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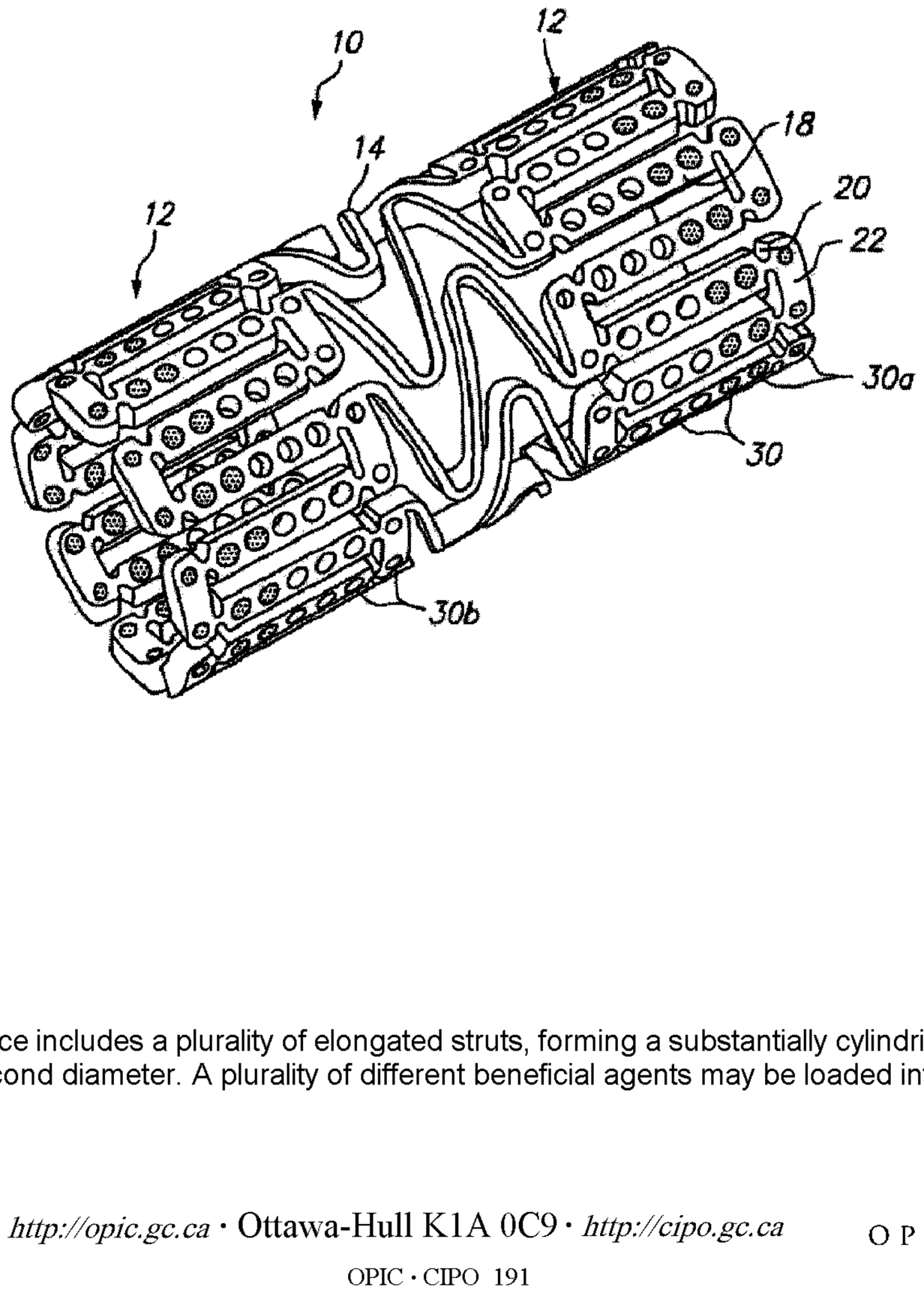
(54) **Titre : AMORCE DE PROMOTEUR D'ADHERENCE POUR SURFACES TRAITEES**
(54) **Title: ADHESION PROMOTING PRIMER FOR COATED SURFACES**



(57) **Abrégé/Abstract:**
An expandable medical device includes a plurality of elongated struts, forming a substantially cylindrical device which is expandable from a first diameter to a second diameter. A plurality of different beneficial agents may be loaded into different openings within the

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(57) **Abrégé(suite)/Abstract(continued):**
struts for delivery to the tissue. For treatment of conditions such as restenosis, different agents are loaded into different openings in the device to address different biological processes involved in restenosis and are delivered at different release kinetics matched to the biological process treated. The different agents may also be used to address different diseases from the same drug delivery device. In addition, anti-thrombotic agents may be affixed to at least a portion of the surfaces of the medical device for the prevention of sub-acute thrombosis. To ensure that the different agents remain affixed to the device as well as to each other, primer layers may be utilized.

Abstract

An expandable medical device includes a plurality of elongated struts, forming a substantially cylindrical device which is expandable from a first diameter to a second diameter. A plurality of different beneficial agents may be loaded into different openings within the struts for delivery to the tissue. For treatment of conditions such as restenosis, different agents are loaded into different openings in the device to address different biological processes involved in restenosis and are delivered at different release kinetics matched to the biological process treated. The different agents may also be used to address different diseases from the same drug delivery device. In addition, anti-thrombotic agents may be affixed to at least a portion of the surfaces of the medical device for the prevention of sub-acute thrombosis. To ensure that the different agents remain affixed to the device as well as to each other, primer layers may be utilized.

ADHESION PROMOTING PRIMER FOR COATED SURFACES

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to tissue-supporting medical devices, and more particularly to expandable, non-removable devices that are implanted within a bodily lumen of a living animal or human to support the organ and maintain patency, and that have openings for delivery of a plurality of beneficial agents to the intervention site as well as a surface coating of an antithrombotic agent. The present invention also relates to primer coatings for use between the antithrombotic agent coating and other therapeutic agent/polymer matrices.

2. Discussion of the Related Art

In the past, permanent or biodegradable devices have been developed for implantation within a body passageway to maintain patency of the passageway. These devices are typically introduced percutaneously, and transported transluminally until positioned at a desired location. These devices are then expanded either mechanically, such as by the expansion of a mandrel or balloon positioned inside the device, or expand themselves by releasing stored energy upon actuation within the body. Once expanded within the lumen, these devices, called stents, become encapsulated within the body tissue and remain a permanent implant.

Known stent designs include monofilament wire coil stents (U.S. Patent No. 4,969,458); welded metal cages (U.S. Patent Nos. 4,733,665 and

4,776,337); and, most prominently, thin-walled metal cylinders with axial slots formed around the circumference (U.S. Patent Nos. 4,733,665; 4,739,762; and 4,776,337). Known construction materials for use in stents include polymers, organic fabrics and biocompatible metals, such as, stainless steel, gold, silver, tantalum, titanium, and shape memory alloys, such as nickel-titanium.

United States Pat. No. 6,241,762

discloses a non-prismatic stent design which remedies several performance deficiencies of previous stents. In addition, preferred embodiments disclosed in this patent provide a stent with large, non-deforming strut and link elements, which may contain holes without compromising the mechanical properties of the strut or link elements, or the device as a whole. Further, these holes may serve as large, protected reservoirs for delivering various beneficial agents to the device implantation site without the need for a surface coating on the stent.

Of the many problems that may be addressed through stent-based local delivery of beneficial agents, one of the most important is restenosis. Restenosis is a major complication that may arise following vascular interventions such as angioplasty and the implantation of stents. Simply defined, restenosis is a wound healing process that reduces the vessel lumen diameter by extracellular matrix deposition and vascular smooth muscle cell proliferation and which may ultimately result in renarrowing or even reocclusion of the lumen. Despite the introduction of improved surgical techniques, devices and pharmaceutical agents, the overall restenosis rate for bare metal stents is still reported in the range of about twenty-five percent to about fifty percent within six to twelve months after an angioplasty

procedure. To treat this condition, additional revascularization procedures are frequently required, thereby increasing trauma and risk to the patient.

Conventional stents with surface coatings of various beneficial agents have shown promising results in reducing restenosis. United States Patent No. 5,716,981, for example, discloses a stent that is surface-coated with a composition comprising a polymer carrier and paclitaxel. The patent offers detailed descriptions of methods for coating stent surfaces, such as spraying and dipping, as well as the desired character of the coating itself: it should "coat the stent smoothly and evenly" and "provide a uniform, predictable, prolonged release of the anti-angiogenic factor." Surface coatings, however, may provide little actual control over the release kinetics of beneficial agents. These coatings are necessarily very thin, typically five to eight microns deep. The surface area of the stent, by comparison is very large, so that the entire volume of the beneficial agent has a very short diffusion path to discharge into the surrounding tissue. The resulting cumulative drug release profile is characterized by a large initial burst, followed by a rapid approach to an asymptote, rather than the desired "uniform, prolonged release," or linear release.

Increasing the thickness of the surface coating has the beneficial effects of improving drug release kinetics including the ability to better control drug release and to allow increased drug loading. However, the increased coating thickness results in an increased overall thickness of the stent wall. This is undesirable for a number of reasons, including potential increased trauma to the vessel lumen during implantation, reduced flow cross-section of the lumen after implantation, and increased vulnerability of the coating to mechanical failure or damage during expansion and implantation. Coating

thickness is one of several factors that affect the release kinetics of the beneficial agent, and limitations on thickness thereby limit the range of release rates, durations, and the like that may be achieved.

Surface coatings may also limit the delivery of multiple drugs from a stent. For example, if multiple drugs were to be released from a surface coating, the release rates, delivery periods and other release characteristics may not be independently controlled in a facile way. However, restenosis involves multiple biological processes and may be treated most effectively by a combination of drugs selected to act on these different biological processes.

A paper entitled "Physiological Transport Forces Govern Drug Distribution for Stent-Based Delivery" by Chao-Wei Hwang et al. has revealed an important interrelationship between the spatial and temporal drug distribution properties of drug eluting stents, and cellular drug transport mechanisms. In pursuit of enhanced mechanical performance and structural properties, stent designs have evolved to more complex geometries with inherent inhomogeneity in the circumferential and longitudinal distribution of stent struts. Examples of this trend are the typical commercially available stents which expand to a roughly diamond or polygonal shape when deployed in a bodily lumen. Both have been used to deliver a beneficial agent in the form of a surface coating. Studies have shown that lumen tissue portions immediately adjacent to the struts acquire much higher concentrations of drug than more remote tissue portions, such as those located in the middle of the "diamond" shaped strut cells. Significantly, this concentration gradient of drug within the lumen wall remains higher over time for hydrophobic beneficial agents, such as paclitaxel or a rapamycin, which have proven to be the most effective anti-restinotics to date. Because local drug

concentrations and gradients are inextricably linked to biological effects, the initial spatial distribution of the beneficial agent sources (the stent struts) is key to efficacy.

In addition to the sub-optimal spatial distribution of beneficial agents, there are further potential disadvantages with surface coated stents. Certain fixed matrix polymer carriers frequently used in the device coatings typically retain a significant percent of the beneficial agent in the coating indefinitely. Since these beneficial agents may be cytotoxic, for example, paclitaxel, sub-acute and chronic problems such as chronic inflammation, late thrombosis, and late or incomplete healing of the vessel wall may occur. Additionally, the carrier polymers themselves are often inflammatory to the tissue of the vessel wall. On the other hand, the use of bio-degradable polymer carriers on stent surfaces may result in "mal-apposition" or voids between the stent and tissue of the vessel wall after the polymer carrier has degraded. The voids permit differential motion between the stent and adjacent tissue. Resulting problems include micro-abrasion and inflammation, stent drift, and failure to re-endothelialize the vessel wall.

Early human clinical trials suggest that there may be certain disadvantages associated with first generation drug delivery devices. Follow-up examination of clinical trial patients at six to eighteen months after drug coated stent implantation indicates that mal-apposition of stent struts to arterial walls and edge effect restenosis may occur in significant numbers of patients. Edge effect restenosis occurs just beyond the proximal and distal edges of the stent and progresses around the stent edges and into the interior (luminal) space, frequently requiring repeat revascularization of the patient.

Another potential disadvantage is that expansion of the stent may stress an overlying polymeric coating causing the coating to peel, crack, or rupture which may effect drug release kinetics or have other untoward effects. These effects have been observed in first generation drug coated stents when these stents are expanded to larger diameters, preventing their use thus far in larger diameter arteries. Further, expansion of such a coated stent in an atherosclerotic blood vessel will place circumferential shear forces on the polymeric coating, which may cause the coating to separate from the underlying stent surface. Such separation may again have untoward effects including embolization of coating fragments causing vascular obstruction.

