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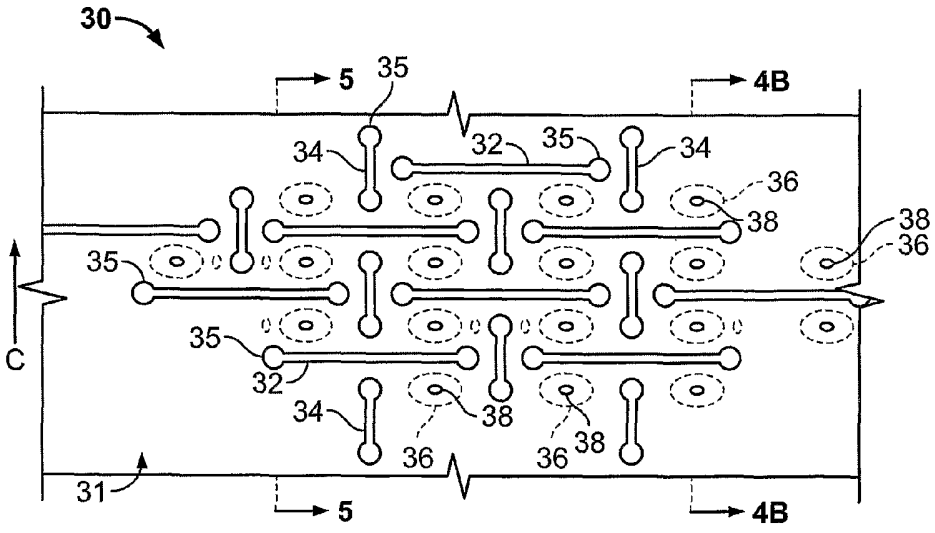
(54) Title: METALLIC DRUG-RELEASING MEDICAL DEVICES AND METHOD OF MAKING SAME




(57) Abstract: Implantable drug-releasing medical devices are fabricated of metallic or pseudometallic films of biocompatible materials having a plurality of microperforations passing through the film in a pattern that imparts fabric-like qualities to the device and/or permits the geometric deformation of the medical device. The implantable medical device is preferably fabricated by vacuum deposition of metallic and/or pseudometallic materials into either single or multi-layered structures with the plurality of microperforations either being formed during deposition or after deposition by selective removal of sections of the deposited film. The implantable medical device is suitable for use as endoluminal or surgical grafts and may be used, for example, as vascular grafts, stent-grafts, skin grafts, shunts, bone grafts, surgical patches, non-vascular conduits, valvular leaflets, filters, occlusion membranes, artificial sphincters, tendons and ligaments.

WO 2006/015161 A2

## Title of the Invention

[001] Metallic Drug-Releasing Medical Devices and Method of Making Same

## Cross-Reference to Related Applications

[002] This application is a continuation-in-part of co-pending U.S. Patent Application Serial No. 10/258,087 filed November 17, 2002 which is a continuation-in-part of co-pending U.S. Application Serial No. 09/716,146 filed November 17, 2000. This application is also related to prior co-pending and commonly assigned U.S. Patent Applications U.S. Serial No. 10/135,316 filed April 29, 2002 and U.S Serial No. 10/135,626 filed April 29, 2002, both of which claim priority to U.S. Provisional Application Serial No. 60/310,617 filed August 7, 2001, and to co-pending and commonly assigned U.S. Patent Application Serial No. 10/258,087, filed October 17, 2002 which corresponds to PCT International Publication No. WO02060506A1 published on August 8, 2002, each of which is hereby incorporated by reference.

## Background of the Invention

[003] The present invention relates generally to implantable metallic medical devices capable of releasing pharmacologically active agents. More specifically, the present invention relates to implantable drug-releasing medical devices, including, for example, surgical and endoluminal vascular grafts, stents, stent-grafts, covered stents, skin grafts, shunts, bone grafts, surgical patches, non-vascular conduits, valvular leaflets, filters, occlusion membranes, sphincters, artificial tendons and ligaments, vascular plugs, and orthopedic and dental implants. More specifically, the present invention relates to implantable medical grafts fabricated of metallic or pseudometallic films of biocompatible materials having a plurality of microperforations passing through the film and having a plurality of drug-releasing pockets defined within the film and positioned between adjacent pairs of microperforations. The plurality of microperforations impart both compliance and a fabric-like quality to the metallic or pseudometallic film of biocompatible material and permit geometric deformation of the film to permit, for example circumferential or longitudinal expansion of a tubular film.

[004] For purposes of this application both metallic and pseudometallic films of biocompatible materials will be referred to collectively as "metal film" or "metallic film." The inventive metal films may be fabricated by conventional wrought metal processing

techniques, or may be made by nanofabrication techniques such as physical vapor deposition or chemical vapor deposition.

**[005]** For purposes of this application the terms "microperforation" or "micro-opening" when used in either the singular or the plural are intended to mean openings having open surface area in the sub-millimeter to nanometer-scale openings.

**[006]** The metal film may have a generally tubular geometry, may have a generally planar geometry, or may be formed into complex geometric shapes. Those skilled in the art will understand, however, that regardless of the particular geometric shape of the metal film, the metal film has generally two opposing surfaces, hereinafter termed first and second metal film surfaces.

**[007]** The drug-releasing pockets are enclosed entirely within the metal film, except for at least one opening in the pocket of sufficient size to allow drug-release therethrough by diffusion, pumping or other active or passive means without being bound to or contained by a polymeric matrix. The drug-releasing pockets are bounded on all sides by the metal film and have a generally pillow-chamber-like or box-chamber-like geometry, with the at least one opening passing through the metal film at either or both of the first and second surfaces of the metal film.

**[008]** In addition to serving as boundaries for the drug-releasing pockets, the plurality of microperforations may serve multiple purposes, including, for example, permitting geometric deformation of the film, imparting a fabric-like quality to the film, and imparting flexibility to the film. The term "fabric-like" is intended to mean a quality of being pliable and/or compliant in a manner similar to that found with natural or synthetic woven fabrics.

**[009]** The inventive implantable grafts are fabricated entirely of self-supporting films made of biocompatible metals or biocompatible pseudometals. The metal films may either be single layer metal films or plural layer films. The terms "metal film," "thin metallic film" and "metal thin film" are used in this application synonymously to refer to single or plural layer films fabricated of biocompatible metals or biocompatible pseudometals having thicknesses greater than 0 mμ and less than about 125 μm. Heretofore in the field of implantable medical devices, it is unknown to fabricate an implantable medical device that comprises a graft at least as one of its elements, such as a covered stent or stent-graft, entirely of self-supporting metal or pseudometal materials. As used herein the term "graft" is

intended to indicate any type of device or part of a device that comprises essentially a material delimited by two surfaces where the distance between said surfaces is the thickness of the graft and that exhibits integral dimensional strength and that has microperforations that pass through the thickness of the graft. The inventive grafts may be formed in planar sheets, toroids, and in other shapes as particular applications may warrant. However, for purposes of illustration only, the present application will refer to tubular grafts. For purposes of this application, the terms "pseudometal" and "pseudometallic" are intended to mean a biocompatible material which exhibits biological response and material characteristics substantially the same as biocompatible metals. Examples of pseudometallic materials include, for example, polymers, composite materials and ceramics. Composite materials are composed of a matrix material reinforced with any of a variety of fibers made from ceramics, metals, carbon, or polymers.

[0010] When implanted into the body, metals are generally considered to have superior biocompatibility than that exhibited by polymers used to fabricate commercially available polymeric grafts. It has been found that when prosthetic materials are implanted, integrin receptors on cell surfaces interact with the prosthetic surface. The integrin receptors are specific for certain ligands *in vivo*. If a specific protein is adsorbed on a prosthetic surface and the ligand exposed, cellular binding to the prosthetic surface may occur by integrin-ligand docking. It has also been observed that proteins bind to metals in a more permanent fashion than they do to polymers, thereby providing a more stable adhesive surface. The conformation of proteins coupled to surfaces of most medical metals and alloys appears to expose greater numbers of ligands and preferentially attract endothelial cells having surface integrin clusters to the metal or alloy surface relative to leukocytes. Finally, metals and metal alloys exhibit greater resistance to degradation of metals relative to polymers, thereby providing greater long-term structural integrity and stable interface conditions.

[0011] Because of their relatively greater adhesive surface profiles, metals are also susceptible to short-term platelet activity and/or thrombogenicity. These deleterious properties may be offset by administration of pharmacologically active antithrombogenic agents in routine use today. Surface thrombogenicity usually disappears 1-3 weeks after initial exposure. Antithrombotic coverage is routinely provided during this period of time for coronary stenting. In non-vascular applications such as musculoskeletal and dental, metals have also greater tissue compatibility than polymers because of similar molecular

considerations. The best article to demonstrate the fact that all polymers are inferior to metals is van der Giessen, WJ. *et al.* Marked inflammatory sequelae to implantation of biodegradable and non-biodegradable polymers in porcine coronary arteries, *Circulation*, 1996:94(7):1690-7.

