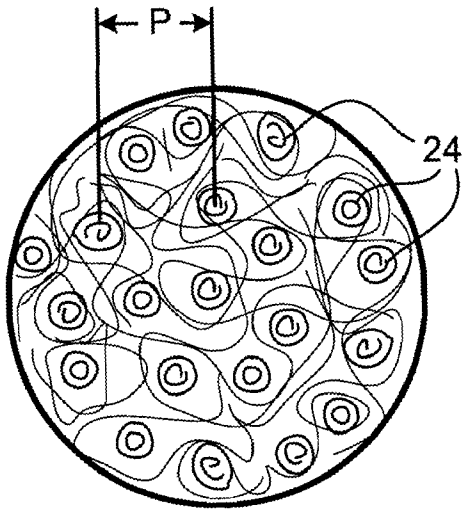



FIG. 2B

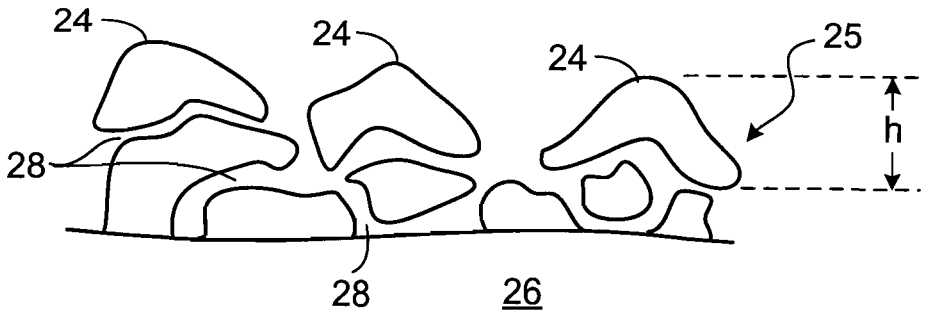



FIG. 2C

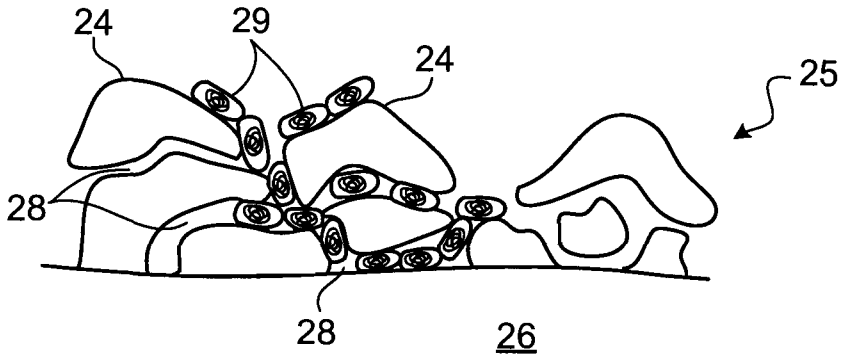