Another problem that may be addressed through stent-based local delivery of beneficial agents is thrombosis. A stent may be coated with an anti-thrombotic agent in addition to one or more therapeutic agents for treating restenosis. However, depending on the coatings on the surface of the stent, for example, an antithrombotic drug coating, additional layer(s) or primer layer(s) may be preferable to enhance the adhesion of other therapeutic agents to the coated surfaces of the stent.

SUMMARY OF THE INVENTION

The adhesion promoting primer for heparin coated surfaces of the present invention overcomes the difficulties briefly described above.

In accordance with one aspect, the present invention is directed to an implantable medical device. The implantable medical device comprising an intraluminal scaffold having a plurality of openings therein, a first coating comprising a material having a first electric charge affixed to at least a

portion of a surface of the intraluminal scaffold and a surface of the plurality of openings, a second coating comprising a material having a second electric charge affixed to at least a portion of the first coating, the second electric charge being opposite of the first electric charge, and at least one therapeutic agent deposited in at least one of the plurality of openings, wherein the second coating is configured as an intermediate layer between the first coating and the at least one therapeutic agent.

In accordance with another aspect, the present invention is directed to an implantable medical device. The implantable medical device comprising a substantially cylindrical intraluminal scaffold which is expandable from a first diameter for delivery into a vessel, to a second diameter for expanding the vessel, the intraluminal scaffold having a luminal surface and an abluminal surface, the distance between the luminal surface and the abluminal surface defining the wall thickness of the intraluminal scaffold, the intraluminal scaffold also including a plurality of openings extending from the luminal to abluminal surface, a first coating comprising a material having a first electric charge affixed to at least a portion of the abluminal surface, the luminal surface and a surface of the plurality of openings, a second coating comprising a material having a second electric charge affixed to at least a portion of the first coating, the second electric charge being opposite of the first electric charge, and at least one therapeutic agent deposited in at least one of the plurality of openings, wherein the second coating is configured as an intermediate bonding layer between the first coating and the at least one therapeutic agent.

In accordance with another aspect, the present invention is directed to a method for coating an intraluminal scaffold having a plurality of openings

therein. The method comprising applying a first coating comprising a material having a first electric charge to at least a portion of a surface of the intraluminal scaffold and a surface of the plurality of openings, applying a second coating comprising a material having a second electric charge to at least a portion of the first coating, the second electric charge being opposite of the first electric charge, and applying at least one therapeutic agent into at least one of the plurality of openings.

In accordance with another aspect of the invention, there is provided an implantable medical device comprising: a substantially cylindrical intraluminal scaffold which is expandable from a first diameter for delivery into a vessel, to a second diameter for expanding the vessel, the intraluminal scaffold having a luminal surface and an abluminal surface, the distance between the luminal surface and the abluminal surface defining the wall thickness of the intraluminal scaffold, the intraluminal scaffold also including a plurality of openings extending from the luminal to abluminal surface; a primer layer including multiple layers, the primer layer covering the luminal surface, the abluminal surface and the surfaces of the plurality of the openings; a first coating comprising a material having a first electric charge affixed to the primer layer; a second coating comprising a material having a second electric charge affixed to the first coating only in the plurality of openings, the second electric charge being opposite of the first electric charge; and at least one therapeutic agent deposited in at least one of the plurality of openings, wherein the second coating is configured as an intermediate layer between the first coating and the at least one therapeutic agent.

In accordance with another aspect of the invention, there is provided an implantable medical device comprising: a substantially cylindrical intraluminal scaffold which is expandable from a first diameter for delivery into a vessel, to a second diameter for expanding the vessel, the intraluminal scaffold having a luminal surface and an abluminal surface, the distance between the luminal surface and the abluminal surface defining the wall thickness of the intraluminal scaffold, the intraluminal scaffold also including a plurality of openings extending from the luminal to abluminal surface; a primer layer including multiple layers, the primer layer covering the luminal surface, the abluminal surface and the surfaces of the plurality of the openings; a first coating comprising a therapeutic agent having a first electric charge affixed to the primer layer; a second coating comprising a material having a second electric charge affixed to the first coating only in the plurality of openings, the

second electric charge being opposite of the first electric charge; and at least one therapeutic agent deposited in the plurality of openings, wherein the second coating is configured as an intermediate layer between the first coating and the at least one therapeutic agent to improve the adhesion between the at least one therapeutic agent and the first coating.

In view of the drawbacks of the prior art, it would be advantageous to provide a stent capable of delivering a relatively large volume of a beneficial agent to a traumatized site in a vessel lumen while avoiding the numerous potential problems associated with surface coatings containing beneficial agents, without increasing the effective wall thickness of the stent, and without adversely impacting the mechanical expansion properties of the stent.

It would further be advantageous to provide a tissue supporting device with different beneficial agents provided in different holes to achieve a desired spatial distribution of two or more beneficial agents.

It would further be advantageous to provide a tissue supporting device with different beneficial agents provided in different holes to achieve a desired different release kinetic for two different beneficial agents from the same device.

It would further be advantageous to provide a tissue supporting device having all surfaces coated with an anti-thrombotic agent and then utilize a primer in the holes or openings therein to increase the adhesion of the one or more beneficial agents that fill the holes.

The present invention is directed to primer compositions and configurations for improving the adhesion of a drug delivery matrix, e.g. therapeutic agent and polymer combination, to openings of a medical device, for example, a stent, that have a heparin coating. The present invention is particularly advantageous where the heparin coating is covalently bonded to a metallic or polymer surface of the medical device. In the present invention, the primer preferably comprises a high molecular weight component or a low molecular weight component, and the drug delivery matrix comprises a drug and/or other beneficial agent and an excipient, preferably a polymeric excipient. In addition, the primer may also preferably comprise a material having an opposite charge with similar density to that of the underlying layer, for example, heparin.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention as illustrated in the accompanying drawings.

Figure 1 is an isometric view of an expandable medical device with a beneficial agent at the ends in accordance with the present invention.

Figure 2 is an isometric view of an expandable medical device with a beneficial agent at a central portion and no beneficial agent at the ends in accordance with the present invention.

Figure 3 is an isometric view of an expandable medical device with different beneficial agents in different holes in accordance with the present invention.

Figure 4 is an isometric view of an expandable medical device with different beneficial agents in alternating holes in accordance with the present invention.

Figure 5 is an enlarged side view of a portion of an expandable medical device with beneficial agent openings in the bridging elements in accordance with the present invention.

Figure 6 is an enlarged side view of a portion of an expandable medical device with a bifurcation opening in accordance with the present invention.

Figure 7 is a cross sectional view of an expandable medical device having a combination of a first agent, such as an anti-inflammatory agent, in a first plurality of holes and a second agent, such as an anti-proliferative agent, in a second plurality of holes in accordance with the present invention.

Figure 8 is a graph of the release rates of one example of an anti-inflammatory and an anti-proliferative delivered by the expandable medical device of Figure 7 in accordance with the present invention.

Figures 9A-9C are partial diagrammatic representations of an alternate exemplary embodiment of an expandable medical device in accordance with the present invention.

Figure 10 illustrates a conjugation reaction between PLGA with a carboxylic acid end group and low molecular weight PEI in accordance with the present invention.

Figure 11 illustrates a conjugation reaction between PLGA with a carboxylic acid end group and high molecular weight or branched PEI in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figure 1 illustrates an expandable medical device having a plurality of holes comprising a beneficial agent for delivery to tissue by the expandable medical device. The expandable medical device 10 illustrated in Figure 1 is cut from a tube of material to form a cylindrical expandable device. The expandable medical device 10 includes a plurality of cylindrical sections 12 interconnected by a plurality of bridging elements 14. The bridging elements 14 allow the tissue supporting device to bend axially when passing through the torturous path of vasculature to a deployment site and allow the device to bend axially when necessary to match the curvature of a lumen to be supported. Each of the cylindrical tubes 12 is formed by a network of elongated struts 18 which are interconnected by ductile hinges 20 and circumferential struts 22. During expansion of the medical device 10 the ductile hinges 20 deform while the struts 18 are not deformed. Further details of one example of the expandable medical device are described in U.S. Patent No. 6,241,762.

As illustrated in Figure 1, the elongated struts 18 and circumferential struts 22 include openings 30, some of which comprise a beneficial agent for delivery to the lumen in which the expandable medical device is implanted. In addition, other portions of the device 10, such as the bridging elements 14, may include openings, as discussed below with respect to Figure 5. Preferably, the openings 30 are provided in non-deforming portions of the device 10, such as the struts 18, so that the openings are non-deforming and the beneficial agent is delivered without risk of being fractured, expelled, or otherwise damaged during expansion of the device. A further description of one example of the manner in which the beneficial agent may be loaded within the openings 30 is

described in U.S. Patent Publication No. 2002/0068919, filed Sep. 7, 2001.

The exemplary embodiments of the present invention may be further refined by using Finite Element Analysis and other techniques to optimize the deployment of the beneficial agents within the openings 30. Basically, the shape and location of the openings 30, may be modified to maximize the volume of the voids while preserving the relatively high strength and rigidity of the struts with respect to the ductile hinges 20. According to one preferred exemplary embodiment of the present invention, the openings have an area of at least 5×10^{-6} square inches, and preferably at least 7×10^{-6} square inches. Typically, the openings are filled, from about fifty percent to about ninety-five percent full of beneficial agent.

Definitions

The terms "agent," "therapeutic agent" or "beneficial agent" as used herein are intended to have the broadest possible interpretation and are used to

include any therapeutic agent or drug, as well as inactive agents such as barrier layers, carrier layers, therapeutic layers, or protective layers.

The terms "drug" and "therapeutic agent" are used interchangeably to refer to any therapeutically active substance that is delivered to a bodily lumen of a living being to produce a desired, usually beneficial, effect. Beneficial agents may include one or more drug or therapeutic agent.

The present invention is particularly well suited for the delivery of antineoplastics, antiangiogenics, angiogenic factors, anti-inflammatories, immuno-suppressants such as a rapamycin, antirestenotics, antiplatelet agents, vasodilators, anti-thrombotics, antiproliferatives, such as paclitaxel, for example, and antithrombins, such as heparin, for example.

The term "erosion" means the process by which components of a medium or matrix are bioresorbed and/or degraded and/or broken down by chemical or physical or enzymatic processes. For example in reference to biodegradable polymer matrices, erosion may occur by cleavage or hydrolysis of the polymer chains, thereby increasing the solubility of the matrix and suspended beneficial agents.

The term "erosion rate" is a measure of the amount of time it takes for the erosion process to occur, usually reported in unit-area per unit-time.

The terms "matrix" or "bioresorbable matrix" are used interchangeably to refer to a medium or material that, upon implantation in a subject, does not elicit a detrimental response sufficient to result in the rejection of the matrix. The matrix typically does not provide any therapeutic responses itself,

though the matrix may contain or surround a beneficial agent, as defined herein. A matrix is also a medium that may simply provide support, structural integrity or structural barriers. The matrix may be polymeric, non-polymeric, hydrophobic, hydrophilic, lipophilic, amphiphilic, and the like. In addition, bioresorbable matrix shall also be understood to mean complete absorption of the matrix by the body over time.

The term "openings" includes both through openings and recesses.

The term "pharmaceutically acceptable" refers to the characteristic of being non-toxic to a host or patient and suitable for maintaining the stability of a beneficial agent and allowing the delivery of the beneficial agent to target cells or tissue.

The term "polymer" refers to molecules formed from the chemical union of two or more repeating units, called monomers. Accordingly, included within the term "polymer" may be, for example, dimers, trimers and oligomers. The polymer may be synthetic, naturally-occurring or semisynthetic. In preferred form, the term "polymer" refers to molecules which typically have a M_W greater than about 3000 and preferably greater than about 10,000 and a M_W that is less than about 10 million, preferably less than about a million and more preferably less than about 200,000. Examples of polymers include but are not limited to, poly-.alpha.-hydroxy acid esters such as, polylactic acid (PLLA or DLPLA), polyglycolic acid, polylactic-co-glycolic acid (PLGA), polylactic acid-co-caprolactone; poly (block-ethylene oxide-block-lactide-co-glycolide) polymers (PEO-block-PLGA and PEO-block-PLGA-block-PEO); polyethylene glycol and polyethylene oxide, poly (block-ethylene oxide-block-propylene oxide-block-ethylene oxide); polyvinyl pyrrolidone;

polyorthoesters; polysaccharides and polysaccharide derivatives such as polyhyaluronic acid, poly (glucose), polyalginic acid, chitin, chitosan, chitosan derivatives, cellulose, methyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, cyclodextrins and substituted cyclodextrins, such as beta-cyclodextrin sulfobutyl ethers; polypeptides and proteins, such as polylysine, polyglutamic acid, albumin; polyanhydrides; polyhydroxy alkonoates such as polyhydroxy valerate, polyhydroxy butyrate, and the like.