**[0012]** Normally, endothelial cells (EC) migrate and proliferate to cover denuded areas until confluence is achieved. Migration, quantitatively more important than proliferation, proceeds under normal blood flow roughly at a rate of 25 μm/hr or 2.5 times the diameter of an EC, which is nominally 10μm. EC migrate by a rolling motion of the cell membrane, coordinated by a complex system of intracellular filaments attached to clusters of cell membrane integrin receptors, specifically focal contact points. The integrins within the focal contact sites are expressed according to complex signaling mechanisms and eventually couple to specific amino acid sequences in substrate adhesion molecules. An EC has roughly 16-22% of its cell surface represented by integrin clusters. Davies, P.F., Robotewskyi A., Griem M.L. Endothelial cell adhesion in real time. *J.Clin.Invest.*1993; 91:2640-2652, Davies, P.F., Robotewski, A., Griem, M.L., Qualitiative studies of endothelial cell adhesion, *J.Clin.Invest.*1994; 93:2031-2038. This is a dynamic process, which implies more than 50% remodeling in 30 minutes. The focal adhesion contacts vary in size and distribution, but 80% of them measure less than 6 $\mu m^2$, with the majority of them being about 1 $\mu m^2$, and tend to elongate in the direction of flow and concentrate at leading edges of the cell. Although the process of recognition and signaling to determine specific attachment receptor response to attachment sites is incompletely understood, availability of attachment sites will favorably influence attachment and migration. It is known that materials commonly used as medical grafts, such as polymers, do not become covered with EC and therefore do not heal after they are placed in the arteries. It is therefore an object of this invention to replace polymeric implant materials with metallic film materials that have a greater healing response, are more hospitable for EC coverage and can heal completely. Furthermore, heterogeneities in the inventive metallic film materials that are in contact with blood flow are preferably controlled by exercising control over processing parameters employed during vacuum deposition of device-forming materials.

**[0013]** There have been numerous attempts to increase endothelialization of implanted medical devices such as stents, including covering the stent with a polymeric material (U.S. Patent No. 5,897,911), imparting a diamond-like carbon coating onto the stent (U.S. Patent No. 5,725,573), covalently binding hydrophobic moieties to a heparin molecule

(U.S. Patent No. 5,955,588), coating a stent with a layer of blue to black zirconium oxide or zirconium nitride (U.S. Patent No. 5,649,951), coating a stent with a layer of turbostratic carbon (U.S. Patent No. 5,387,247), coating the tissue-contacting surface of a stent with a thin layer of a Group VB metal (U.S. Patent No. 5,607,463), imparting a porous coating of titanium or of a titanium alloy, such as Ti-Nb-Zr alloy, onto the surface of a stent (U.S. Patent No. 5,690,670), coating the stent, under ultrasonic conditions, with a synthetic or biological, active or inactive agent, such as heparin, endothelium derived growth factor, vascular growth factors, silicone, polyurethane, or polytetrafluoroethylene, U.S. Patent No. 5,891,507), coating a stent with a silane compound with vinyl functionality, then forming a graft polymer by polymerization with the vinyl groups of the silane compound (U.S. Patent No. 5,782,908), grafting monomers, oligomers or polymers onto the surface of a stent using infrared radiation, microwave radiation or high voltage polymerization to impart the property of the monomer, oligomer or polymer to the stent (U.S. Patent No. 5,932,299). However, all these approaches do not address the lack of endothelialization of polymer grafts.

**[0014]** It is, therefore, desirable to fabricate the present invention of metallic and/or pseudometallic materials fabricated in such a manner as to control the mechanical, physical and chemical properties of the material. The inventive metal devices may be fabricated of pre-existing conventional wrought metallic materials, such as stainless steel or nitinol hypotubes, or may be fabricated by vacuum deposition techniques, such as physical vapor deposition or chemical vapor deposition. In accordance with the present invention, it is preferable to fabricate the inventive implantable devices by vacuum deposition. Vacuum deposition permits greater control over many material characteristics and properties of the resulting formed device. For example, vacuum deposition permits control over grain size, grain phase, grain material composition, bulk material composition, surface topography, mechanical properties, such as transition temperatures in the case of a shape memory alloy. Moreover, vacuum deposition processes will permit creation of devices with greater material purity without the introduction of large quantities of contaminants that adversely affect the material, mechanical or biological properties of the implanted device. Vacuum deposition techniques also lend themselves to fabrication of more complex devices than those susceptible of manufacture by conventional cold-working techniques. For example, multi-layer structures, complex geometrical configurations, extremely fine control over material tolerances, such as thickness or surface uniformity, are all advantages of vacuum deposition processing.

**[0015]** In vacuum deposition technologies, materials are formed directly in the desired geometry, *e.g.*, planar, tubular, etc. The common principle of vacuum deposition processes is to take a material in a minimally processed form, such as pellets or thick foils, known as the source material and atomize them. Atomization may be carried out using heat, as is the case in physical vapor deposition, or using the effect of collisional processes, as in the case of sputter deposition, for example. In some forms of deposition, a process, such as laser ablation, which creates microparticles that typically consist of one or more atoms, may replace atomization; the number of atoms per particle may be in the thousands or more. The atoms or particles of the source material are then deposited on a substrate or mandrel to directly form the desired object. In other deposition methodologies, chemical reactions between ambient gas introduced into the vacuum chamber, *i.e.*, the gas source, and the deposited atoms and/or particles are part of the deposition process. The deposited material includes compound species that are formed due to the reaction of the solid source and the gas source, such as in the case of chemical vapor deposition. In most cases, the deposited material is then either partially or completely removed from the substrate, to form the desired product.

**[0016]** A first advantage of vacuum deposition processing is that vacuum deposition of the metallic and/or pseudometallic films permits tight process control and films may be deposited that have regular, homogeneous atomic and molecular pattern of distribution along their fluid-contacting surfaces. Different process parameters employed in vacuum deposition processing may be controlled to fabricate achieve metallic and/or pseudometallic films with controlled material properties, atomic and molecular constitution and controlled surface heterogeneities. Process parameters which may be controlled in exercising control over the properties of the resulting deposited film include, for example, target composition, shape and construction, target and/or substrate temperature, rate of deposition, shape and construction of the magnetron, shape and strength of the magnetic field, the strength of the applied electrical field, the partial pressure of gases during deposition, the chamber pressure, the substrate composition and/or topography, or vacuum chamber configuration. Vacuum deposition of device-forming films avoids the marked variations in surface composition, creating predictable oxidation and organic adsorption patterns and has predictable interactions with water, electrolytes, proteins and cells. Particularly, EC migration is supported by a homogeneous distribution of binding domains that serve as natural or implanted cell attachment sites, in order to promote unimpeded migration and attachment.

**[0017]** Secondly, in addition to materials and devices that are made of a single metal or metal alloy, henceforth termed a layer, the inventive grafts may be comprised of a layer of biocompatible material or of a plurality of layers of biocompatible materials formed upon one another into a self-supporting multilayer structure because multilayer structures are generally known to increase the mechanical strength of sheet materials, or to provide special qualities by including layers that have special properties such as superelasticity, shape memory, radio-opacity, corrosion resistance etc. A special advantage of vacuum deposition technologies is that it is possible to deposit layered materials and thus films possessing exceptional qualities may be produced (*cf.*, H. Holleck, V. Schier: Multilayer PVD coatings for wear protection, *Surface and Coatings Technology*, Vol. 76-77 (1995) pp. 328-336). Layered materials, such as superstructures or multilayers, are commonly deposited to take advantage of some chemical, electronic, or optical property of the material as a coating; a common example is an antireflective coating on an optical lens. Multilayers are also used in the field of thin film fabrication to increase the mechanical properties of the thin film, specifically hardness and toughness.

**[0018]** Thirdly, the design possibilities for possible configurations and applications of the inventive graft are greatly enhanced by employing nanofabrication methodologies. Vacuum deposition is an additive technique that lends itself toward fabrication of substantially uniformly thin materials with potentially complex three dimensional geometries and structures that cannot be cost-effectively achieved, or in some cases achieved at all, by employing conventional wrought fabrication techniques. Additionally, subtractive processes, such as photolithography, etching, including, without limitation, chemical etching and laser etching or electrical discharge machining (EDM) may be employed to selectively remove materials from a pre-existing film and create very small scale, e.g., $10^{-8}$ to $10^{-10}$ features in the film.

**[0019]** Conversely, conventional wrought metal fabrication techniques may entail smelting, hot working, cold working, heat treatment, high temperature annealing, precipitation annealing, grinding, ablation, wet etching, dry etching, cutting and welding. All of these processing steps have disadvantages including contamination, material property degradation, ultimate achievable configurations, dimensions and tolerances, biocompatibility and cost. For example conventional wrought processes are not suitable for fabricating tubes having diameters greater than about 20mm diameter, nor are such processes suitable for fabricating materials having wall thicknesses down to about 5 μm with sub-μm tolerances.

**[0020]** While the inventive metal or pseudometal drug-releasing graft may be fabricated of conventionally fabricated wrought materials, in accordance with the best mode contemplated for the present invention, the inventive drug-releasing graft is preferably fabricated by vacuum deposition techniques. By vacuum depositing the metal and/or pseudometallic film as the precursor material for the inventive drug-releasing graft, it is possible to more stringently control the material, biocompatibility and mechanical properties of the resulting film material and graft than is possible with conventionally fabricated graft-forming materials. The inventive self-supporting graft may be used alone, *i.e.*, the whole implantable device may be made of a single graft, or it may be a part of a structure where the graft is used in conjunction either with other grafts, or in conjunction with other structural elements, such as scaffolds, stents, and other devices. The term "in conjunction" may mean actual connection, such as that made by welding, fusing, or other joining methods, as well as being made from the same piece of material by forming some area of the piece into a graft and some other area of the piece into another member or part of the device.