FIG. 2D

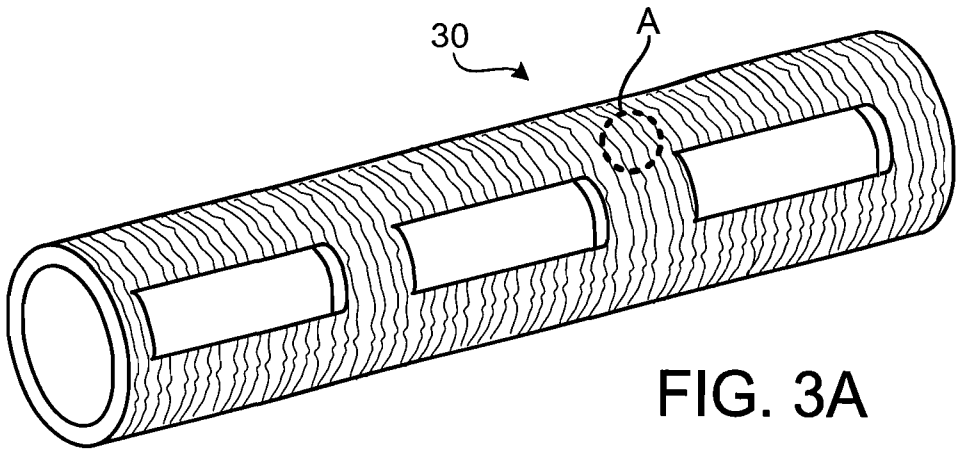



FIG. 3A

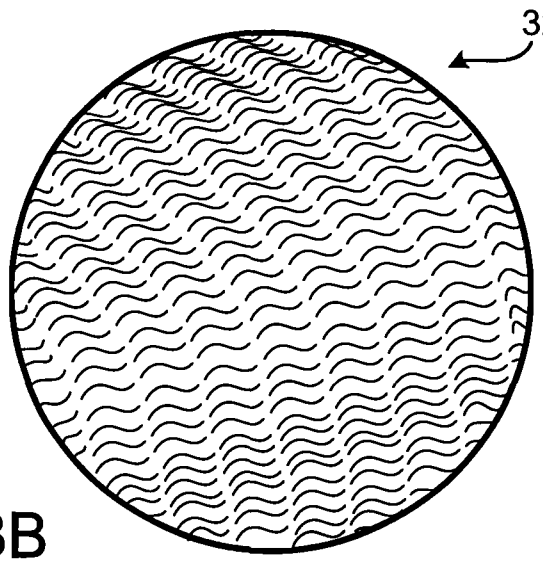



FIG. 3B