The term "primarily" with respect to directional delivery, refers to an amount greater than about fifty percent of the total amount of therapeutic agent provided to a blood vessel is provided in the primary direction.

The various exemplary embodiments of the present invention described herein provide different beneficial agents in different openings in the expandable device or beneficial agent in some openings and not in others. The particular structure of the expandable medical device may be varied without departing from the spirit of the invention. Since each opening is filled independently, individual chemical compositions and pharmacokinetic properties may be imparted to the beneficial agent in each opening.

One example of the use of different beneficial agents in different openings in an expandable medical device or beneficial agents in some openings and not in others, is in addressing edge effect restenosis. As discussed above, current generation coated stents may have a difficulty with edge effect restenosis or restenosis occurring just beyond the edges of the stent and progressing around the stent and into the interior luminal space.

The causes of edge effect restenosis in first generation drug delivery stents are currently not well understood. It may be that the region of tissue injury due to angioplasty and/or stent implantation extends beyond the diffusion range of current generation beneficial agents such as paclitaxel, which tends to partition strongly in tissue. A similar phenomenon has been observed in radiation therapies in which low doses of radiation at the edges of stent have proven stimulatory in the presence of an injury. In this case, radiating over a longer length until uninjured tissue is irradiated solved the problem. In the case of drug delivery stents, placing higher doses or higher concentrations of beneficial agents along the stent edges, placing different agents at the stent edges which diffuse more readily through the tissue, or placing different beneficial agents or combinations of beneficial agents at the edges of the device may help to remedy the edge effect restenosis problem.

Figure 1 illustrates an expandable medical device 10 with "hot ends" or beneficial agent provided in the openings 30a at the ends of the device in order to treat and reduce edge effect restenosis. The remaining openings 30b in the central portion of the device may be empty (as shown) or may contain a lower concentration of beneficial agent.

Other mechanisms of edge effect restenosis may involve the cytotoxicity of particular drugs or combinations of drugs. Such mechanisms could include a physical or mechanical contraction of tissue similar to that seen in epidermal scar tissue formation, and the stent might prevent the contractile response within its own boundaries, but not beyond its edges. Further, the mechanism of this latter form of restenosis may be related to sequelae of sustained or local drug delivery to the arterial wall that is manifest even after the drug itself is no longer present in the wall. That is, the restenosis may be a

response to a form of noxious injury related to the drug and/or the drug carrier. In this situation, it might be beneficial to exclude certain agents from the edges of the device.

Figure 2 illustrates an alternate exemplary embodiment of an expandable medical device 200 having a plurality of openings 230 in which the openings 230b in a central portion of the device are filled with a beneficial agent and the openings 230a at the edges of the device remain empty. The device of Figure 2 is referred to as having "cool ends."

In addition to use in reducing edge effect restenosis, the expandable medical device 200 of Figure 2 may be used in conjunction with the expandable medical device 10 of Figure 1 or another drug delivery stent when an initial stenting procedure has to be supplemented with an additional stent. For example, in some cases the device 10 of Figure 1 with "hot ends" or a device with uniform distribution of drug may be implanted improperly. If the physician determines that the device does not cover a sufficient portion of the lumen a supplemental device may be added at one end of the existing device and slightly overlapping the existing device. When the supplemental device is implanted, the device 200 of Figure 2 is used so that the "cool ends" of the medical device 200 prevent double-dosing of the beneficial agent at the overlapping portions of the devices 10, 200.

Figure 3 illustrates a further alternate exemplary embodiment of the invention in which different beneficial agents are positioned in different holes of an expandable medical device 300. A first beneficial agent is provided in holes 330a at the ends of the device and a second beneficial agent is provided in holes 330b at a central portion of the device. The beneficial

agent may contain different drugs, the same drugs in different concentrations, or different variations of the same drug. The exemplary embodiment of Figure 3 may be used to provide an expandable medical device 300 with either "hot ends" or "cool ends."

Preferably, each end portion of the device 300 which includes the holes 330a comprising the first beneficial agent extends at least one hole and up to about fifteen holes from the edge. This distance corresponds to about 0.005 to about 0.1 inches from the edge of an unexpanded device. The distance from the edge of the device 300 which includes the first beneficial agent is preferably about one section, where a section is defined between the bridging elements.

Different beneficial agents comprising different drugs may be disposed in different openings in the stent. This allows the delivery of two or more beneficial agents from a single stent in any desired delivery pattern. Alternately, different beneficial agents comprising the same drug in different concentrations may be disposed in different openings. This allows the drug to be uniformly distributed to the tissue with a non-uniform device structure.

The two or more different beneficial agents provided in the devices described herein may comprise (1) different drugs; (2) different concentrations of the same drug; (3) the same drug with different release kinetics, i.e., different matrix erosion rates; or (4) different forms of the same drug. Examples of different beneficial agents comprising the same drug with different release kinetics may use different carriers to achieve the elution profiles of different shapes. Some examples of different forms of the same drug include forms of a drug having varying hydrophilicity or lipophilicity.

In one example of the device 300 of Figure 3, the holes 330a at the ends of the device are loaded with a first beneficial agent comprising a drug with a high lipophilicity while holes 330b at a central portion of the device are loaded with a second beneficial agent comprising the drug with a lower lipophilicity. The first high lipophilicity beneficial agent at the "hot ends" will diffuse more readily into the surrounding tissue reducing the edge effect restenosis.

The device 300 may have an abrupt transition line at which the beneficial agent changes from a first agent to a second agent. For example, all openings within 0.05 inches of the end of the device may comprise the first agent while the remaining openings comprise the second agent. Alternately, the device may have a gradual transition between the first agent and the second agent. For example, a concentration of the drug in the openings may progressively increase (or decrease) toward the ends of the device. In another example, an amount of a first drug in the openings increases while an amount of a second drug in the openings decreases moving toward the ends of the device.

Figure 4 illustrates a further alternate exemplary embodiment of an expandable medical device 400 in which different beneficial agents are positioned in different openings 430a, 430b in the device in an alternating or interspersed manner. In this manner, multiple beneficial agents may be delivered to tissue over the entire area or a portion of the area supported by the device. This exemplary embodiment will be useful for delivery of multiple beneficial agents where combination of the multiple agents into a single composition for loading in the device is not possible due to interactions or

stability problems between the beneficial agents.

In addition to the use of different beneficial agents in different openings to achieve different drug concentrations at different defined areas of tissue, the loading of different beneficial agents in different openings may be used to provide a more even spatial distribution of the beneficial agent delivered in instances where the expandable medical device has a non-uniform distribution of openings in the expanded configuration.

The use of different drugs in different openings in an interspersed or alternating manner allows the delivery of two different drugs which may not be deliverable if combined within the same polymer/drug matrix composition. For example, the drugs themselves may interact in an undesirable way. Alternately, the two drugs may not be compatible with the same polymers for formation of the matrix or with the same solvents for delivery of the polymer/drug matrix into the openings.

Further, the exemplary embodiment of Figure 4 having different drugs in different openings in an interspersed arrangement provide the ability to deliver different drugs with very different desired release kinetics from the same medical device or stent and to optimize the release kinetic depending on the mechanism of action and properties of the individual agents. For example, the water solubility of an agent greatly affects the release of the agent from a polymer or other matrix. A highly water soluble compound will generally be delivered very quickly from a polymer matrix, whereas, a lipophilic agent will be delivered over a longer time period from the same matrix. Thus, if a hydrophilic agent and a lipophilic agent are to be delivered as a dual drug combination from a medical device, it is difficult to achieve a

desired release profile for these two agents delivered from the same polymer matrix.

The system of Figure 4 allows the delivery of a hydrophilic and a lipophilic drug easily from the same stent. Further, the system of Figure. 4 allows the delivery two agents at two different release kinetics and/or administration periods. Each of the initial release in the first twenty-four hours, the release rate following the first twenty-four hours, the total administration period and any other characteristics of the release of the two drugs may be independently controlled. For example the release rate of the first beneficial agent can be arranged to be delivered with at least forty percent (preferably at least fifty percent) of the drug delivered in the first twenty-four hours and the second beneficial agent may be arranged to be delivered with less than twenty percent (preferably less than ten percent) of the drug delivered in the first twenty-four hours. The administration period of the first beneficial agent may be about three weeks or less (preferably two weeks or less) and the administration period of the second beneficial agent may be about four weeks or more.

Restenosis or the recurrence of occlusion post-intervention, involves a combination or series of biological processes. These processes include the activation of platelets and macrophages. Cytokines and growth factors contribute to smooth muscle cell proliferation and upregulation of genes and metalloproteinases lead to cell growth, remodeling of extracellular matrix, and smooth muscle cell migration. A drug therapy which addresses a plurality of these processes by a combination of drugs may be the most successfully antirestenotic therapy. The present invention provides a means to achieve such a successful combination drug therapy.

The examples discussed below illustrate some of the combined drug systems which benefit from the ability to release different drugs in different holes or openings. One example of a beneficial system for delivering two drugs from interspersed or alternating holes is the delivery of an anti-inflammatory agent or an immunosuppressant agent in combination with an antiproliferative agent or an anti-migratory agent. Other combinations of these agents may also be used to target multiple biological processes involved in restenosis. The anti-inflammatory agent mitigates the initial inflammatory response of the vessel to the angioplasty and stenting and is delivered at a high rate initially followed by a slower delivery over a time period of about two weeks to match the peak in the development of macrophages which stimulate the inflammatory response. The antiproliferative agent is delivered at a relatively even rate over a longer time period to reduce smooth muscle cell migration and proliferation.

In addition to the examples that are be given below, the following chart illustrates some of the useful two drug combination therapies which may be achieved by placing the drugs into different openings in the medical device.

	PTX	2-Cda	Epothilone D	Imatinibmesylate Gleevec	Rapamycin analog	Pime-crolimus	PKC-412	Dexa-methasone	Fargli-tazar	Insulin	VIP	ApoA-I milano
PTX	x			x		x	x	x		x	x	x
2-CdA		x		x	x	x	x		s			
Epothilone D				x			x	x		x	x	x
Imatinib mesylate Gleevec					x	x	x	x				
Rapamycin analog							x	x		x	x	x
Pimecrolimus							x	x		x	x	x
PKC-412								x		x	x	x
Dexamethasone											x	x
Farglitazar											x	x
Insulin											x	
VIP												x
ApoA-I milano												

The placement of the drugs in different openings allows the release kinetics to be tailored to the particular agent regardless of the hydrophobilicity or lipophobicity of the drug. Examples of some arrangements for delivery of a lipophilic drug at a substantially constant or linear release rate are described in WO 04/110302 published on Dec. 23, 2004.

Examples of some of the arrangements for delivery of hydrophilic drug are described in WO 04/043510, published on May 27, 2004. The hydrophilic drugs listed above include CdA, Gleevec™, VIP, insulin, and ApoA-1 milano. The lipophilic drugs listed above include paclitaxel, Epothilone D, rapamycin, pimecrolimus, PKC-412 and Dexamethazone. Farglitazar is partly liphophillic and partly hydrophilic.

In addition to the delivery of multiple of drugs to address different biological processes involved in restenosis, the present invention may deliver two different drugs for treatment of different diseases from the same stent. For example, a stent may deliver an anti-proliferative, such as paclitaxel or a limus drug from one set of openings for treatment of restenosis while delivering a myocardial preservative drug, such as insulin, from other openings for the treatment of acute myocardial infarction.