## Summary of the Invention

**[0021]** In accordance with a preferred embodiment of the invention, there is provided a self-supporting graft member having a wall thickness between about 1mμ to about 75 mμ, a plurality of microperforations passing through the wall thickness of the graft and a plurality of enclosed pockets positioned between adjacent pairs of microperforations and formed within the wall thickness of the graft or formed upon a surface of the graft and having a plurality of drug-releasing openings communicating between an enclosed chamber within each enclosed pocket and external the enclosed pocket. The graft member may assume virtually any geometric configuration, including sheets, tubes or rings, but preferably is provided as a generally tubular configuration. The plurality of microperforations serve to impart geometric compliance to the graft, geometric distendability to the graft and/or limit or permit the passage of body fluids or biological matter through the graft, such as facilitating transmural endothelialization while preventing fluid flow through the wall of the graft under normal physiological conditions. The plurality of microperforations also impart a fabric-like quality to the graft by imparting pliability and/or elastic, plastic or superelastic compliance to the graft, such as that required for longitudinal flexibility in the case of a vascular graft.

**[0022]** In accordance with a preferred embodiment of the invention, the drug-releasing pockets are positioned intermediate adjacent pairs of microperforations and reside entirely with the wall thickness of the graft material and are bounded entirely by the graft material, with at least one opening communicating between an internal chamber within the drug-releasing pocket and external the graft.

**[0023]** In accordance with an alternate embodiment of the invention, the drug-releasing pockets are positioned on either a first or second surface of the graft and the drug-releasing pockets bounded on at least one surface, but not entirely, by the graft material, with at least one opening communicating between a chamber within the drug-releasing pocket and external the graft.

**[0024]** In a first embodiment, the graft may be made from plastically deformable materials such that upon application of a force, the microperforations geometrically deform to impart permanent enlargement of one or more axes of the graft, such as length in the case of a planar graft, *e.g.*, a surgical patch graft, or diameter, such as in the case of a tubular graft, *e.g.*, a vascular graft. In a second embodiment, the graft may be fabricated of elastic or superelastic materials. Elastic and/or superelastic materials will permit the microperforations to geometrically deform under an applied force in a manner that allows for a recoverable change in one or more axes of the graft.

**[0025]** The applied force may also be utilized to deform openings in the implantable material which communicate with drug-releasing chambers in the implantable material and, thereby, release the drug from the implantable material. For example, a balloon mounted on a catheter may be employed as the source of the applied force to the implantable material.

**[0026]** The positioning and conformation of the drug-releasing pockets may be controlled to enable the force applied from the geometric deformation of the plurality of microperforations to transfer to the drug-releasing pockets, thereby serving to apply a pumping-like force to release a metered dose of the agent within the drug-releasing pockets. Alternatively, the pockets may be isolated from the strain resulting from the geometric deformation of the plurality of microperforations to prevent release of the agent during geometric deformation of the drug-releasing graft.

**[0027]** It is desirable, in accordance with the preferred embodiments of the invention, to position the drug-releasing pockets in an even distribution about circumferential and longitudinal axes of the device so as to provide substantially uniform coverage and release

about all axes of the device. However, in accordance with alternative embodiments of the invention, the drug-releasing pockets may be positioned such that different longitudinal or circumferential regions of the device have higher or lower densities and distribution of the drug-releasing pockets. By varying the position, density, size and distribution of the drug-releasing pockets relative to position along the axes of the device, drug dosage may be controlled as a function of position of the drug-releasing pockets.

**[0028]** With current polymer-coated drug-releasing stents, the drug releases substantially uniformly about the circumference of the polymer, and along the length of the device. There is, however, a significant reduction in released drug concentration at the proximal and distal ends of the device where there is little polymer surface area from which the drug may release. In comparison, with the present invention, the positions of the drug-releasing pockets may be selected during device design and fabrication to directionally release drug, *i.e.*, luminally, abluminally, at selected positions along either the longitudinal or circumferential axis of the device or from either or both of the proximal and distal ends of the device.

**[0029]** In each of the first and second embodiments of the invention, the graft may be fabricated in such a manner as to have fabric-like qualities by controlling the film thickness, material properties and geometry of the plurality of microperforations. Furthermore, in such cases where minimally invasive delivery is required, such as for endoluminal delivery of vascular grafts, the first and second embodiments allow for delivery using balloon expansion and self-expansion, respectively, or a combination of both. Minimally invasive delivery may also be accomplished by folding the graft for delivery similar to the manner in which an angioplasty balloon is creased and fluted or folded. The graft may be delivered by unfolding the device *in vivo* either by assistance such as by using a balloon, or by the graft material's plastic, elastic or superelastic properties or by a combination thereof. The plurality of microperforations may be patterned in such a manner as to allow for additional dimensional enlargement of the drug-releasing graft member *in vivo* by elastic or plastic deformation such as a radially expansive positive pressure.

**[0030]** For some applications it is preferable that the size of each of the plurality of microperforations be such as to permit cellular migration through each opening, without permitting fluid flow there through. In this manner, for example, blood cannot flow through the plurality of microperforations (in their deformed or un-deformed state), but various cells or proteins may freely pass through the plurality of microperforations to promote graft

healing *in vivo*. For other applications, moderate amounts of fluid flow through the plurality of deformed or un-deformed microperforations may be acceptable. For example, endoluminal saphenous vein grafts may be fabricated with microperforations that serve the dual function of permitting transmural endothelialization while also excluding biological debris, such as thrombus from passing through the wall thickness of the graft, effectively excluding detrimental matter from entering the circulation. In this example, each of the plurality of microperforations in either their deformed or undeformed state, may exceed several hundred microns.

**[0031]** Those skilled in the art will understand that a direct relationship exists between the size of pores and the overall ratio of expansion or deformability of an implantable graft. Generally, therefore, it is appreciated that pore sizes must increase in order to increase the effective attainable degree of expansion or deformation of the graft.

**[0032]** For applications where large deformation and small pore size are both requirements, in accordance with another aspect of the inventive graft embodiment, it is contemplated that two or more graft members are employed such as diametrically concentric grafts for tubular configurations. The two or more graft members have a pattern of a plurality of microperforations passing there through, with the plurality of patterned microperforations being positioned out of phase relative to one another such as to create a tortuous cellular migration pathway through the wall of the concentrically engaged first and second graft members as well as a smaller effective pore size. The two or more graft members may each be drug-releasing grafts or a combination of drug-releasing and non-drug-releasing grafts. For example, a lumenal graft only may be drug-releasing to release a pharmacologically active agent into the blood-stream, while a concentrically positioned non-releasing graft may be an ablumenal graft, alternatively, the relative position of the lumenal and ablumenal grafts may be switched such that the ablumenal graft is drug-releasing and the lumenal graft is non-releasing.

**[0033]** In order to facilitate cellular migration through and healing of the first and second graft members *in vivo*, it may be preferable to provide additional cellular migration pathways that communicate between the plurality of microperforations in the first and second graft members. These additional cellular migration pathways, if necessary, may be imparted as 1) a plurality of projections formed on either the luminal surface of the second graft or the abluminal surface of the first graft, or both, which serve as spacers and act to maintain an annular opening between the first and second graft members that permits cellular migration

and cellular communication between the plurality of microperforations in the first and second graft members, 2) a plurality of microgrooves, which may be random, radial, helical, or longitudinal relative to the longitudinal axis of the first and second graft members, the plurality of microgrooves being of a sufficient size to permit cellular migration and propagation along the groove, the microgrooves serve as cellular migration conduits between the plurality of microperforations in the first and second graft members, or 3) where the microperforations are designed to impart an out of plane motion of the graft material upon deformation, thereby keeping a well defined space between the planes originally defining the facing surfaces of the grafts.

**[0034]** Each of the drug-releasing graft or the non-releasing graft members may be formed as a monolayer film, or may be formed from a plurality of film layers formed one upon another. The particular material used to form each layer of biocompatible metal and/or pseudometal is chosen for its biocompatibility, corrosion-fatigue resistance and mechanical properties, *i.e.*, tensile strength, yield strength. The metals include, without limitation, the following: titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, such as zirconium-titanium-tantalum alloys, nitinol, and stainless steel. Additionally, each layer of material used to form the graft may be doped with another material for purposes of improving properties of the material, such as radiopacity or radioactivity, by doping with tantalum, gold, or radioactive isotopes. Alternatively, pseudometallic materials may include polymers, carbon-fiber or ceramics.

## Brief Description of the Drawings

**[0035]** Figure 1 is a perspective view of the inventive drug-releasing graft.

**[0036]** Figure 2 is a fragmentary cross-sectional view taken along line 2-2 of Figure 1.

**[0037]** Figure 3 is a fragmentary plan view of an embodiment of the inventive drug-releasing graft depicting a pattern of chambers and openings in the graft.

**[0038]** Figure 4A is a fragmentary plan view of an alternative embodiment of the inventive drug-releasing graft depicting a pattern of chambers and openings in the graft.

**[0039]** Figure 4B is a cross-sectional view taken along line 4B-4B of Figure 4A.

**[0040]** Figure 5 is a fragmentary cross-sectional view taken along line 5-5 of Figure 4A.

**[0041]** Figure 6 is a fragmentary cross-sectional view taken along line 6-6 of Figure 3.

**[0042]** Figure 7 is a fragmentary cross-sectional view of an alternative embodiment of the present invention.

**[0043]** Figure 8 is a process flow diagram illustrating methods of making the inventive implantable drug-releasing medical device.