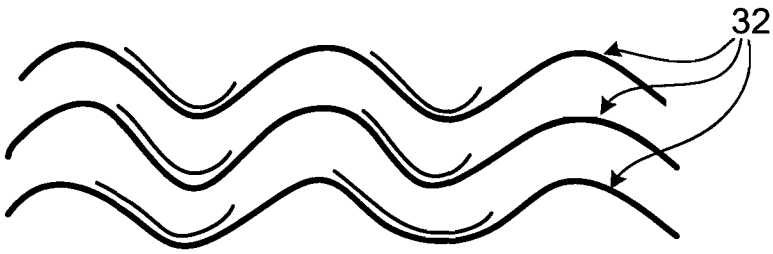



FIG. 3C

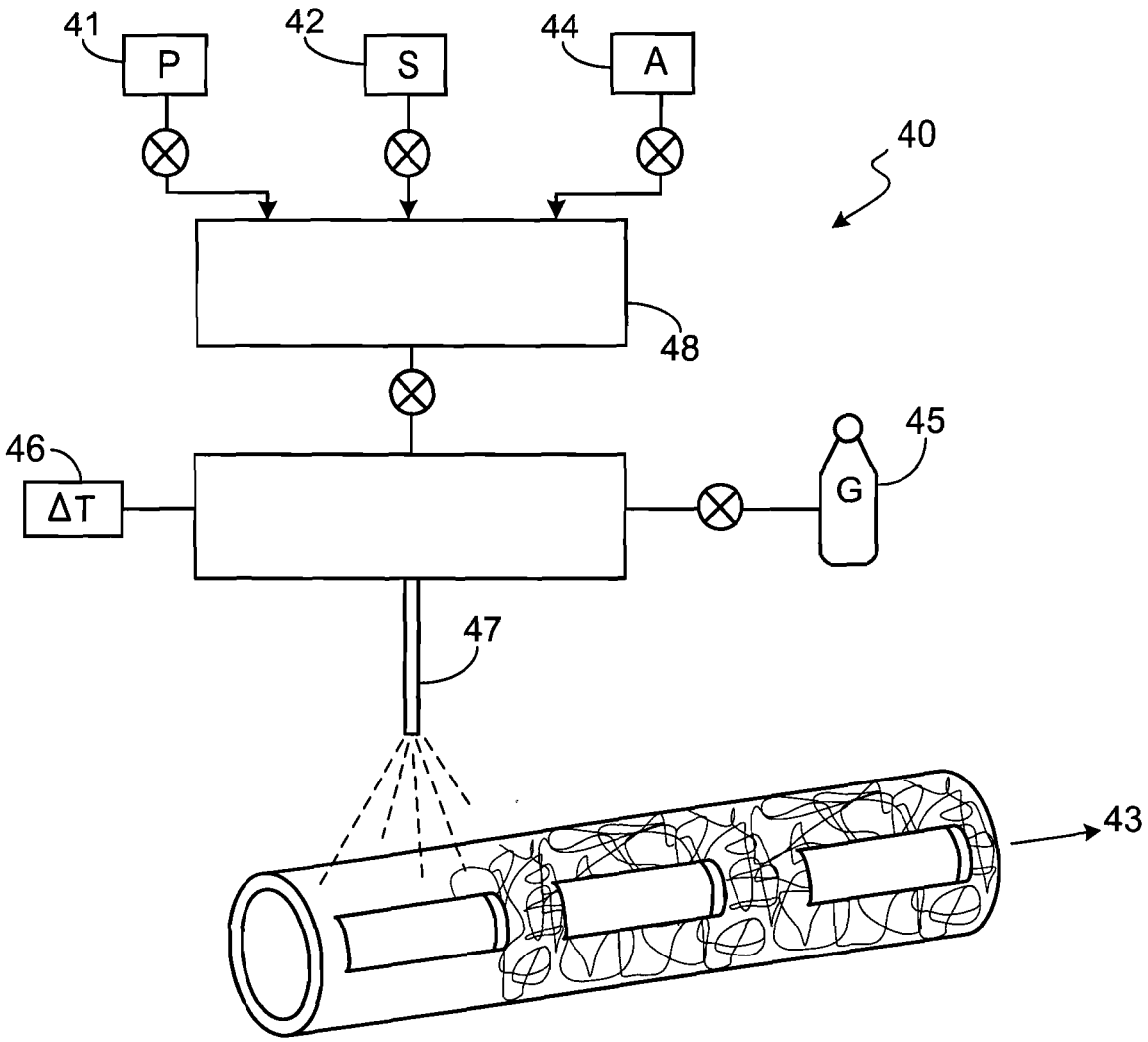



FIG. 4

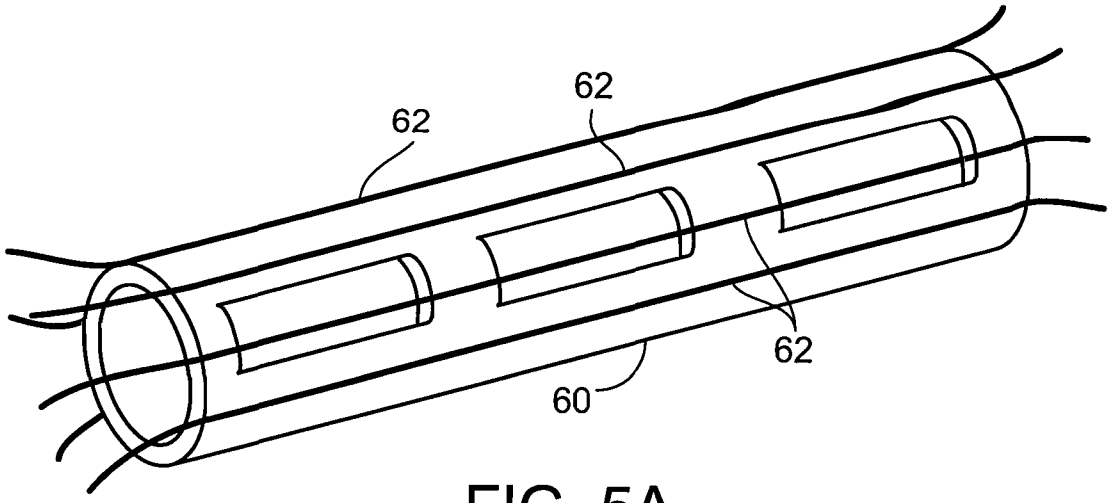