In many of the known expandable devices and for the device illustrated in Figure 5 the coverage of the device 500 is greater at the cylindrical tube portions 512 of the device than at the bridging elements 514. Coverage is defined as the ratio of the device surface area to the area of the lumen in which the device is deployed. When a device with varying coverage is used to deliver a beneficial agent contained in openings in the device, the beneficial agent concentration delivered to the tissue adjacent the cylindrical tube portions 512 is greater that the beneficial agent delivered to the tissue adjacent the bridging elements 514. In order to address this longitudinal variation in device structure and other variations in device coverage which lead to uneven beneficial agent delivery concentrations, the concentration of the beneficial agent may be varied in the openings at portions of the device to achieve a more even distribution of the beneficial agent throughout the tissue. In the case of the exemplary embodiment illustrated in Figure 5, the openings 530a in the tube portions 512 include a beneficial agent with a lower drug concentration than the openings 530b in the bridging elements 514. The uniformity of agent delivery may be achieved in a variety of manners including varying the drug concentration, the opening diameter or shape, the amount of agent in the opening (i.e., the percentage of the opening filed), the matrix material, or the form of the drug.

Another example of an application for the use of different beneficial agents in different openings is in an expandable medical device 600, as illustrated in Figure 6, configured for use at a bifurcation in a vessel. Bifurcation devices include a side hole 610 which is positioned to allow blood flow through a side branch of a vessel. One example of a bifurcation device is described in U.S. Patent No. 6,293,967.

The bifurcation device 600 includes the side hole feature 610 interrupting the regular pattern of beams which form a remainder of the device. Since an area around a bifurcation is a particularly problematic area for restenosis, a concentration of an antiproliferative drug may be increased in openings 630a at an area surrounding the side hole 610 of the device 600 to deliver increased concentrations of the drug where needed. The remaining openings 630b in an area away from the side opening contain a beneficial agent with a lower concentration of the antiproliferative. The increased antiproliferative delivered to the region surrounding the bifurcation hole may be provided by a different beneficial agent containing a different drug or a different beneficial agent containing a higher concentration of the same drug.

In addition to the delivery of different beneficial agents to the mural or abluminal side of the expandable medical device for treatment of the vessel wall, beneficial agents may be delivered to the luminal side of the expandable medical device to prevent or reduce thrombosis. Drugs which are delivered into the blood stream from the luminal side of the device may be located at a proximal end of the device or a distal end of the device.

The methods for loading different beneficial agents into different openings in

an expandable medical device may include known techniques such as dipping and coating and also known piezoelectric micro-jetting techniques. Micro-injection devices may be computer controlled to deliver precise amounts of two or more liquid beneficial agents to precise locations on the expandable medical device in a known manner. For example, a dual agent jetting device may deliver two agents simultaneously or sequentially into the openings. When the beneficial agents are loaded into through openings in the expandable medical device, a luminal side of the through openings may be blocked during loading by a resilient mandrel allowing the beneficial agents to be delivered in liquid form, such as with a solvent. The beneficial agents may also be loaded by manual injection devices.

EXAMPLE 1

Figure 7 illustrates a dual drug stent 700 having an anti-inflammatory agent and an antiproliferative agent delivered from different holes in the stent to provide independent release kinetics of the two drugs which are specifically programmed to match the biological processes of restenosis. According to this example, the dual drug stent includes an anti-inflammatory agent pimecrolimus in a first set of openings 710 in combination with the antiproliferative agent paclitaxel in a second set of openings 720. Each agent is provided in a matrix material within the holes of the stent in a specific inlay arrangement designed to achieve the release kinetics illustrated in Figure 8. Each of the drugs are delivered primarily murally for treatment of restenosis.

As illustrated in Figure 7, pimecrolimus is provided in the stent for directional delivery to the mural side of the stent by the use of a barrier 712 at the

luminal side of the hole. The barrier 712 is formed by a biodegradable polymer. The pimecrolimus is loaded within the holes in a manner which creates a release kinetics having dual phases. A first phase of the release of pimecrolimus is provided by a murally located region 716 of the matrix which has a fast release formulation including pimecrolimus and biodegradable polymer (PLGA) with a high percentage of drug, such as about ninety percent drug to about ten percent polymer. A second phase of the release is provided by a central region 714 of the matrix with pimecrolimus and biodegradable polymer (PLGA) in a ratio of about fifty percent drug to fifty percent polymer. As may be seen on the graph of Figure 8, the first phase of the pimecrolimus release delivers about fifty percent of the loaded drug in about the first twenty-four hours. The second phase of the release delivers the remaining fifty percent over about two weeks. This release is specifically programmed to match the progression of the inflammatory process following angioplasty and stenting. In addition to or as an alternative to changing the drug concentration between the two regions to achieve the two phase release, different polymers or different comonomer ratios of the same polymer may be used in two drug different regions to achieve the two different release rates.

The paclitaxel is loaded within the openings 720 in a manner which creates a release kinetic having a substantially linear release after the first approximately twenty-four hours, as illustrated in Figure 8. The paclitaxel openings 720 are loaded with three regions including a base region 722 of primarily polymer with minimal drug at a luminal side of the hole, a central region 724 with paclitaxel and polymer (PLGA) provided in a concentration gradient, and a cap region 726 with primarily polymer which controls release of the paclitaxel. The paclitaxel is released with an initial release in the first

day of about five to about fifteen percent of the total drug load followed by a substantially linear release for about twenty to ninety days. Additional examples of arrangements for paclitaxel in the holes with a concentration gradient are described in WO 04/110302 set forth above.

Figure 7 illustrates the drug, barrier, and cap regions as distinct regions within the openings for ease of illustration. It should be understood that these regions indistinct and formed by a blending of the different areas. Thus, although the barrier layers are primarily polymer without drug, depending on the manufacturing processes employed, some small amount of drug of the subsequent region can be incorporation into the barrier region.

The amount of the drugs delivered varies depending on the size of the stent. For a three mm by six mm stent the amount of pimecrolimus is about fifty to about three hundred micrograms preferably about one hundred to about two hundred fifty micrograms. The amount of paclitaxel delivered from this stent is about five to about fifty micrograms preferably about ten to about thirty micrograms. In one example, about two hundred micrograms of pimecrolimus and about twenty micrograms of paclitaxel are delivered. The drugs may be located in alternating holes in the stent. However, in view of the large difference in the doses to be delivered between the two drugs, it may be desirable to place the paclitaxel in every third of fourth hole in the stent. Alternatively, the holes for delivery of the low dose drug (paclitaxel) may be made smaller than the holes for the high dose.

The polymer/drug inlays are formed by computer controlled piezoelectric injection techniques as described in WO 04/026182 published on Apr. 1, 2004. The inlays of

the first agent may be formed first followed by the inlays of the second agent using the piezoelectric injector. Alternately, the system of WO 04/02182 may be equipped with dual piezoelectric dispensers for dispensing the two agents at the same time.

EXAMPLE 2

According to this example, the dual drug stent includes the Gleevec in the first set of openings 710 in combination with the antiproliferative agent paclitaxel in the second set of openings 720. Each agent is provided in a matrix material within the holes of the stent in a specific inlay arrangement designed to achieve the release kinetics illustrated in Figure 8.

The Gleevec is delivered with a two phase release including a high initial release in the first day and then a slow release for one to two weeks. The first phase of the Gleevec release delivers about fifty percent of the loaded drug in about the first twenty-four hours. The second phase of the release delivers the remaining fifty percent over about one-two weeks. The paclitaxel is loaded within the openings 720 in a manner which creates a release kinetics having a substantially linear release after the first approximately twenty-four hours, as illustrated in Figure 8 and as described above in Example 1.

The amount of the drugs delivered varies depending on the size of the stent. For a three mm by six mm stent the amount of Gleevec is about two hundred to about five hundred micrograms, preferably about three hundred to about four hundred micrograms. The amount of paclitaxel delivered from this stent is about five to about fifty micrograms, preferably about ten to about thirty

micrograms. As in Example 1, the drugs may be located in alternating holes in the stent or interspersed in a non-alternating manner. The polymer/drug inlays are formed in the manner described in Example 1.

EXAMPLE 3

According to this example, the dual drug stent includes the PKC-412 (a cell growth regulator) in the first set of openings in combination with the antiproliferative agent paclitaxel in the second set of openings. Each agent is provided in a matrix material within the holes of the stent in a specific inlay arrangement designed to achieve the release kinetics discussed below.

The PKC-412 is delivered at a substantially constant release rate after the first approximately twenty-four hours, with the release over a period of about four to sixteen weeks, preferably about six to twelve weeks. The paclitaxel is loaded within the openings in a manner which creates a release kinetic having a substantially linear release after the first approximately twenty-four hours, with the release over a period of about four to sixteen weeks, preferably about six to twelve weeks.

The amount of the drugs delivered varies depending on the size of the stent. For a three mm by six mm stent the amount of PKC-412 is about one hundred to about four hundred micrograms, preferably about one hundred fifty to about two hundred fifty micrograms. The amount of paclitaxel delivered from this stent is about five to about fifty micrograms, preferably about ten to about thirty micrograms. As in Example 1, the drugs may be located in alternating holes in the stent or interspersed in a non-alternating manner. The polymer/drug inlays are formed in the manner described in

Example 1.

Therapeutic Agents

The present invention relates to the delivery of anti-restenotic agents including paclitaxel, rapamycin, cladribine (CdA), and their derivatives, as well as other cytotoxic or cytostatic agents and microtubule stabilizing agents. Although anti-restenotic agents have been primarily described herein, the present invention may also be used to deliver other agents alone or in combination with anti-restenotic agents. Some of the therapeutic agents for use with the present invention which may be transmitted primarily luminally, primarily murally, or both and may be delivered alone or in combination include, but are not limited to, antiproliferatives, antithrombins, immunosuppressants including sirolimus, antilipid agents, anti-inflammatory agents, antineoplastics, antiplatelets, angiogenic agents, anti-angiogenic agents, vitamins, antimitotics, metalloproteinase inhibitors, NO donors, estradiols, anti-sclerosing agents, and vasoactive agents, endothelial growth factors, estrogen, beta blockers, AZ blockers, hormones, statins, insulin growth factors, antioxidants, membrane stabilizing agents, calcium antagonists, retenoid, bivalirudin, phenoxodiol, etoposide, ticlopidine, dipyridamole, and trapidil alone or in combinations with any therapeutic agent mentioned herein. Therapeutic agents also include peptides, lipoproteins, polypeptides, polynucleotides encoding polypeptides, lipids, protein-drugs, protein conjugate drugs, enzymes, oligonucleotides and their derivatives, ribozymes, other genetic material, cells, antisense, oligonucleotides, monoclonal antibodies, platelets, prions, viruses, bacteria, and eukaryotic cells such as endothelial cells, stem cells, ACE inhibitors, monocyte/macrophages or vascular smooth muscle cells to name but a few

examples. The therapeutic agent may also be a pro-drug, which metabolizes into the desired drug when administered to a host. In addition, therapeutic agents may be pre-formulated as microcapsules, microspheres, microbubbles, liposomes, niosomes, emulsions, dispersions or the like before they are incorporated into the therapeutic layer. Therapeutic agents may also be radioactive isotopes or agents activated by some other form of energy such as light or ultrasonic energy, or by other circulating molecules that can be systemically administered. Therapeutic agents may perform multiple functions including modulating angiogenesis, restenosis, cell proliferation, thrombosis, platelet aggregation, clotting, and vasodilation.

Anti-inflammatories include but are not limited to non-steroidal anti-inflammatories (NSAID), such as aryl acetic acid derivatives, e.g., Diclofenac; aryl propionic acid derivatives, e.g., Naproxen; and salicylic acid derivatives, e.g., Diflunisal. Anti-inflammatories also include glucocoriticoids (steroids) such as dexamethasone, aspirin, prednisolone, and triamcinolone, pirfenidone, meclofenamic acid, tranilast, and nonsteroidal anti-inflammatories. Anti-inflammatories may be used in combination with antiproliferatives to mitigate the reaction of the tissue to the antiproliferative.