## Detailed Description of the Preferred Embodiments

**[0044]** With the foregoing as background, we turn now to a description of the present invention with reference the preferred embodiments thereof and with reference to the accompanying figures. As noted above, the inventive microporous metallic implantable devices may assume a wide number of geometric configurations, including, for example, planar sheets, tubes, toroids or other geometric configurations. For ease of reference, however, the accompanying figures and the following description of the invention will refer to tubular implantable graft members. Those skilled in the art, however, will understand that this is merely an exemplary geometric configuration and is not intended to limit the scope of the invention to tubular members or be limited in application to graft members.

**[0045]** With particular reference to Figures 1-2, the inventive implantable medical device 10 is illustrated as a graft. It will be understood that the device 10 is described herein only as a non-limiting example of the inventive implantable medical device, and that the inventive implantable medical may assume other geometries, and be used for other applications or indications. Device 10 consists generally of a body member 12 comprising a coherent metal or pseudometallic material and having a first surface 14 and a second surface 16 and a thickness 18 intermediate the first surface 14 and the second surface 16. A plurality of microperforations 20 is provided that pass through at least one of the first surface 14, the second surface 16 or the thickness 18 of the body member 12 with interperforation regions 22 of the body member 12 being located between adjacent pairs of microperforations 20. The plurality of microperforations 20 each may have a geometric configuration that is susceptible of geometric change under the application or release of an externally applied load, or upon a phase change in the material, such as a shape memory or superelastic change. Alternatively,

the plurality of microperforations 20 may have a pattern and geometric configuration that imparts a fabric-like quality and compliance to the material of device 10. A plurality of drug-releasing chambers 15 are provided in the interperforation regions 22 intermediate adjacent pairs of microperforations 20 and retain a pharmacologically active agent 24 for release through at least one microperforation 20 in fluid flow communication with the drug-releasing chambers 15.

**[0046]** Each of the plurality of microperforations 20 in the undeformed state preferably has an open surface area less than about 2 $mm^2$, with the total open surface area of the graft in the undeformed state being between 0.001 to 99%. The open surface area of the plurality of microperforations and the open surface area of the graft may change considerably upon deformation of the plurality of microperforations 20. Both the size of the microperforations 20 in the deformed and undeformed state and the total open area of the body member 12 in the deformed and undeformed state may be selected in view of the following non-exclusive factors based on the graft application: 1) the desired compliance of the device 10, 2) the desired strength of the device 10, 3) desired stiffness of the device 10, 4) the desired degree of geometric enlargement of the microperforations 20 upon deformation, 5) in some cases, such as with vascular grafts, the desired delivery profile and post delivery profile, and 6) the drug release profile for delivering the pharmacologically active agent from the drug-releasing pockets.

**[0047]** In accordance with a preferred embodiment of the present invention, the plurality of microperforations 20 is patterned in such a manner as to define regions of the body member which permit, but do not require deformation of the device 10. The thickness 18 is between 0.1μm and 75μm, preferably between 1μm and 50μm. When fabricated within these thickness ranges, the device 10 has a thickness 18 which is thinner than the wall thickness of conventional non-metallic implantable grafts and that of conventional metal endoluminal stents.

**[0048]** The plurality of microperforations 20 is patterned in a regular array forming a regular array of microperforations 20 in both the longitudinal and circumferential axes of the body member 12. For purposes of reference, the pattern of microperforations 20 will, hereinafter, be described with reference to a planar X-Y axes, which in a tubular member will correspond to the longitudinal or circumferential axes of the tubular member. Those of ordinary skill in the art will understand that reference to X-axis or Y-axis when applied to a tubular member may be used such that the term "X-axis" may correspond to either the

longitudinal axis or circumferential direction of the tubular member and the term "Y-axis" may refer to the corresponding circumferential direction or longitudinal axis or the tubular member.

**[0049]** It will be appreciated by those of ordinary skill in the art that individual different geometric patterns may have associated intended uses, function or mechanical requirements of a particular device. Thus, the particular intended use of the inventive device 10 will be a consideration in the selection of the particular geometric pattern for the plurality of microperforations 20. For example, where the inventive device 10 has an intended use as a free-standing implantable endoluminal vascular graft, a large circumferential expansion ratio and longitudinal flexibility may be desirable. Thus, a particular geometry of the plurality of microperforations 20 that offers these properties will be selected. The plurality of microperforations 20 also affect the material properties of the inventive device 10. For example, the geometry each microperforation 20 may be altered so that each microperforation 20 exhibits stress-strain relief capabilities or the microperforations 20 may control whether geometric deformation of the microperforations 20 are plastic, elastic or superelastic deformation. Thus, both the geometry of the individual microperforations 20, the orientation of the microperforations 20 relative to the X-Y axis of the device 10 and the pattern of the microperforations 20 may be selected to directly impart, affect or control the mechanical and material properties of the device 10.

**[0050]** The plurality of drug-releasing chambers 15 may reside entirely within the thickness 18 of the body member 12, may reside entirely without the thickness 18 of the body member 12 and be proximate either the first surface 14 or the second surface 16, or both, of the body member 12, or be defined by a recess in at least one of the first surface 14 and the second surface 16 and enclosed therebetween. One skilled in the art will understand that the first surface 14 and the second surface 16 may be opposing surfaces of a single member, or may be surfaces of plural members positioned adjacent one another as is illustrated by phantom line 37 in Figure 5.

**[0051]** Suitable pharmacologically active agents include, without limitation, paclitaxel, taxol, rapamycin, rapamycin derivatives, such as those disclosed in U.S. Patent Application Publication 2003/0170287 published September 11, 2003, sirolimus, rapamune, tacrolimus, dexamethasone, everolimus, ABT-578 (a rapamycin analogue that inhibits the mTOR cell cycle regulatory protein), and growth factors, such as VEG-F. The pharmacologically active agents may be loaded into the plurality of drug-releasing chambers

15 by employing a pharmacologically acceptable carrier. The term "pharmacologically active agents" as used herein is used synonymously with "drug(s)".

**[0052]** The pharmacologically active agents may be incorporated into or affixed to the device 10 in a number of ways and utilizing any biocompatible materials; it may be incorporated into *e.g.* a polymer or a polymeric matrix and sprayed onto the device. A mixture of the pharmacologically active agents and the polymeric material may be prepared in a solvent or a mixture of solvents and applied to the device 10 also by dip-coating, brush coating and/or dip/spin coating, the solvent component being allowed to evaporate to leave a film with entrapped drugs. In the case of stents where the drug(s) is delivered from micropores, struts or channels, a solution of a polymer may additionally be applied as an outlayer to control the drug(s) release; alternatively, the active agent may be comprised in the micropores, struts, channels or internal chambers and the active co-agent may be incorporated in the outlayer, or vice versa. The active agent may also be affixed in an inner layer of the stent and the active co-agent in an outer layer, or vice versa. The drug(s) may also be attached by a covalent bond, *e.g.* esters, amides or anhydrides, to the stent surface, involving chemical derivatization. The drug(s) may also be incorporated into a biocompatible porous ceramic coating, *e.g.* a nanoporous ceramic coating. The medical device of the invention is configured to release the active co-agent concurrent with or subsequent to the release of the active agent.

**[0053]** Examples of polymeric materials include hydrophilic, hydrophobic or biocompatible biodegradable materials, *e.g.* polycarboxylic acids; cellulosic polymers; starch; collagen; hyaluronic acid; gelatin; lactone-based polyesters or copolyesters, *e.g.* polylactide; polyglycolide; polylactide-glycolide; polycaprolactone; polycaprolactone-glycolide; poly(hydroxybutyrate); poly(hydroxyvalerate); polyhydroxy(butyrate-co-valerate); polyglycolide-co-trimethylene carbonate; poly(diaxanone); polyorthoesters; polyanhydrides; polyaminoacids; polysaccharides; polyphospoeters; polyphosphoester-uretha- ne; polycyanoacrylates; polyphosphazenes; poly(ether-ester) copolymers, *e.g.* PEO-PLLA, fibrin; fibrinogen; or mixtures thereof; and biocompatible non-degrading materials, e.g. polyurethane; polyolefins; polyesters; polyamides; polycaprolactame; polyimide; polyvinyl chloride; polyvinyl methyl ether; polyvinyl alcohol or vinyl alcohol/olefin copolymers, e.g. vinyl alcohol/ethylene copolymers; polyacrylonitrile; polystyrene copolymers of vinyl monomers with olefins, *e.g.* styrene acrylonitrile copolymers, ethylene methyl methacrylate copolymers; polydimethylsiloxane; poly(ethylene-vinylacetate); acrylate based polymers or coplymers, *e.g.* polybutylmethacrylate, poly(hydroxyethyl methylmethacrylate); polyvinyl

pyrrolidinone; fluorinated polymers such as polytetrafluoethylene; cellulose esters e.g. cellulose acetate, cellulose nitrate or cellulose propionate; or mixtures thereof.

**[0054]** When a polymeric matrix is used, it may comprise 2 layers, *e.g.* a base layer in which the drug(s) is/are incorporated, *e.g.* ethylene-co-vinylacetate and polybutylmethacrylate, and a top coat, *e.g.* polybutylmethacrylate, which is drug(s)-free and acts as a diffusion-control of the drug(s). Alternatively, the active agent may be comprised in the base layer and the active co-agent may be incorporated in the outlayer, or vice versa.