FIG. 5A

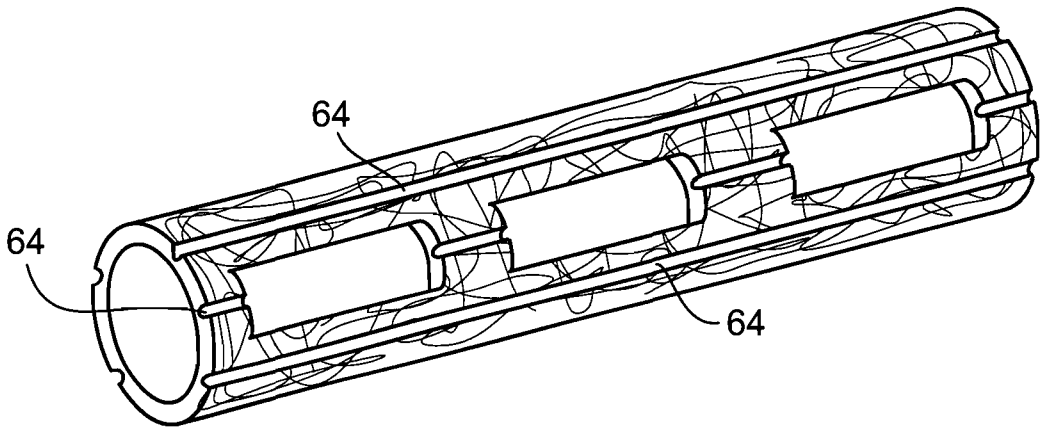



FIG. 5B

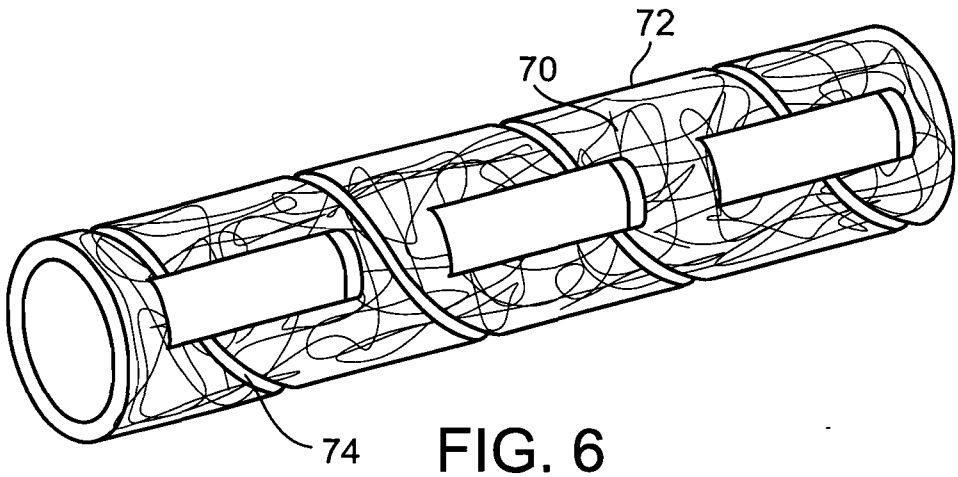



FIG. 6