The agents may also include anti-lymphocytes; anti-macrophage substances; immunomodulatory agents; cyclooxygenase inhibitors; anti-oxidants; cholesterol-lowering drugs; statins and angiotens in converting enzyme (ACE); fibrinolytics; inhibitors of the intrinsic coagulation cascade; antihyperlipoproteinemics; and anti-platelet agents; anti-metabolites, such as 2-chlorodeoxy adenosine (2-CdA or cladribine); immuno-suppressants including sirolimus, everolimus, tacrolimus, etoposide, and mitoxantrone; anti-leukocytes such as 2-CdA, IL-1 inhibitors, anti-CD116/CD18 monoclonal

antibodies, monoclonal antibodies to VCAM or ICAM, zinc protoporphyrin; anti-macrophage substances such as drugs that elevate NO; cell sensitizers to insulin including glitazones; high density lipoproteins (HDL) and derivatives; and synthetic facsimile of HDL, such as lipator, lovestatin, pranastatin, atorvastatin, simvastatin, and statin derivatives; vasodilators, such as adenosine, and dipyridamole; nitric oxide donors; prostaglandins and their derivatives; anti-TNF compounds; hypertension drugs including Beta blockers, ACE inhibitors, and calcium channel blockers; vasoactive substances including vasoactive intestinal polypeptides (VIP); insulin; cell sensitizers to insulin including glitazones, P par agonists, and metformin; protein kinases; antisense oligonucleotides including resten-NG; antiplatelet agents including tirofiban, eptifibatide, and abciximab; cardio protectants including, VIP, pituitary adenylate cyclase-activating peptide (PACAP), apoA-I milano, amlodipine, nicorandil, cilostaxone, and thienopyridine; cyclooxygenase inhibitors including COX-1 and COX-2 inhibitors; and petidose inhibitors which increase glycolitic metabolism including omnipatrilat. Other drugs which may be used to treat inflammation include lipid lowering agents, estrogen and progestin, endothelin receptor agonists and interleukin-6 antagonists, and Adiponectin. Therapeutic agents may also include phosphodiesterase inhibitors (PDEi), such as cilastazol and adenosine receptor agonists, preferably A_{2A} receptor, agonists such as regadenoson.

Agents may also be delivered using a gene therapy-based approach in combination with an expandable medical device. Gene therapy refers to the delivery of exogenous genes to a cell or tissue, thereby causing target cells to express the exogenous gene product. Genes are typically delivered by either mechanical or vector-mediated methods.

Some of the agents described herein may be combined with additives which preserve their activity. For example additives including surfactants, antacids, antioxidants, and detergents may be used to minimize denaturation and aggregation of a protein drug. Anionic, cationic, or nonionic surfactants may be used. Examples of nonionic excipients include but are not limited to sugars including sorbitol, sucrose, trehalose; dextrans including dextran, carboxy methyl (CM) dextran, diethylamino ethyl (DEAE) dextran; sugar derivatives including D-glucosaminic acid, and D-glucose diethyl mercaptal; synthetic polyethers including polyethylene glycol (PEO) and polyvinyl pyrrolidone (PVP); carboxylic acids including D-lactic acid, glycolic acid, and propionic acid; surfactants with affinity for hydrophobic interfaces including n-dodecyl-.beta.-D-maltoside, n-octyl-.beta.-D-glucoside, PEO-fatty acid esters (e.g. stearate (myrj 59) or oleate), PEO-sorbitan-fatty acid esters (e.g. Tween™ 80, PEO-20 sorbitan monooleate), sorbitan-fatty acid esters (e.g. SPAN™ 60, sorbitan monostearate), PEO-glyceryl-fatty acid esters; glyceryl fatty acid esters (e.g. glyceryl monostearate), PEO-hydrocarbon-ethers (e.g. PEO-10 oleyl ether; triton X-100; and Lubrol. Examples of ionic detergents include but are not limited to fatty acid salts including calcium stearate, magnesium stearate, and zinc stearate; phospholipids including lecithin and phosphatidyl choline; (PC) CM-PEG; cholic acid; sodium dodecyl sulfate (SDS); docusate (AOT); and taumocholic acid.

In accordance with another exemplary embodiment, a stent or intraluminal scaffold as described herein, may be coated with an anti-thrombotic agent in addition to one or more therapeutic agents deposited in the holes or openings. In one exemplary embodiment, the stent may be fabricated with the openings therein and prior to the addition or deposition of other

therapeutic agents into the openings, an anti-thrombotic agent, with or without a carrier vehicle (polymer or polymeric matrix) may be affixed to the stent or a portion thereof. In this exemplary embodiment, the luminal and abluminal surfaces of the stent may be coated with the anti-thrombotic agent or coating, as well as the surfaces of the walls of the openings. In an alternative exemplary embodiment, a stent may first be coated with an anti-thrombotic agent or coating and then the openings may be fabricated. In this exemplary embodiment, only the luminal and abluminal surfaces would have the anti-thrombotic agent or coating and not the walls of the openings. In each of these embodiments any number of anti-thrombotic agents may be affixed to all or portions of the stents. In addition, any number of known techniques may be utilized to affix the anti-thrombotic agent to the stent such as that utilized with the HEPACOAT™ on the Bx Velocity® Coronary Stent from Cordis Corporation. Alternatively, the stents may be manufactured with a rough surface texture or have a micro-texture to enhance cell attachment and endothelialization, independently of or in addition to the anti-thrombotic coating. In addition, any number of therapeutic agents may be deposited into the openings and different agents may be utilized in different regions of the stent.

As described above, it is important to note that any number of drugs and or agents may be utilized in accordance with the present invention including: antiproliferative/antimitotic agents including natural products such as vinca alkaloids (i.e. vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (i.e. etoposide, teniposide), antibiotics (dactinomycin (actinomycin D) daunorubicin, doxorubicin and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin, enzymes (L-asparaginase which systemically metabolizes L-asparagine and

deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents such as G(GP)II_bIII_a inhibitors and vitronectin receptor antagonists; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nirtosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes – dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs (fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine {cladribine}); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (i.e. estrogen); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory; antisecretory (breveldin); antiinflammatory: such as adrenocortical steroids (cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6α-methylprednisolone, triamcinolone, betamethasone, and dexamethasone), non-steroidal agents (salicylic acid derivatives i.e. aspirin; para-aminophenol derivatives i.e. acetominophen; indole and indene acetic acids (indomethacin, sulindac, and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate); immunosuppressives: (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); angiogenic

agents: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) platelet derived growth factor (PDGF), erythropoetin; angiotensin receptor blocker; nitric oxide donors; anti-sense oligionucleotides and combinations thereof; cell cycle inhibitors, mTOR inhibitors, and growth factor signal transduction kinase inhibitors.

Referring now to Figure 9A, 9B and 9C, there is illustrated a diagrammatic representation of a portion of a stent.

As illustrated in Figure 9A the stent 900 comprises a plurality of substantially circular openings 902. In this exemplary embodiment, the plurality of substantially circular openings 902 extend through the wall of the stent 900. In other words, the plurality of substantially circular openings 902 extend from the abluminal surface of the stent 904 to the abluminal surface of the stent 906, wherein the wall thickness is defined as the distance between the luminal and abluminal surfaces. In other embodiments; however, the openings need not extend through the wall of the stent 900. For example, the openings or reservoirs may extend partially from either the luminal or abluminal surfaces or both. The stent 900 in Figure 9A has untreated surfaces 904 and 906 and empty openings 902.

In Figure 9B, at least one surface has been coated with a therapeutic agent 908. The therapeutic agent preferably comprises an anti-thrombotic agent such as heparin; however, any anti-thrombotic agent may be utilized. The anti-thrombotic agent may be affixed utilizing any technique as briefly described above. In this exemplary embodiment, both the abluminal and luminal surfaces have an anti-thrombotic agent affixed thereto. In addition, as there is nothing in the plurality of substantially circular openings 902 at

this juncture, the walls of the openings 902 may also have some anti-thrombotic agent affixed thereto. The amount of anti-thrombotic agent affixed to the walls of the openings 910 depends on how the agent is affixed. For example, if the agent is affixed by dip coating, the walls of the openings will have more agent affixed thereto than if the agent is affixed utilizing a spray coating technique. As described herein, in this exemplary embodiment, all exposed surfaces have a substantial anti-thrombotic coating affixed thereto; however, in alternate exemplary embodiments, only specific surfaces may have an anti-thrombotic affixed thereto. For example, in one exemplary embodiment, only the surface in contact with the blood may be treated with the anti-thromobotic agent. In yet another alternate exemplary embodiment, one or both surfaces may be coated with the anti-thrombotic agent while the walls of the openings are not. This may be accomplished in a number of ways including plugging the openings prior to coating or creating the openings after the anti-thrombotic agent is affixed.

Figure 9C illustrates a completed stent in accordance with this exemplary embodiment. As illustrated in this figure, the plurality of substantially circular openings 902 have been filled with one or more therapeutic agents for treating vascular diseases such as restenosis and inflammation or any other dieses as described herein. Each opening 902 may be filled with the same therapeutic agent or different agents as described in detail above. As illustrated in the figure, these different agents 912, 914 and 916 are used in a particular pattern; however, as detailed above, any combination is possible as well as utilizing a singe agent with different concentrations. The drugs, such as a rapamycin, may be deposited in the openings 902 in any suitable manner. Techniques for depositing the agent include micro-pippetting and/or ink-jet filling methods. In one exemplary embodiment, the drug filling

may be done so that the drug and/or drug/polymer matrix in the opening will be below the level of the stent surfaces so that there is no contact with the surrounding tissue. Alternately, the openings may be filled so that the drug and/or drug/polymer matrix may contact the surrounding tissue. In addition, the total dose of each of the drugs, if multiple drugs are utilized, may be designed with maximal flexibility. Additionally, the release rate of each of the drugs may be controlled individually. For example, the openings near the ends may contain more drugs to treat edge restenosis.

In accordance with this exemplary embodiment, the hole or openings may be configured not only for the most efficacious drug therapy, but also for creating a physical separation between different drugs. This physical separation may aid in preventing the agents from interacting.

As used herein, rapamycin includes rapamycin and all analogs, derivatives and conjugates that bind to FKBP12, and other immunophilins and possesses the same pharmacologic properties as rapamycin including inhibition of TOR. In addition, all drugs and agents described herein in their analogs, derivatives and conjugates.

As described herein, a stent having through-holes, holes, reservoirs or openings therein may be coated with an anti-thrombotic agent and/or drug or combination of drugs such as those described herein, and the openings filled with one or more therapeutic agents alone or in combination with one or more polymers. Essentially, the stent may be fabricated with the openings therein and prior to the addition or deposition of therapeutic agents alone or in combination with one or more polymers into the openings, an anti-thrombotic agent, with or without a carrier vehicle, may be affixed to the stent or a portion

thereof. In the exemplary embodiment as described herein, the luminal and abluminal surfaces of the stent as well as the surfaces of the walls of the openings may be coated with the anti-thromobotic agent. In this exemplary embodiment, the anti-thrombotic agent comprises heparin or its various derivatives such as low molecular-weight heparin (LMWH), although any number of suitable anti-thrombotic agents may be utilized. Heparin and/or LMWH have very high negative charges.

The entire surface of the stent described herein, including the interior surfaces of the through-holes or openings that become reservoirs for the therapeutic agent and/or combination polymers and therapeutic agent, is first given a covalently bonded heparin coating. The heparin coating itself is bonded to the metal surface of the stent by its own primer comprising alternating layers of poly(ethyleneimine), a strongly cationic polymer known by the abbreviation PEI, and dextran sulfate, a polymeric anion. The application of this type of primer is known in the art and is set forth in a number of patents, including U.S. Patent Nos. 5,213,898, 5,049,403, 6,461,665 and 6,767,405. More specifically, the heparin is covalently bonded to the primer, including the PEI-dextran sulfate layers, which is in turn bonded to the metal surface. Once all surfaces are coated with the heparin mixture, each of the holes or reservoirs are filled utilizing one of the processes described herein.

In accordance with another exemplary embodiment, the present invention is directed to primer compositions and configurations for improving the adhesion of a drug delivery matrix, e.g. therapeutic agent and polymer combination, to a heparin coated surface of a medical device, for example, a stent. The present invention is particularly advantageous where the heparin coating is covalently

bonded to a metallic or polymer surface of the medical device. In the present invention, the primer preferably comprises a high molecular weight component or a low molecular weight component, and the drug delivery matrix comprises a drug and/or other beneficial agent and an excipient, preferably a polymeric excipient. In addition, the primer may also preferably comprise a material having an opposite electrical charge and similar charge density to that of the underlying layer, for example, heparin.

The concept of a primer on top of a heparin layer or coating to increase the bonding of a heparin coated surface to any other matrix or coating is unique given that typically the heparin surface is utilized to confer anti-thromobotic properties and hence will not be covered in practical uses. In the present invention, it is only the interior wall surfaces of the holes or openings in the stent that hold the drug-polymer reservoirs that will be covered with the primer of the present invention, thus increasing the adhesion between the two layers and limiting the potential loss of the drug-polymer matrix without substantially affecting the heparin surface outside the reservoirs. It is important to note that the heparin blocking primers in accordance with the present invention are biocompatible in their original intended uses.