**[0055]** The plurality of drug-releasing chambers 15 and the associated plurality of microperforations 20 may be similarly dimensioned and positioned generally uniformly along both the longitudinal axis and the circumferential axis of the device 10 to achieve a generally uniform drug delivery profile from the device 10. Alternatively, the drug-releasing chambers 15 and the associated plurality of microperforations 20 may be sized and positioned differentially about the circumferential and longitudinal axes of the device 10 to provide different dosage vs. position relationships or dosage vs. time relationships. Moreover, at least some of the plurality of microperforations 20 may be positioned on either or both of the luminal and abluminal surfaces of the device in order to release the drug from the outer circumference of the device 10 and/or from the inner circumference of the deice 10. Drug concentration releasing over time may be regulated by providing differentially dimensioned microperforations 20 which permit different release rates for the drug and may be controlled to achieve desired concentration plateaus over an extended period of time.

**[0056]** Additionally, conventional polymer-coated drug-releasing stents have release profiles which release drug about the entire circumferential axis of the coating, with a significant drop off of concentration from the proximal and distal ends of the device. This concentration drop off is often associated with end restenosis known in the art as the "candy-wrapper effect." By permitting wide variability in positioning of the drug-releasing chambers 15 and the associated microperforations 20, the directional orientation, position and concentration of drug release may be controlled in the device 10 of the present invention.

**[0057]** Exemplary, non-limiting, geometric patterns for the plurality of microperforations 20 in Figures 1-2 are shown in Figure 4A. Figures 4A and 4B depict an implantable drug-releasing device 30 having a longitudinal axis L and a circumferential axis C, denominated by directional arrows L and C, respectively in Figure 4A, with Figure 4B being a transverse cross-sectional view taken along the circumferential axis C of device 30

depicted in Figure 4A. A plurality of first elongate microperforations 32 having a common orientation parallel to the longitudinal axis L of the device 30 are provided and pass through the thickness of the device 30 and the first and/or second surfaces 31, thereof. Circumferentially adjacent pairs of first elongate microperforations 32 are longitudinally offset such that the terminus of each first elongate microperforation 32 resides circumferentially adjacent an intermediate region of the adjacent first elongate microperforation 32.

**[0058]** A plurality of second elongate microperforations 34 are provided that have a common orientation parallel to the circumferential axis C of the device 30 and pass through the thickness of the device 30 and the first or second surfaces 31, thereof. A single second elongate microperforation 34 is positioned intermediate adjacent pairs of the first elongate microperforations 32, with each terminus of the second elongate microperforations 32 residing proximate an intermediate region of a circumferentially adjacent first elongate microperforation 32.

**[0059]** Each of the first and second generally elongate microperforations 32, 34 preferably have terminal fillets 35 on each opposing ends of each elongate microperforation 32, 34. The terminal fillets 35 serve a strain relief function that aids in strain distribution through the interperforation regions 22 between adjacent slots 32 and 34.

**[0060]** Those skilled in the art will understand that each of the microperforations 20 may have any of a wide variety of geometric configuration, dimension and surface area, and that the elongate slot configuration of the exemplary configuration in Figures 4A and 4B are for illustration purposes only. Alternative microperforation 20 geometries are disclosed, for example, in commonly assigned co-pending U.S. Patent Applications Serial No. 60/414,209 10/135,316 and 10/135,626, both filed September 26, 2002 and Serial No. 10/672,695, filed September 26, 2003, both entitled "Implantable Graft and Methods of Making Same", both of which are commonly assigned with the present application and both of which are hereby expressly incorporated by reference for purposes of illustrating a wide variety of suitable microperforation 20 geometries.

**[0061]** Of particular significance to the present invention is the provision of a plurality of drug-releasing chambers 36. In accordance with one embodiment of the invention, as illustrated in Figures 4A and 5, the plurality of drug-releasing chambers 36 may reside entirely within the thickness of the device 30, intermediate the first 31 and second 33

surfaces of the device 30. Alternatively, as illustrated in Figures 3 and 6, the drug releasing chambers 36 may reside adjacent either the first 21 or second 23 surfaces of the device 10, and be bounded by a second layer of device material 46 which acts as an enclosing cap for the drug releasing chamber 36. The plurality of openings 20 preferably pass through the second layer of device material 46 and communicate with the drug releasing chamber 36 to permit release of the drug therefrom. Finally, in accordance with a third embodiment depicted in Figure 7, the drug-releasing chambers may be formed as recesses 56 in a first layer of a device material 52, which is then covered by a second layer of a device material 54 having a plurality of openings 58 passing therethrough patterned such that at least one opening 58 positionally corresponds to one of the recesses 56.

**[0062]** Thus, one embodiment of the present invention provides a new metallic and/or pseudometallic implantable graft that is biocompatible, geometrically changeable either by folding and unfolding or by application of a plastically, elastically or superelastically deforming force, and capable of endoluminal delivery with a suitably small delivery profile. Suitable metal materials to fabricate the inventive graft are chosen for their biocompatibility, mechanical properties, *i.e.*, tensile strength, yield strength, and their ease of fabrication. The compliant nature of the inventive graft material may be employed to form the graft into complex shapes by deforming the inventive graft over a mandrel or fixture of the appropriate design. Plastic deformation and shape setting heat treatments may be employed to ensure the inventive implantable members 10 retain a desired conformation.

**[0063]** According to a first preferred method of making the graft of the present invention, the drug-releasing device is fabricated of at least two vacuum deposited metallic and/or pseudometallic films into which the plurality of microperforations are formed. The at least two films are conjoined in such a manner as to form a pattern of internal chambers in an interfacial region between the two films. The plurality of release openings are then formed through one or both of the at least two films and in communication with the pattern of internal chambers. Finally, a pharmacologically active agent is loaded through the release openings.

**[0064]** In accordance with a second preferred method of making the device of the present invention, a first layer of device-forming material is vacuum deposited, a pattern of a sacrificial material is then imparted onto a surface of the first layer of device-forming material, then a second layer of device-forming material is vacuum deposited onto the first layer and the sacrificial material. The plurality of microperforations is formed through the

first and second layers of device-forming material between regions where the sacrificial material is present. A plurality of releasing-openings is then formed through at least one of the first and second layer of device-forming material and in communication with the regions of the sacrificial material. The sacrificial material is then removed, such as by chemical etching specific for the sacrificial material, through the release openings. The pharmacologically active agent may then be loaded through the releasing openings.

**[0065]** The methods 50 of making the inventive drug-releasing device of the present invention are illustrated in Figure 8. A first material blank of either a conventionally fabricated or of a vacuum deposited biocompatible metal or pseudometallic material is provided at step 52. If a sacrificial material is to be employed to form the drug-releasing pockets of the device, it is deposited in a pattern corresponding to the positions of the drug-releasing pockets onto the first material blank at step 56, then a second material blank is provided at step 56 and conjoined at step 58 to the first material blank from step 52. Methods of depositing patterns of material onto another material surface are well-known in the art of semiconductor processing and may be accomplished by, for example, photolithography. If the drug-releasing pockets are not being formed by employing a sacrificial material at step 56, then the first material blank from step 52 and the second material blank from step 56 are conjoined at step 58 without the intervening sacrificial material. The conjoining step 58 may be accomplished in at least one of two manners. First, the first material blank from step 52 may be conjoined to the second material blank from step 54 by juxtaposing the first material blank and the second material blank and creating a pattern of welds 37 in the interperforation regions 22 that define boundaries for the drug-releasing chambers 36 (See, *e.g*, Fig. 4B and Fig. 5). The pattern of welds 37 may be formed by spot welding, laser welding, ultrasonic welding, chemical adhesion or such other suitable methods of joining two similar or dissimilar biocompatible metals or pseudometals.

**[0066]** A second method for conjoining the first material blank from step 52 with the second material blank from step 54 is to vacuum deposit the second material blank onto the first material blank. In this second method, it is desirable to employ the pattern of sacrificial material from step 56 since the second material blank will conform to the topography of the first material blank and it will not be technically feasible under currently known fabrication techniques to create the drug-releasing chambers between the deposited layers of the first material blank and the second material blank without subsequent removal of portions of the first and second material blanks. In this manner, the second material blank from step 54 will

be formed on the first material blank from step 52 and over the sacrificial material from step 56, and will conform to the topography of the first material blank and the sacrificial material.

**[0067]** Under the first method, that being to join pre-existing first and second material blanks and circumscribe the drug-releasing chambers by the weld junctions, a plurality of openings communicating with the drug-releasing chambers may be formed at step 60 either after the first and second material blanks are conjoined or may be formed at step 60 prior to conjoining the materials as reflected by the double-headed arrows between step 60 and steps 52 and 54, respectively. Under the second method, that being to vacuum deposit a second material blank at step 54 over the first material blank and the sacrificial material, step 60, i.e., forming the plurality of openings communicating with the drug-releasing chambers will need to be conducted after the first and second material blanks are conjoined as step 58, so that deposition of either or both of the first and second material blanks, and deposition of the sacrificial material may occur without occluding or obstructing the plurality of openings.