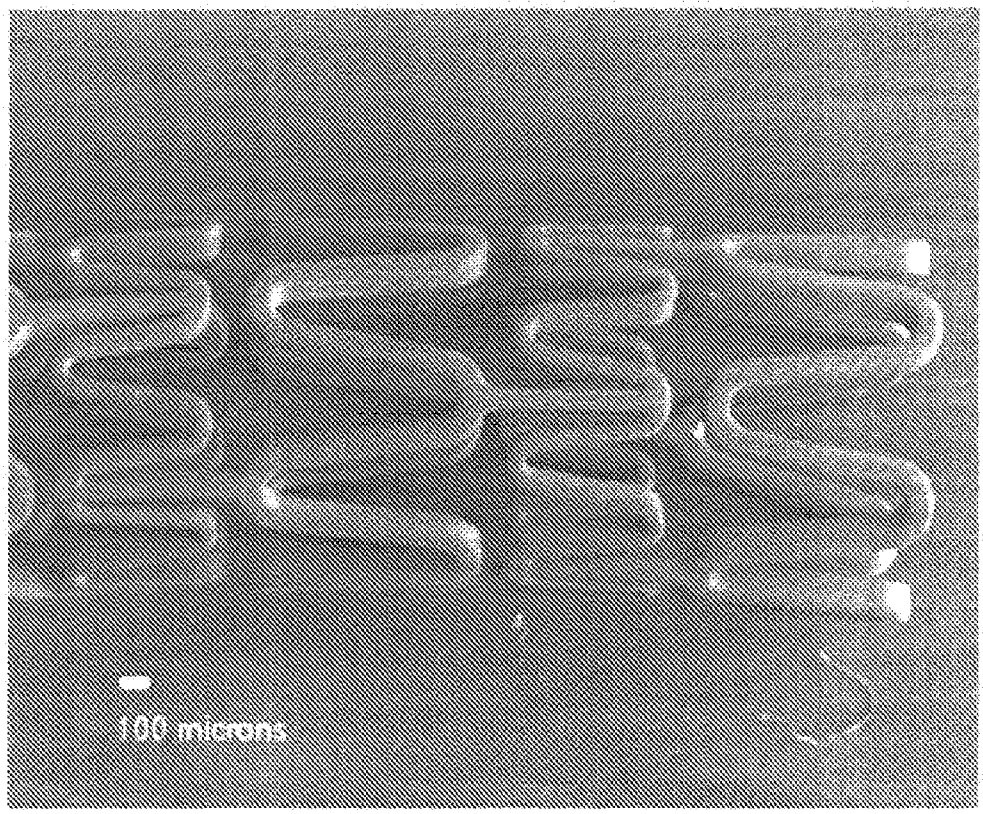

100 microns

FIG. 7

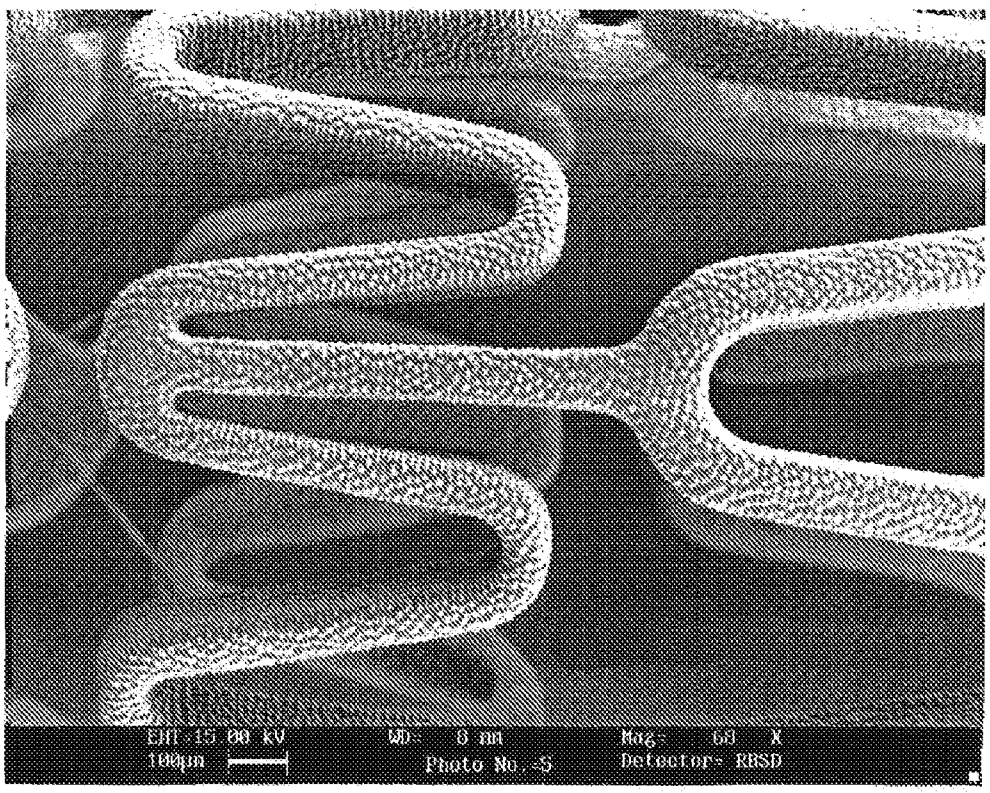

Eht 15.00 kV
WD= 8 mm
Mag= 63 X
100µm
Photo No.=5