The primer of the present invention may be utilized with any type of stent. In the exemplary embodiment described herein, the primer is utilized with the stent or stents illustrated in Figures 1, 2, 3 and 4.

In accordance with one exemplary embodiment, the primer comprises polymer-poly(ethyleneimine) conjugates, for example polylactic-co-glycolic acid (PLGA) and poly(ethyleneimine) PEI and/or PLGA-protamine. Poly(ethyleneimine) is a strongly cationic polymer that binds to certain

negatively charged proteins or polysaccharides. In addition to PEI, the other material useful in this conjugate is protamine. Protamine is an approved low molecular weight protein drug that is utilized as an antidote to heparin. It is sparsely solution in water. In this manner, the primer may simultaneously interact strongly with both the heparin coating and the drug containing matrix, thus improving the adhesion between the two substances. Since heparin is a poly(anionic) species, it is anticipated that a poly(cationic) species such as protamine would bond well to the heparin, but would be sufficiently hydrophobic in the other sections of its structure to allow good bonding of the PLGA component of the drug polymer matrix in the reservoir.

The bonding reactions between PLGA and PEI and PEI and heparin may be ionic-bonding or covalent-bonding reactions. Figure 10 illustrates an example of covalent-bonding between PLGA and PEI. More specifically, Figure 10 illustrates the conjugation reaction between PLGA with a carboxylic acid end group and low molecular weight PEI. Alternatively, the primer may comprise a high molecular weight PEI or a branched PEI. Referring to Figure 11, there is illustrated the conjugation reaction between PLGA with a carboxylic acid end group and a high molecular weight or branched PEI. As illustrated, the reaction may be configured for a one-to-one ratio or a conjugate of PLGA-PEI-PLGA for a 2:1 ratio between PLGA and PEI.

The Table below illustrates the effectiveness of PEI as a primer for increasing the adhesion of the drug/polymer complex to the heparin coated surfaces. The test stents are immersed in a testing medium comprising a phosphate buffer saline and bovine serum albumin which simulates physiological fluid conditions. The drug/polymer complex comprises a rapamycin and PLGA.

		Percent (%) of Empty Reservoirs versus Initial Total Reservoirs (after immersion in PBS-BSA)											
Heparin coated stent		Initial	Day 7	Day 14	Day 21	Day 28	Day 30	Day 35	Day 42	Day 49	Day 60	Day 75	Day 90
No primer	Avg	0%	--	0%	0.3%	3.1%	--	3.7%	4.1%	4.8%	4.8%	5.1%	5.3%
	Stdev	0%	--	0%	0.4%	2.1%	--	2.0%	2.0%	1.2%	1.2%	1.3%	1.5%
	RSD	n/a	--	n/a	124.9%	68.3%	--	56.0%	48.5%	25.3%	25.3%	25.1%	28.4%
Primed with 0.25% PEI (linear) in Water	Avg	0.0%	0.0%	--	--	--	0.0%				0.0%		
	Stdev	0.0%	0.0%	--	--	--	0.0%				0.0%		
	RSD	n/a	n/a	--	--	--	n/a				n/a		
Primed with 0.5% PEI (linear) in Water	Avg	0%	--	0%	0%	0%	--	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
	Stdev	0%	--	0%	0%	0%	--	0%	0%	0%	0%	0%	0%
	RSD	n/a	--	n/a	n/a	n/a	--	n/a	n/a	n/a	n/a	n/a	n/a
Primed with 0.5% PEI (linear) in DMSO	Avg	0%	--	0%	0%	0%	--	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
	Stdev	0%	--	0%	0%	0%	--	0%	0%	0%	0%	0%	0%
	RSD	n/a	--	n/a	n/a	n/a	--	n/a	n/a	n/a	n/a	n/a	n/a
Primed with 0.5% PEI (branched) in Water	Avg	0%	--	0%	0%	0%	--	0%	0%	0%	0%	0%	0%
	Stdev	0%	--	0%	0%	0%	--	0%	0%	0%	0%	0%	0%
	RSD	n/a	--	n/a	n/a	n/a	--	n/a	n/a	n/a	n/a	n/a	n/a
Primed with 0.5% PEI (branched) in DMSO	Avg	0%	--	0%	0%	0%	--	0%	0%	0%	0%	0%	0%
	Stdev	0%	--	0%	0%	0%	--	0%	0%	0%	0%	0%	0%
	RSD	n/a	--	n/a	n/a	n/a	--	n/a	n/a	n/a	n/a	n/a	n/a
Primed with 0.75% PEI (linear) in Water	Avg	0.0%	0.0%	--	--	--	0.0%				0.0%		
	Stdev	0.0%	0.0%	--	--	--	0.0%				0.0%		
	RSD	n/a	n/a	--	--	--	n/a				n/a		

In an alternate exemplary embodiment, the primer may comprise low molecular weight complexing cations to heparin, including benzalkonium chloride and/or oligomeric arginine peptides, or high molecular weight complexing cations, including polylysine, poly(arginine), protamine, poly(dimethylaminoethyl) methacrylate or poly (dimethylaminoethyl) acrylate.

In accordance with the present invention, the process for increasing adhesion of the drug complex to the heparin may include the application of the adhesion promoting primer followed by polymer/drug fill solution or the application of the adhesion promoting primer followed by carboxyl-ended PLGA or a blend of carboxyl-ended and regular PLGA and PLGA/drug fill solution.

The primer of the present invention will be applied to the interior, heparin coated walls of the holes or openings in the stent prior to the openings being filled with a local drug delivery matrix. In other words, in the finished drug eluting stent, the primer will occupy a space between the surface of the heparin coating and the body of the drug delivery matrix and will increase the adhesion between the heparin coating and the drug delivery matrix. The enhancement of adhesion is achieved through multiple factors, including the reduction of osmolarity/water infiltration of the heparin coating in use after the charge neutralization by a cationic primer, reduced aqueous solubility of heparin/cationic primer complex as compared to the heparin surface alone, ionic bonding, covalent bonding and better physical adhesion between the primer and the polymer/drug matrix due to surface tension and the like.

In another exemplary embodiment of the present invention, the primer of the present invention will preferably have a portion of its molecular structure that is positively charged for bonding to the negatively charged heparin coating, and a portion that is hydrophobic, hydrophilic, or balanced for bonding to the polymer component of the drug delivery matrix. This portion of the primer will vary depending on the nature of the drug delivery matrix. More specifically, the primer is designed to improve the adhesion of the drug delivery matrix to the heparin coated openings of the stent so that none or substantially none of the

openings or reservoirs lose their contents when the stent comes into contact with water based fluids, such as saline, blood and/or intercellular fluid.

Although the primer of the present invention has been described specifically to increasing the adhesion between the heparin coated interior walls of a stent reservoir and the drug/polymer mixture filling the reservoir, it may be useful for the attachment or bonding of any substrate to a portion of a heparin coated surface. For example, blood contacting plastic medical devices are often coated with heparin to minimize thrombosis on the device, but it may be desired to bond later to that surface. A mixture of the primers of the present invention in a solvent could be applied to a selected area of the device, the solvent evaporated to provide a primer coated area on the heparin surface, then subsequently a new subsystem could be bonded to the primer covered area.

The primer material will be advantageously applied as a solution of the polymeric primer in a solvent such as dimethyl sulfoxide (DMSO), N-methylpyrrolidone, or water mixtures thereof and may be introduced into the reservoirs using any of the filling techniques described in the instant application. Such a primer solution could then be dried to provide the coating of the primer layer over the heparin coated surface. Preferably, the application of the primer layer will require only a single deposition step in the stent filling process. The selection of a suitable solvent for the deposition of a cationic primer is determined primarily by its ability to dissolve a primer and its compatibility with the filling apparatus and process described herein.

The present invention may be simply characterized as an implantable medical device. The medical device comprises an intraluminal scaffold having a plurality of openings therein, a first coating comprising a material having a first electric charge affixed to at least a portion of a surface of the intraluminal scaffold and a surface of the plurality of openings, a second coating comprising a material having a second electric charge affixed to at least a portion of the first coating, the second electric charge being opposite of the first electric charge, and at least one therapeutic agent deposited in at least one of the plurality of openings, wherein the second coating is configured as an intermediate layer between the first coating and the at least one therapeutic agent.

The first coating may comprise any suitable anti-thrombotic as described herein. For example, a polysaccharide such as heparin may be utilized. The second coating may comprise a polymeric cation or a polymeric conjugate having cationic segments as described herein. Examples of polymeric cations include oligomeric arginine peptides, polylysine, poly(arginine), protamine, poly(dimethylaminoethyl) poly(ethyleneimine). Examples of polymeric cationic conjugates include a first component such as polylactic-co-glycolic acid and the second component comprises any of the cations set forth above. The therapeutic agent may comprise an anti-restenotic, an anti-inflammatory, an anti-thrombotic, an anti-proliferative, an agent for minimizing damage to infarcted tissue or any combination thereof.

In a more general sense, the concept of the present invention may be expanded to include primers that increase the bonding strength between hydrophilic and hydrophobic surfaces. For example, other hydrophilic surfaces of interest are the so called “lubricious” coatings, such as those

utilized in conjunction with catheters. These hydrophilic surfaces are often also covalently bonded, but may be just conformal coatings. Examples of chemical structures that occur in lubricious coatings are those based on polyvinylpyrrolidone, hydroxyethyl methacrylate, poly(ethylene oxide) or poly(ethylene glycol) and the like.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. An implantable medical device comprising:

a substantially cylindrical intraluminal scaffold which is expandable from a first diameter for delivery into a vessel, to a second diameter for expanding the vessel, the intraluminal scaffold having a luminal surface and an abluminal surface, the distance between the luminal surface and the abluminal surface defining the wall thickness of the intraluminal scaffold, the intraluminal scaffold also including a plurality of openings extending from the luminal to abluminal surface;

a primer layer including multiple layers, the primer layer covering the luminal surface, the abluminal surface and the surfaces of the plurality of the openings;

a first coating comprising a therapeutic agent having a first electric charge affixed to the primer layer;

a second coating comprising a material having a second electric charge affixed to the first coating only in the plurality of openings, the second electric charge being opposite of the first electric charge; and

at least one therapeutic agent deposited in the plurality of openings, wherein the second coating is configured as an intermediate layer between the first coating and the at least one therapeutic agent to improve the adhesion between the at least one therapeutic agent and the first coating.

2. The implantable medical device according to claim 1, wherein the first coating comprises an anti-thrombotic agent.

3. The implantable medical device according to claim 2, wherein the anti-thrombotic agent comprises a polysaccharide.

4. The implantable medical device according to claim 3, wherein the polysaccharide comprises sulfated polysaccharides.

5. The implantable medical device according to claim 3, wherein the polysaccharide comprises heparin.

6. The implantable medical device according to claim 1, wherein the second coating comprises a polymeric cation.

7. The implantable medical device according to claim 6, wherein the polymeric cation is selected from the group consisting of an oligomeric arginine peptide, polylysine, poly(arginine), protamine, poly(dimethylaminoethyl) methacrylate, poly(dimethylaminoethyl acrylate) and poly(ethyleneimine).

8. The implantable medical device according to claim 1, wherein the second coating comprises a polymeric conjugate.

9. The implantable medical device according to claim 8, wherein the polymeric conjugate comprises a first component comprising a bioabsorbable polymer and a second component is selected from the group consisting of an oligomeric arginine peptide, polylysine, poly(arginine), protamine, poly(dimethylaminoethyl) methacrylate, poly(dimethylaminoethyl acrylate) and poly(ethyleneimine).

10. The implantable medical device according to claim 9, wherein the bioabsorbable polymer comprises poly(lactic-co-glycolic acid).

11. The implantable medical device according to claim 10, wherein the at least one therapeutic agent is selected from the group consisting of an anti-restenotic, an anti-inflamatory, an anti-thrombotic, an anti-proliferative and a cardioprotectant for minimizing damage to infarcted tissue.