**[0068]** The plurality of internal chambers are created at step 62 either as an integral result of the conjoining step 58 where the first and second material blanks are welded to one another, or as a result of removing the sacrificial material through the plurality of openings formed in step 60. Finally, a pharmacologically active agent may be loaded at step 64 into the drug-releasing chambers as the final step in making the inventive drug-releasing device.

**[0069]** The plurality of microperforations in either or both of the first and second material blanks may be formed either before or after the materials are conjoined. Where a vacuum deposition process is employed in practicing the method, those skilled in the art will find that it is better to form the plurality of microperforations after the first and second material blanks are conjoined at step 58. Where the first and second material blanks are conjoined by welding, those skilled in the art will find it more desirable to form the plurality of microperforations prior to conjoining the first and second material blanks.

**[0070]** The plurality of microperforations may be formed by masking the material blank to expose only those regions defining the plurality of microperforations. The exposed regions are then subjected to removal either by etching, such as by wet or dry chemical etching processing, with the etchant being selected based upon the material of the precursor blank, or by machining, such as by laser ablation or EDM. Alternatively, when employing the vacuum deposition techniques, a pattern mask corresponding to the plurality of microperforations may be interposed between the target and the source and the metal or

pseudometal deposited through the pattern mask to form the patterned microperforations. Further, when employing the vacuum deposition, plural film layers maybe deposited to form a multilayer film structure of the film prior to or concurrently with forming the plurality of microperforations. Alternatively, plurality layers of material blanks may be employed and conjoined by welding. Those skilled in the art will understand, however, that device profile issues will likely be attendant to employing the method whereby non-vacuum deposited material blanks are employed due to the difficulty of producing ultra-thin material blanks on the order of between about 0.1 μm to about 15 μm using conventional non-vacuum deposition production methods.

**[0071]** Thus, the present invention provides a new metallic and/or pseudometallic implantable drug-releasing material for forming a wide variety of drug-delivery devices that is biocompatible, compliant, geometrically changeable either by folding and unfolding or by application of a plastically, elastically or superelastically deforming force, and, in some cases, capable of endoluminal delivery with a suitably small delivery profile and suitably low post-delivery profile. Suitable metal materials to fabricate the inventive graft are chosen for their biocompatibility, mechanical properties, *i.e.*, tensile strength, yield strength, and in the case where vapor deposition is deployed, their ease of deposition include, without limitation, the following: titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, such as zirconium-titanium-tantalum alloys, nitinol, chromium-cobalt alloy and stainless steel. Examples of pseudometallic materials potentially useful with the present invention include, for example, composite materials and ceramics.

**[0072]** The present invention also provides a method of making the inventive drug-delivery material by vacuum deposition of a metal or pseudometal material blank and formation of the microperforations either by removing sections of deposited material, such as by etching, EDM, ablation, or other similar methods, or by interposing a pattern mask, corresponding to the microperforations, between the target and the source during deposition processing. Alternatively, a pre-existing metal and/or pseudometallic material blanks manufactured by conventional non-vacuum deposition methodologies, such as wrought hypotube or sheet, may be obtained, and the microperforations formed in the pre-existing metal and/or pseudometallic film by removing sections of the film, such as by etching, EDM, ablation, or other similar methods. An advantage of employing multilayer film structures to form the inventive drug-releasing material is that differential functionalities may be imparted

in the discrete layers. For example, a radiopaque material such as tantalum may form one layer of a structure while other layers are chosen to provide the graft with its desired mechanical and structural properties.

**[0073]** In accordance with the preferred embodiment of fabricating the inventive microporous metallic implantable drug-releasing device in which the device is fabricated from vacuum deposited nitinol tube, a cylindrical deoxygenated copper substrate is provided. The substrate is mechanically and/or electropolished to provide a substantially uniform surface topography for accommodating metal deposition thereupon. A cylindrical hollow cathode magnetron sputtering deposition device was employed, in which the cathode was on the outside and the substrate was positioned along the longitudinal axis of the cathode. A cylindrical target consisting either of a nickel-titanium alloy having an atomic ratio of nickel to titanium of about 50-50% and which can be adjusted by spot welding nickel or titanium wires to the target, or a nickel cylinder having a plurality of titanium strips spot welded to the inner surface of the nickel cylinder, or a titanium cylinder having a plurality of nickel strips spot welded to the inner surface of the titanium cylinder is provided. It is known in the sputter deposition arts to cool a target within the deposition chamber by maintaining a thermal contact between the target and a cooling jacket within the cathode. In accordance with the present invention, it has been found useful to reduce the thermal cooling by thermally insulating the target from the cooling jacket within the cathode while still providing electrical contact to it. By insulating the target from the cooling jacket, the target is allowed to become hot within the reaction chamber. Two methods of thermally isolating the cylindrical target from the cooling jacket of the cathode were employed. First, a plurality of wires having a diameter of 0.0381mm were spot welded around the outer circumference of the target to provide an equivalent spacing between the target and the cathode cooling jacket. Second, a tubular ceramic insulating sleeve was interposed between the outer circumference of the target and the cathode cooling jacket. Further, because the Ni-Ti sputtering yields can be dependant on target temperature, methods which allow the target to become uniformly hot are preferred.

**[0074]** The deposition chamber was evacuated to a pressure less than or about 2-5 x $10^{-7}$ Torr and pre-cleaning of the substrate is conducted under vacuum. During the deposition, substrate temperature is preferably maintained within the range of 300 and 700 degrees Centigrade. It is preferable to apply a negative bias voltage between 0 and -1000 volts to the substrate, and preferably between -50 and -150 volts, which is sufficient to cause

energetic species arriving at the surface of the substrate. During deposition, the gas pressure is maintained between 0.1 and 40 mTorr but preferably between 1 and 20 mTorr. Sputtering preferably occurs in the presence of an Argon atmosphere. The argon gas must be of high purity and special pumps may be employed to reduce oxygen partial pressure. Deposition times will vary depending upon the desired thickness of the deposited tubular film.

**[0075]** After deposition of the first material, a copper sacrificial layer was vacuum deposited onto the first material. A photolithography mask corresponding to the desired pattern of the sacrificial material was applied onto the copper sacrificial layer and the entire assembly immersed in nitric acid which specifically etched the undesired regions of the copper sacrificial layer, leaving only the desired sacrificial regions corresponding to the position of the drug-releasing chambers. Other modes of chemical etching, photoetching, ablative techniques, such as laser etching or machining techniques, such as electric discharge machining (EDM) may be employed to remove undesired regions of the sacrificial material.

**[0076]** A second layer of nickel-titanium was vacuum deposited following the foregoing procedures onto the first material blank and the sacrificial copper. After deposition of the second nickel-titanium layer, a plurality of openings were laser cut through the second layer of nickel-titanium and into the sacrificial copper, then the entire assembly was immersed in nitric acid for a period of time sufficient to etch the copper sacrificial material through the plurality of openings, leaving a plurality of drug-releasing chambers between the first and the second layers of nickel-titanium alloy.

**[0077]** In accordance with the present invention, it has been found desirable when employing a non-biocompatible sacrificial metal, such as copper or hexavalent chromium, for example, to include a diffusion barrier between the first material and the sacrificial material, and then between the patterned sacrificial material and the second layer of material deposited onto the sacrificial material. It has been found that certain metals, such as copper, tend to diffuse into the surface of the first material blank and the second material blank under vacuum deposition conditions. Since the presence of non-biocompatible metals is undesirable, interposing a diffusion barrier which is removable with the sacrificial material serves to prevent metal diffusion and the presence of undesirable metals in the finished device. Suitable diffusion barriers may include, for example, titanium nitrides, silicon oxides, TiSiN or tantalum, which is, itself, biocompatible and would not require removal.

**[0078]** After deposition, the plurality of microperforations are formed in the tube by removing regions of the deposited film by etching, such as chemical or photoetching, ablation, such as by excimer laser or by EDM, or the like. After the plurality of microperforations are formed, the formed microporous film is removed from the copper substrate by exposing the substrate and film to a nitric acid bath for a period of time sufficient to remove dissolve the copper substrate.

**[0079]** While the present invention has been described with reference to its preferred embodiments, those of ordinary skill in the art will understand and appreciate that variations in materials, dimensions, geometries, and fabrication methods may be or become known in the art, yet still remain within the scope of the present invention which is limited only by the claims appended hereto.

What is claimed is:

1. A drug-releasing medical device, comprising:

a. a body member comprising a material selected from the group consisting of metallic and pseudometallic materials and having a first surface, a second surface and a thickness intermediate the first surface and the second surface;

b. a plurality of enclosed chambers disposed entirely within the thickness of the body member;

c. at least one opening passing through at least one of the first surface and the second surface and communicating with one of the plurality of enclosed chambers; and

d. at least one pharmacologically active agent disposed within the plurality of enclosed chambers and releasable through the at least one opening.

2. The drug-releasing medical device according to Claim 1, wherein the body member further comprises a thin metallic film.

3. The drug-releasing medical device according to Claim 1, wherein the material of the body member is made of a metallic material selected from the group consisting of titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum, and alloys thereof, cobalt chromium alloy, stainless steel and nickel-titanium alloy.

4. The drug-releasing medical device according to Claim 1, further comprising a biocompatible polymer covering the at least one of a plurality of openings.

5. The drug-releasing medical device according to Claim 2, further comprising a plurality of openings patterned in the body member to directionally release the at least one pharmacologically active agent from proximal and distal ends of the body member.