Detector= RBSD

FIG. 8

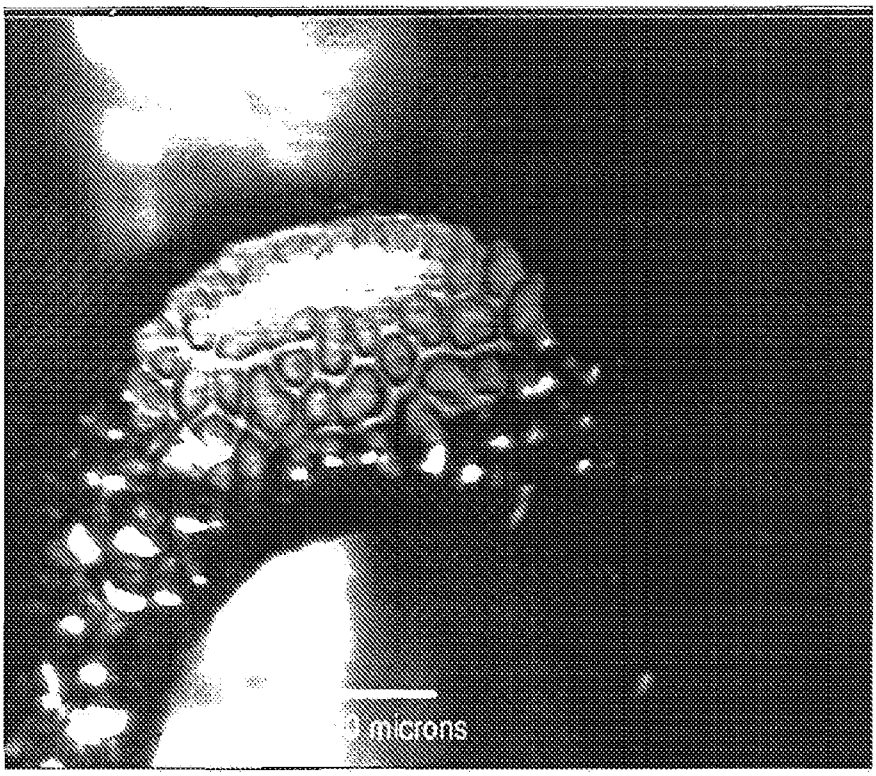



FIG. 9

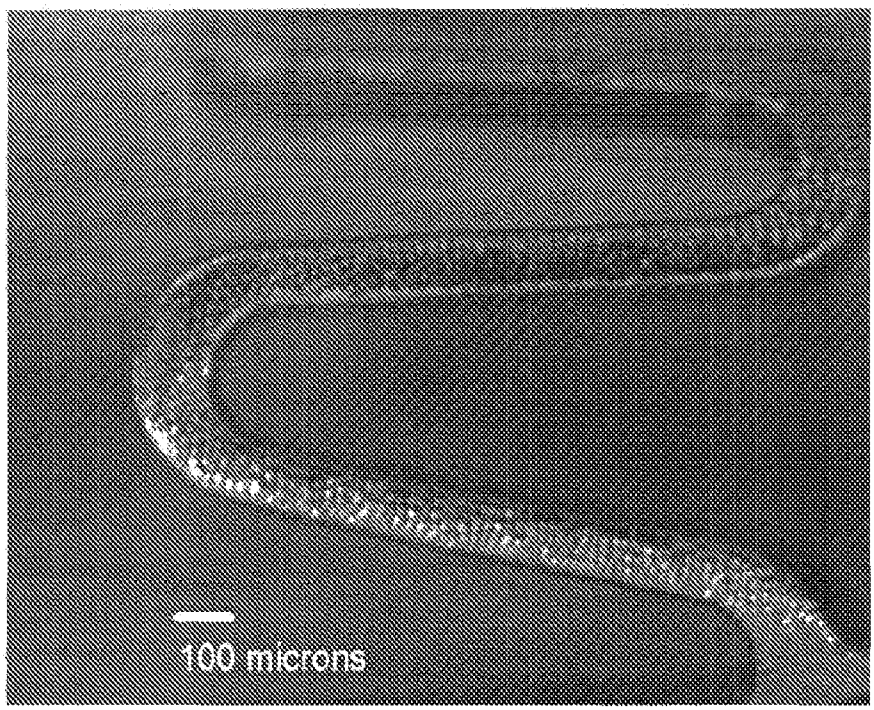



FIG. 10