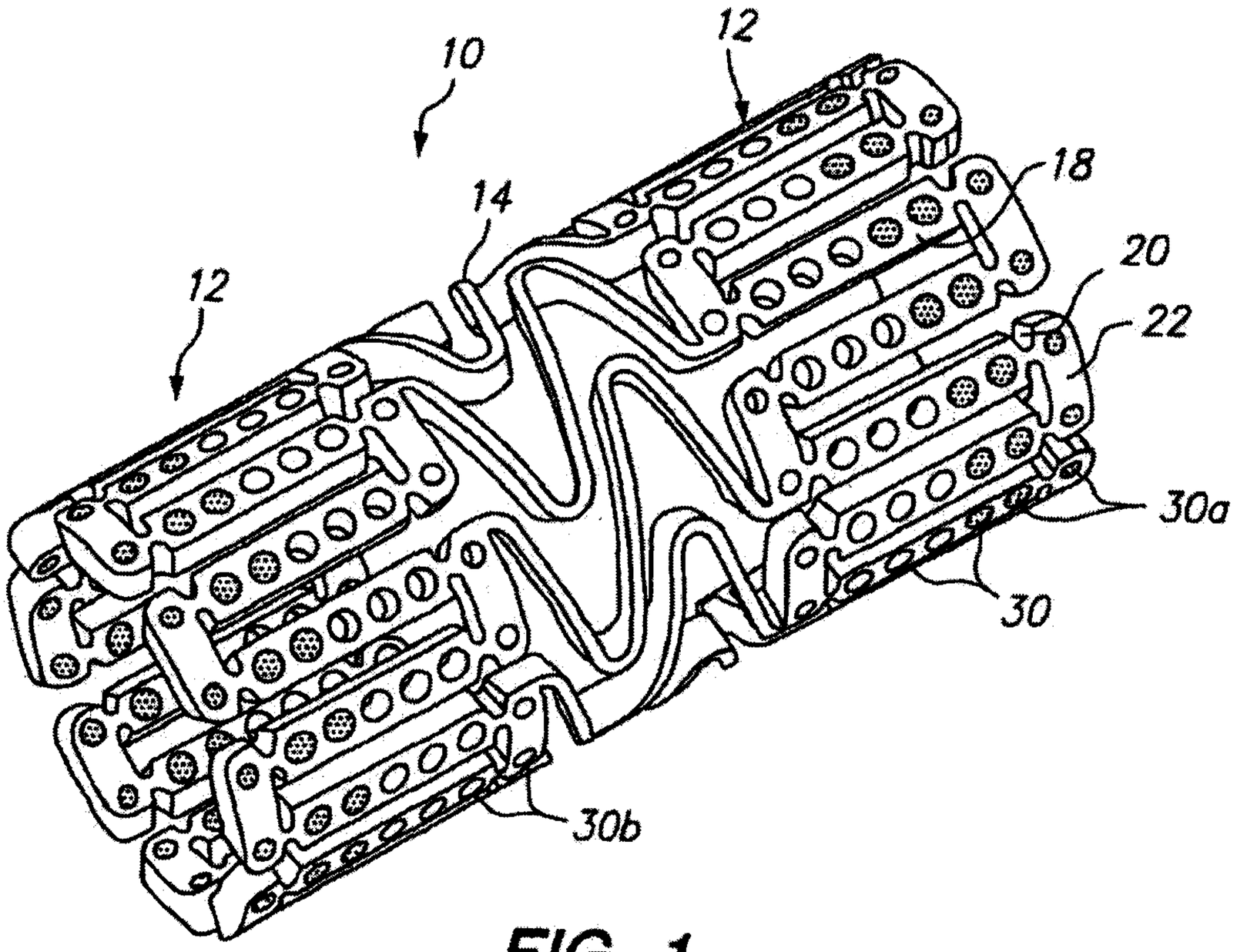


FIG. 1

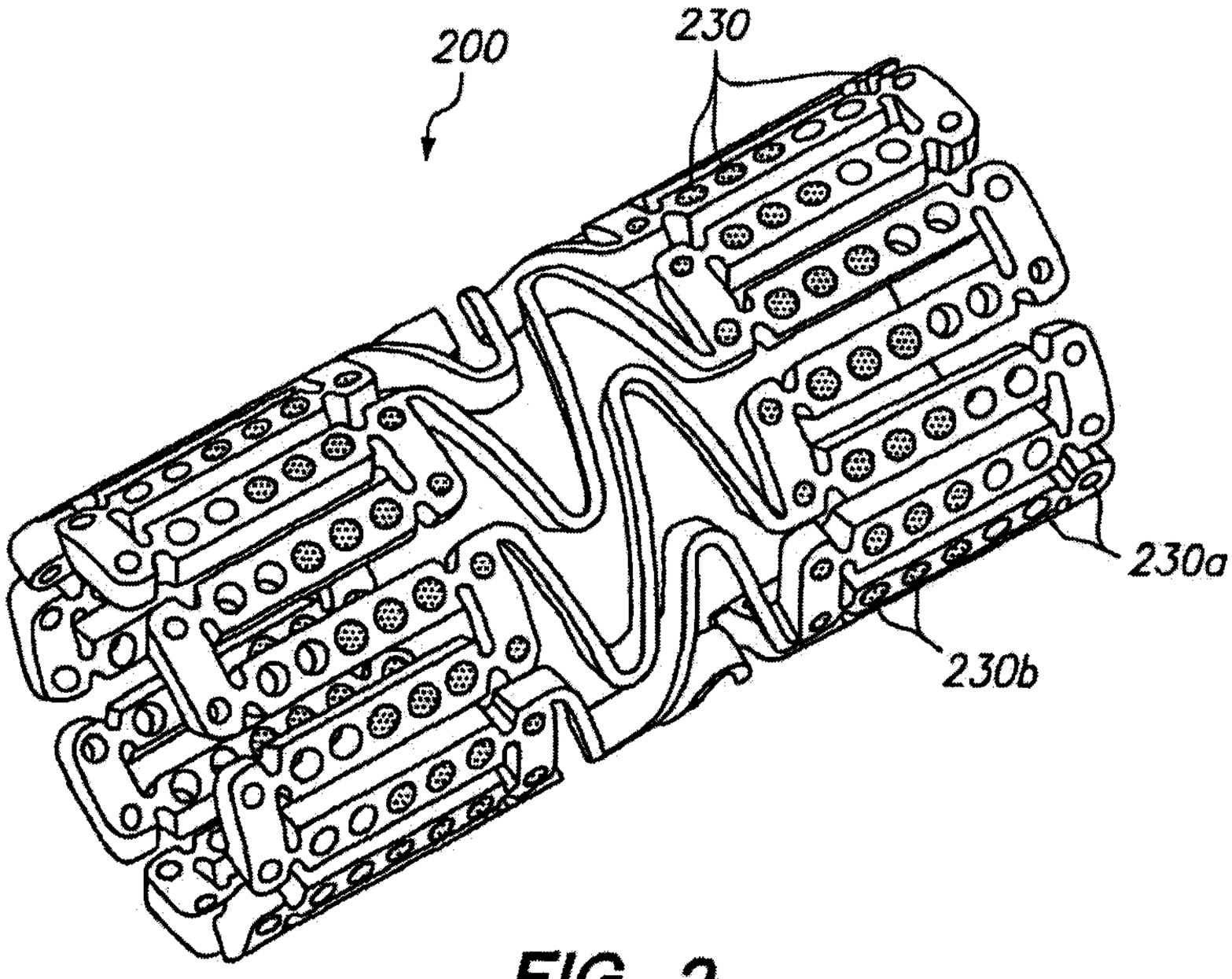


FIG. 2

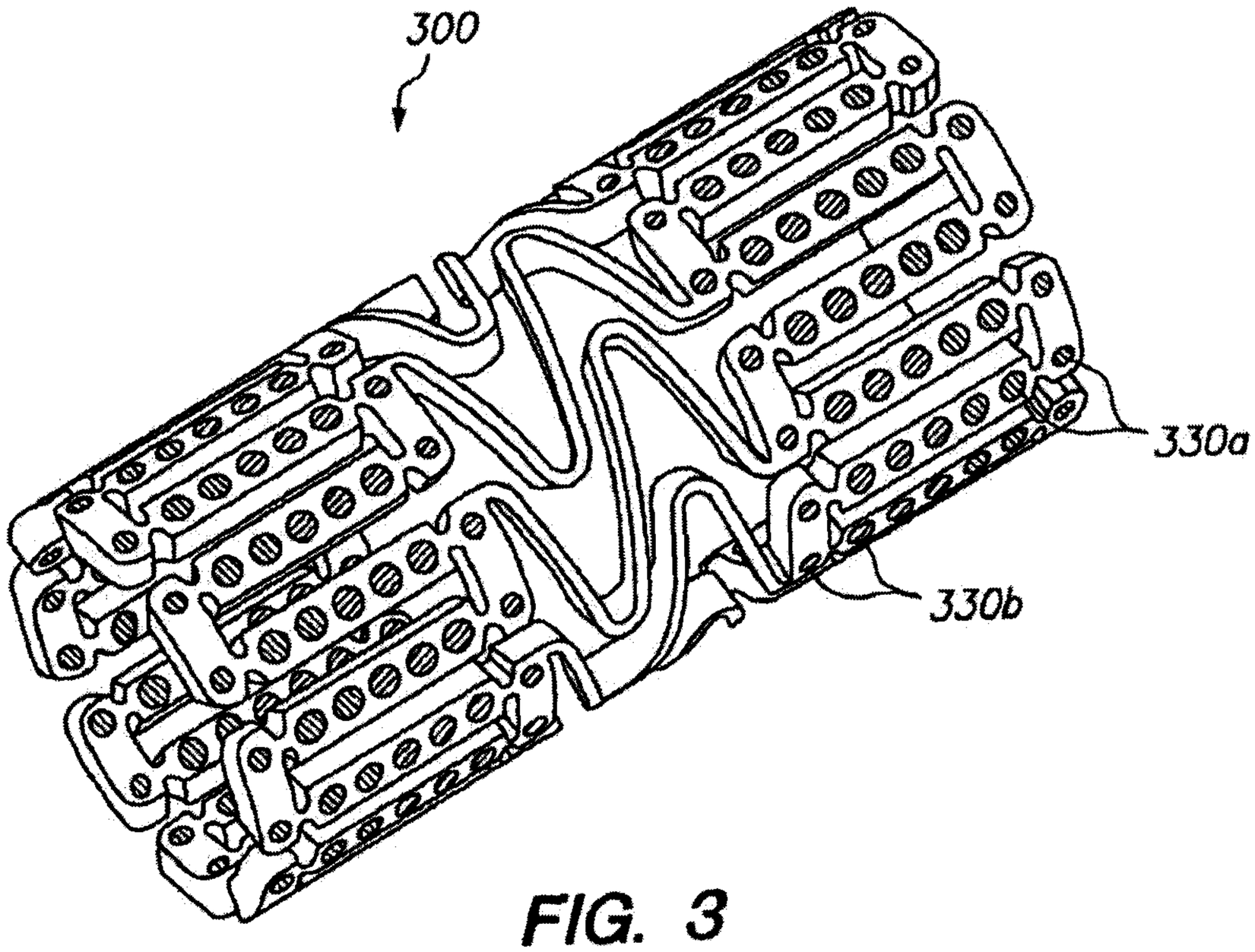


FIG. 3

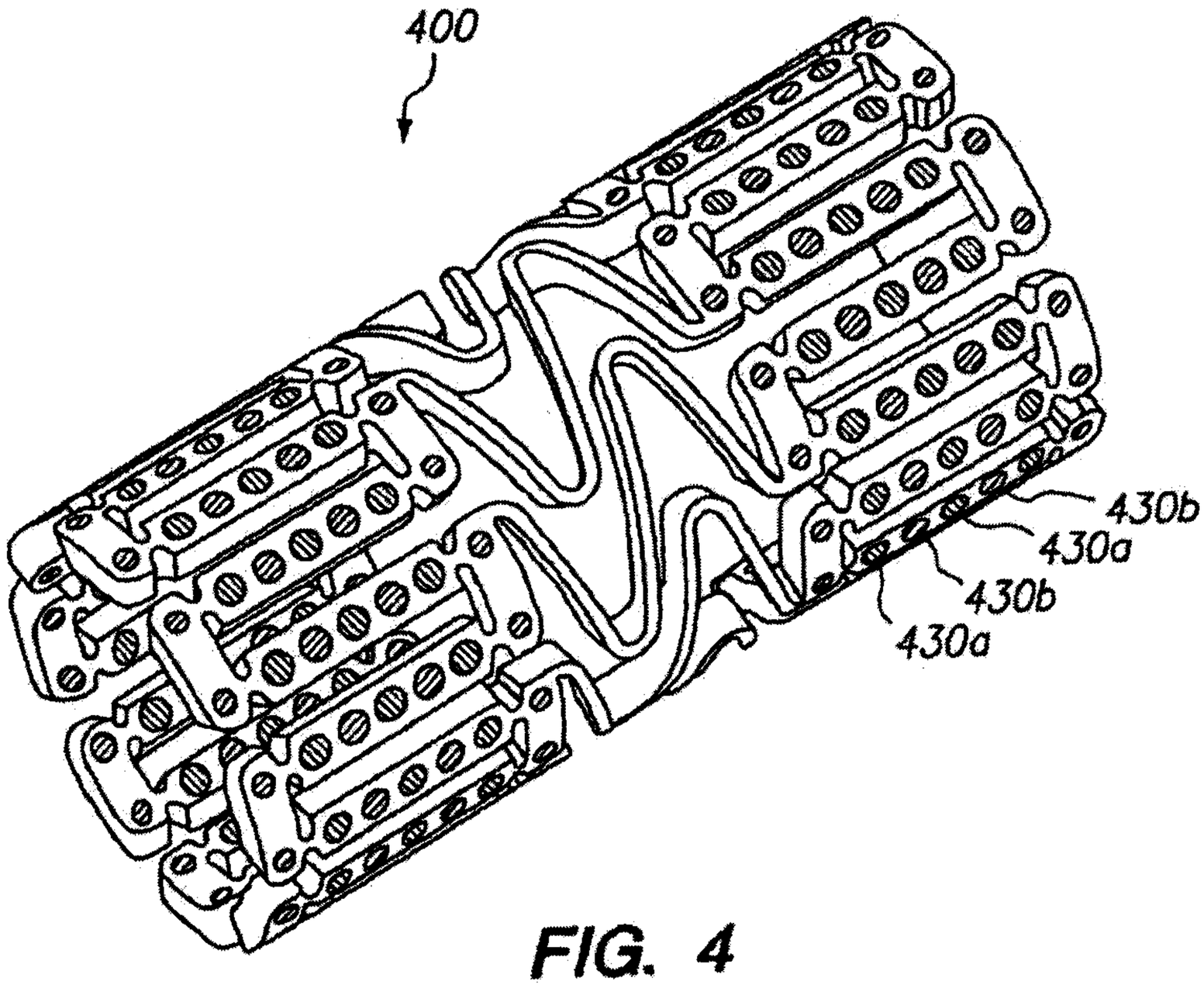