6. The drug-releasing medical device according to Claim 1, wherein the plurality of openings are arrayed about at least one of longitudinal and circumferential axes of the device in such a manner as to provide differential drug release along the at least one of the longitudinal and circumferential axes of the body member.

7. The drug-releasing medical device according to Claim 6, wherein the plurality of openings have differential opening sizes sufficient to provide differential drug release rates.

8. The drug-releasing medical device according to Claim 1, wherein the body member further comprises a tubular member, the first surface further comprises a luminal surface of the tubular member and the second surface further comprises an abluminal surface of the tubular member.

9. The drug-releasing medical device according to Claim 8, wherein the at least one of a plurality of openings pass through at least one of the luminal surface and abluminal surface of the tubular member.

10. The drug-releasing medical device according to Claim 1, wherein the plurality of enclosed chambers are substantially evenly distributed about circumferential and longitudinal axes of the tubular member.

11. The drug-releasing medical device according to Claim 10, wherein the at least one opening communicates with at least one of the ablumenal and lumenal surfaces of the tubular member.

12. The drug-releasing medical device according to Claim 1, further comprising a polymeric carrier for the at least one pharmacologically active agent.

13. The drug-releasing medical device according to Claim 1, further comprising a polymeric material at least partially occluding the at least one opening.

14. The drug-releasing medical device according to Claim 1, wherein the device is selected from the group consisting of stents, covered stents, vascular grafts, cardiovascular patches, soft tissue patches, surgical membranes, vascular plugs, embolic protection devices, cardiac valves, venous valves, angioplasty balloons, orthopedic implants, dental implants, plastic reconstructive implants, penile implants, intrauterine devices, and subcutaneous implants.

15. The drug-releasing medical device according to Claim 1, wherein the body member further comprises at least two layers of material, a first layer forming the first surface and a second layer forming the second surface, the at least two layers of material being conjoined to one another at spaced intervals, wherein the plurality of enclosed chambers are formed between the conjoined regions of the at least two layers of material.

16. The drug-releasing medical device according to Claim 15, wherein the plurality of enclosed chambers are defined on at least lateral aspects thereof and one of an upper or lower aspect of each enclosed chamber by a recess in a first layer of material and by a second layer of material conjoined onto the first layer of material thereby enclosing each of the plurality of enclosed chambers.

17. A drug-releasing medical device, comprising:

a. a body member comprising at least two layers of material, a first layer forming a first surface of the body member and a second layer forming a second surface, the at least two layers of material being conjoined to one another at spaced intervals to form a plurality of enclosed chambers disposed entirely within a thickness of the body member;

b. at least one opening passing through at least one of the first surface and the second surface and communicating with at least one of the plurality of enclosed chambers; and

c. at least one pharmacologically active agent disposed within the plurality of enclosed chambers and releasable through the at least one opening.

18. The drug-releasing medical device according to Claim 17, wherein the at least two layers of material consist essentially of a material selected from the group consisting of a biocompatible metal and a biocompatible pseudometal.

19. The drug-releasing medical device according to Claim 18, wherein the biocompatible metal further comprises a metallic material selected from the group consisting of titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum, and alloys thereof, cobalt chromium alloy, stainless steel and nickel-titanium alloy.

20. The drug-releasing medical device according to Claim 17, further comprising a polymer material covering at least one of the first and second surfaces of the body member.

21. The drug-releasing medical device according to Claim 17, further comprising a polymer material disposed within at least some of the plurality of enclosed chambers with the pharmacologically active agent.

22. A method of making a drug-releasing device, comprising the steps of:

a. Providing a first layer and a second layer of a biocompatible material;

b. Conjoining the first layer and the second layer in such a manner as to define a plurality of internal chambers intermediate the first layer and second layer;

c. Providing at least one opening passing through at least one of the first layer and the second layer and communicating with at least one of the plurality of internal chambers; and

d. Loading at least one pharmacologically active agent into the at least of a plurality of internal chambers in a form sufficient to be elutable through the at least one opening.

23. The method according to Claim 22, wherein step (a) further comprises the step of forming the first layer and the second layer of biocompatible material by a vacuum deposition process.

24. The method according to Claim 23, wherein the first layer and the second layer of biocompatible material are a metal or pseudometal selected from the group consisting of titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum, and alloys thereof, cobalt chromium alloy, stainless steel and nickel-titanium alloy, ceramic, biocompatible polymer and carbon-fiber matrices.

25. The method according to Claim 22, wherein the plurality of internal chambers are partially defined in the first layer of vacuum deposited material, and the second layer of vacuum deposited material is conjoined onto the first layer of vacuum deposited material.

26. The method according to Claim 22, further comprising the step of providing a sacrificial material between the first and second layers of biocompatible material.

27. The method according to Claim 26, further comprising the step of patterning the vacuum depositing a sacrificial material before depositing the second layer of biocompatible material thereupon.

28. The method according to Claim 26, further comprising the step of applying a diffusion barrier between the first layer of biocompatible material and patterning the sacrificial material before depositing the second layer biocompatible material thereupon.

29. The method according to Claim 28, further comprising the step of applying a diffusion barrier between the sacrificial material and the second layer of biocompatible material and the sacrificial material.

30. The method according to Claim 26, further comprising the step of removing the sacrificial material through the at least one opening passing through at least one of the first layer and the second layer and communicating with at least one of the plurality of internal chambers of biocompatible material.

31. The method according to Claim 29, further comprising the step of removing the sacrificial material through the at least one opening passing through at least one of the first layer and the second layer and communicating with at least one of the plurality of internal chambers.

32. The method according to Claim 30, further comprising the step of removing the diffusion barrier through the at least one opening passing through at least one of the first layer and the second layer and communicating with at least one of the plurality of internal chambers.

33. The method according to Claim 31, wherein the step of removing the diffusion barrier further comprises etching the diffusion barrier.