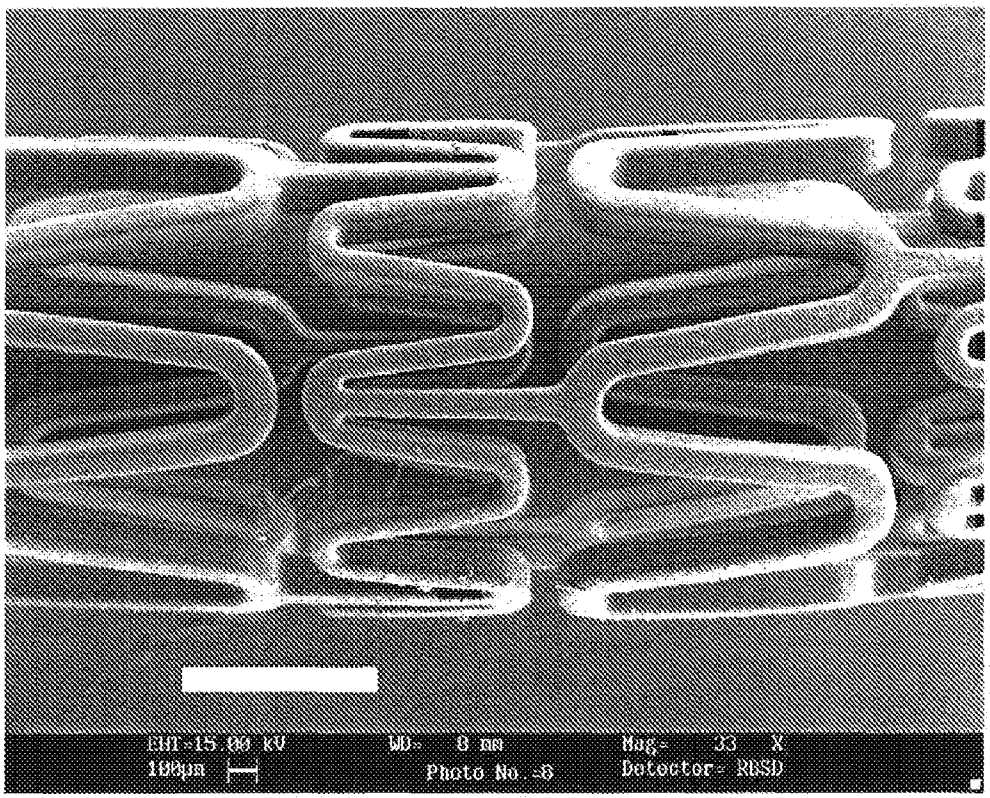

EHT=15.00 kV
WD= 8 mm
Mag= 33 X
100µm
Photo No.=6
Detector= RBSD

FIG. 11

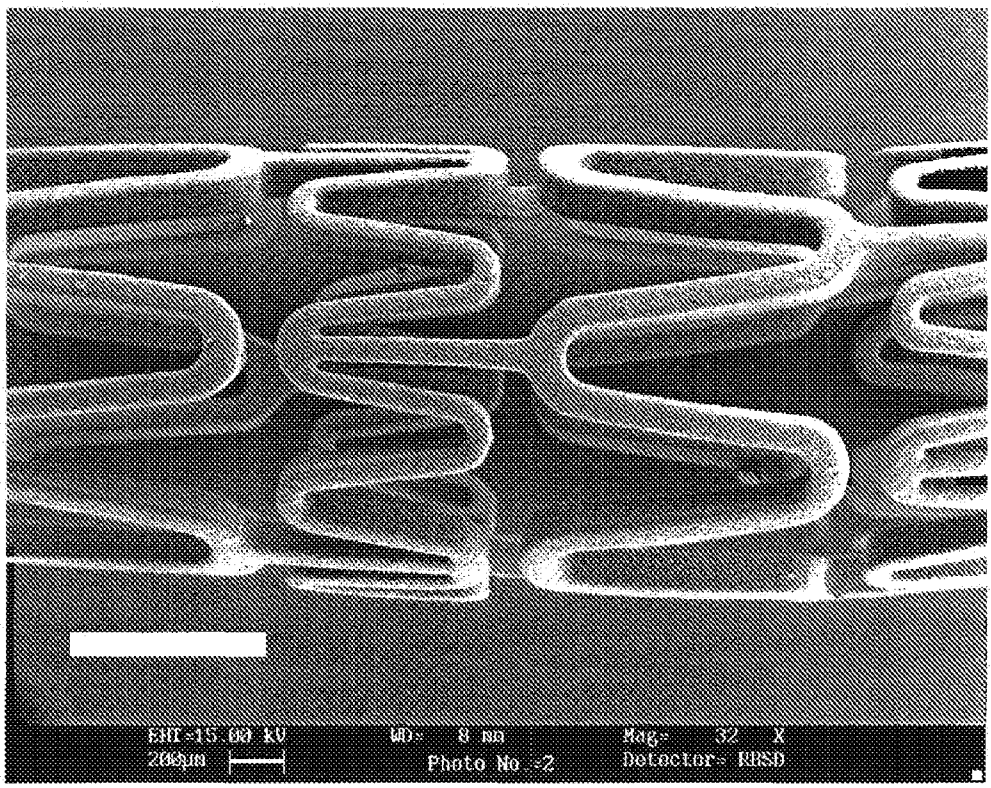

EHT=15.00 kV
WD= 8 mm
Mag= 32 X
200µm
Photo No.=2
Detector= RBSD

FIG. 12

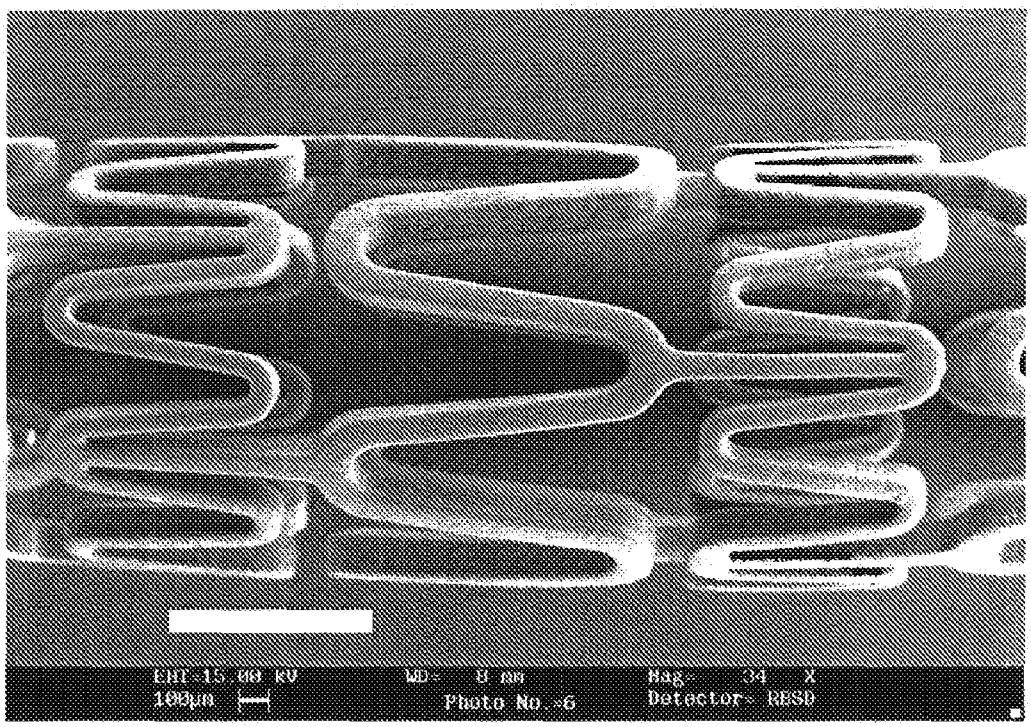



FIG. 13