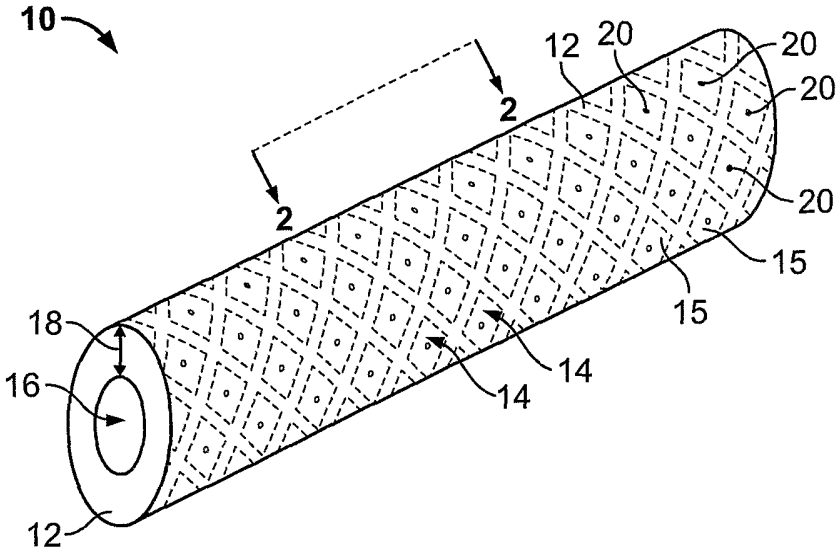



FIG. 1

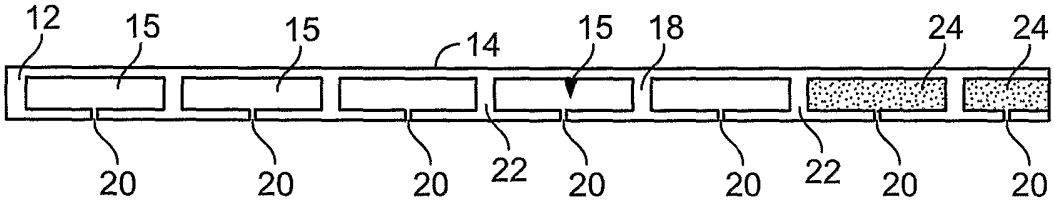



FIG. 2

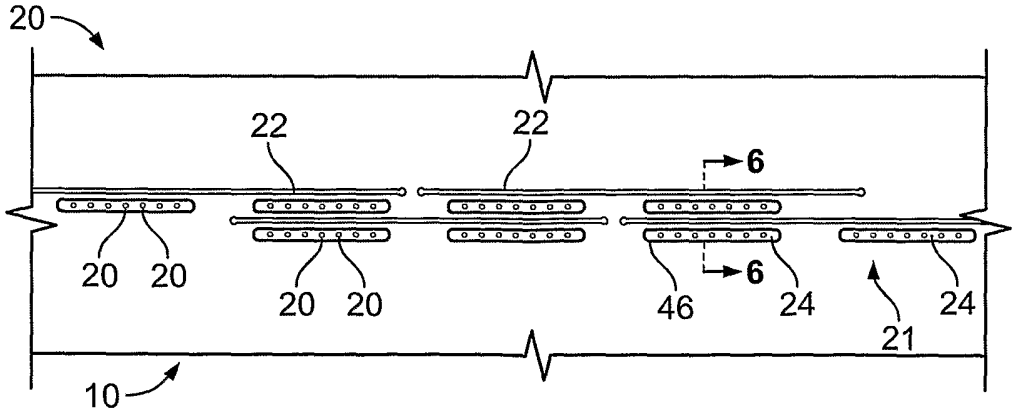
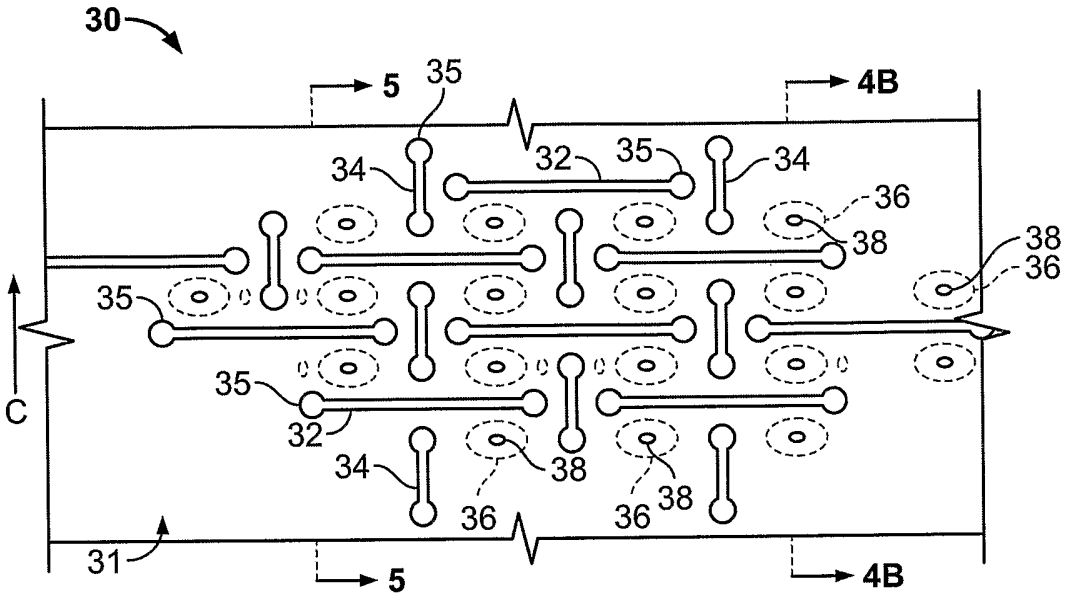



FIG. 3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4B
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C
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32
34
38
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36
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31
5
4B

FIG. 4A

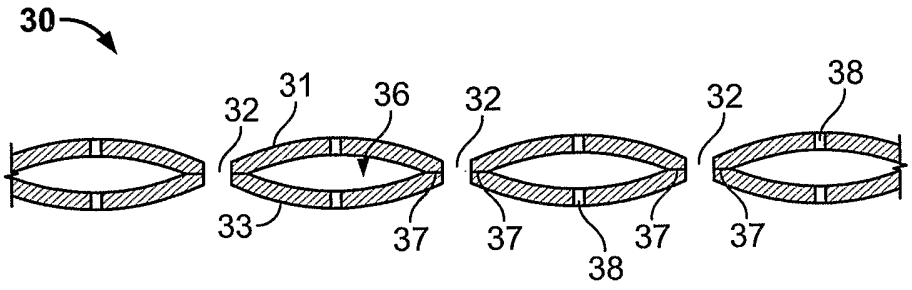
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FIG. 4B

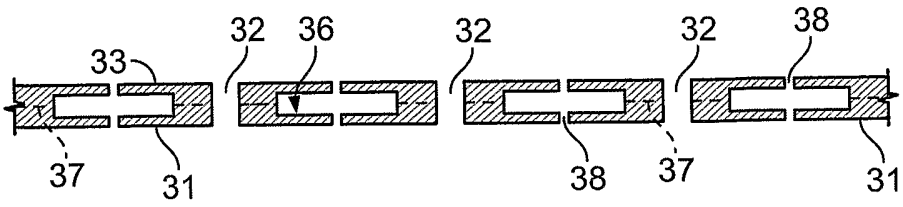


FIG. 5

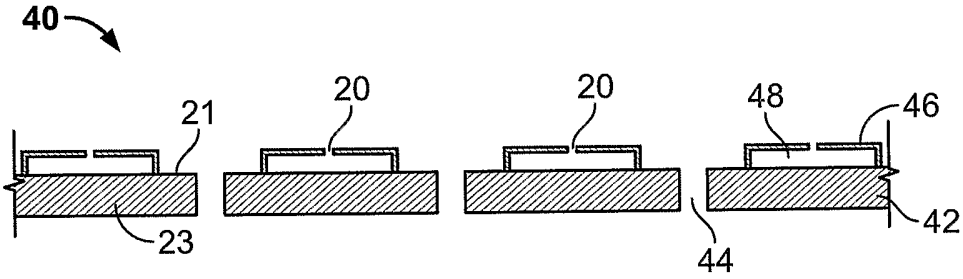


FIG. 6

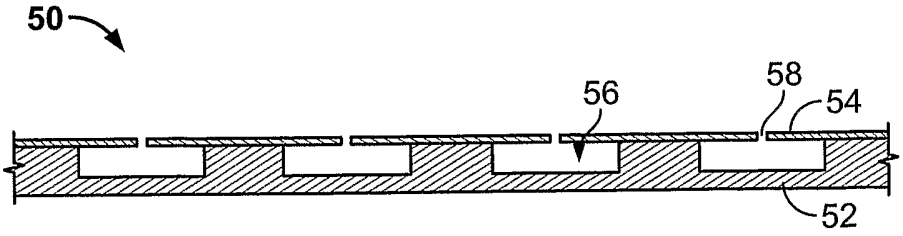


FIG. 7

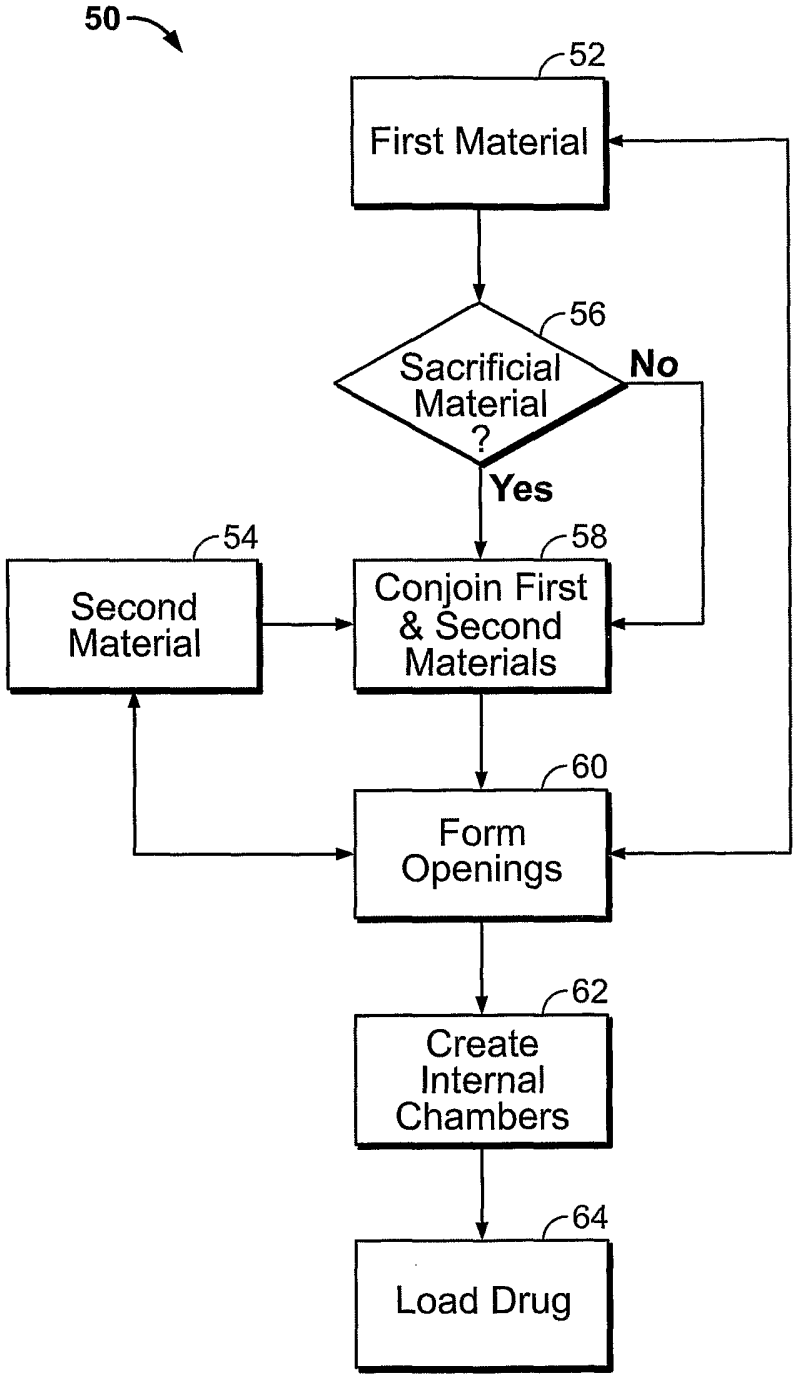
50
52
First Material
56
Sacrificial Material ?
No
Yes
54
Second Material
58
Conjoin First & Second Materials
60
Form Openings
62
Create Internal Chambers
64
Load Drug

FIG. 8