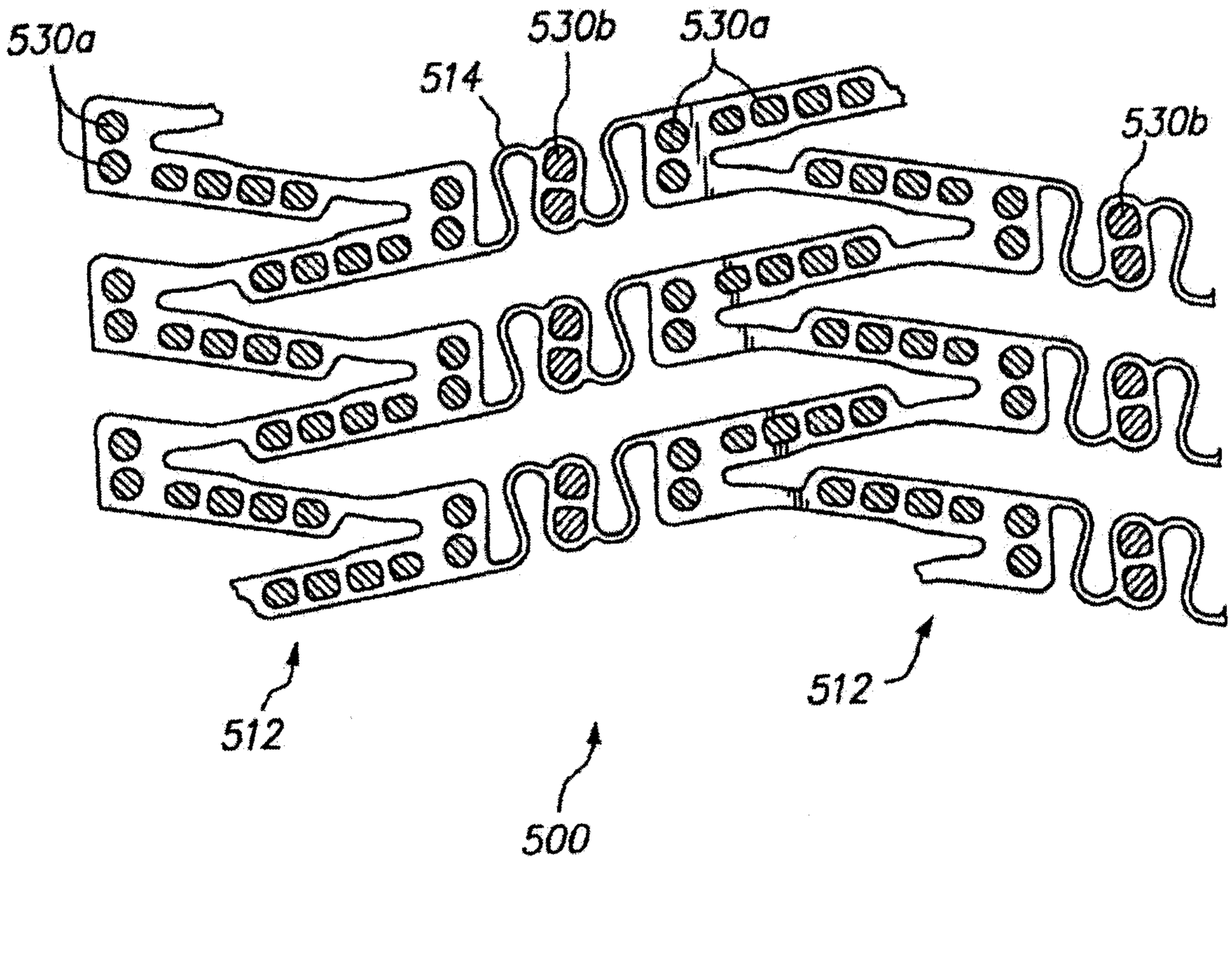


FIG. 4

FIG. 5



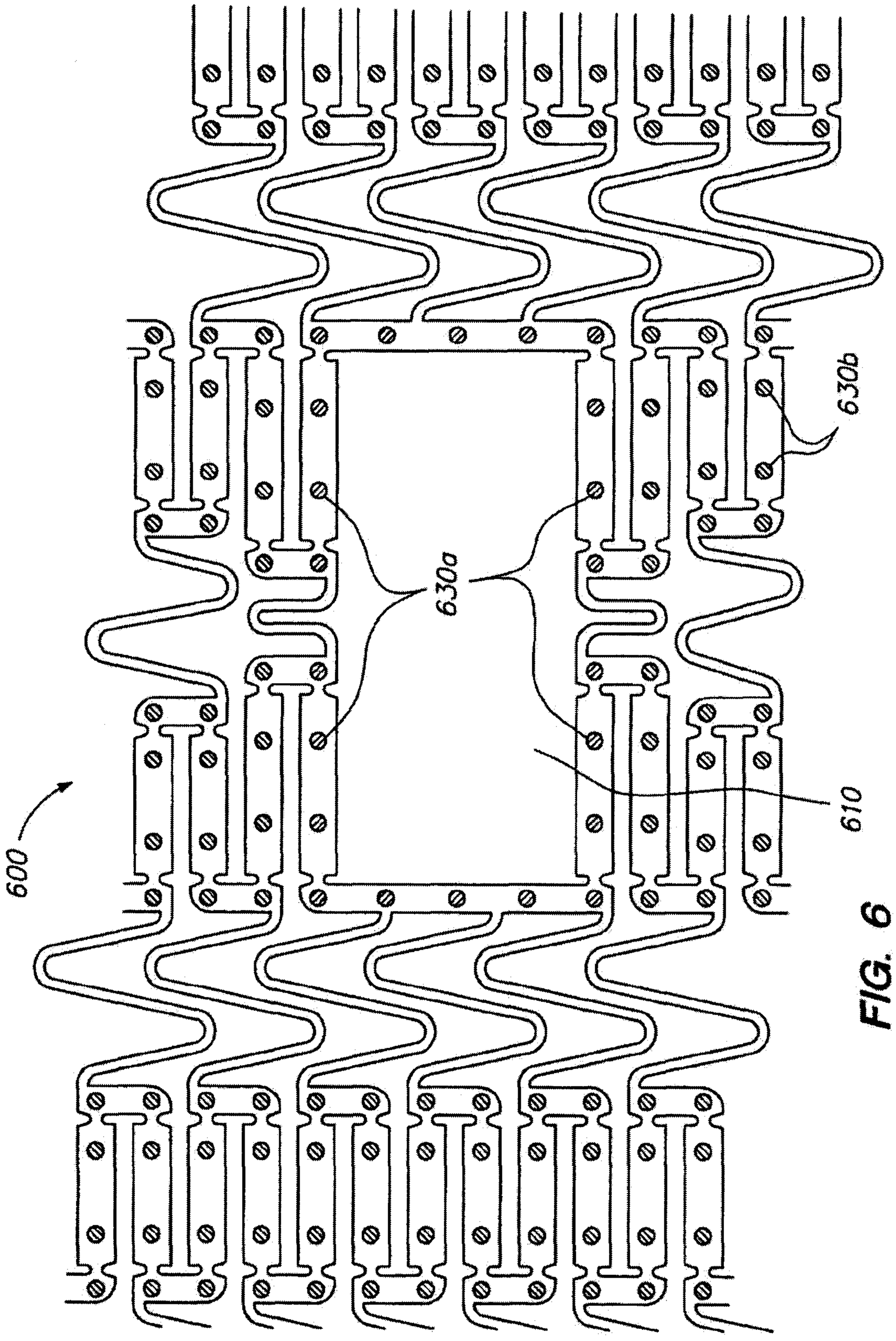


FIG. 6

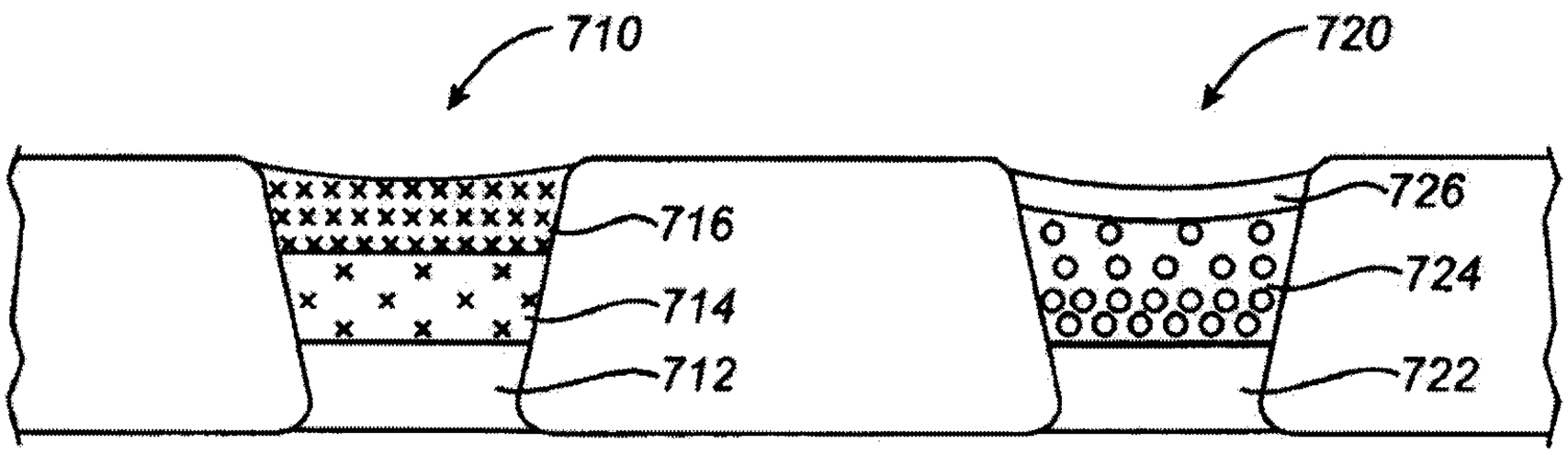

710
720
716
714
712
726
724
722
700

FIG. 7

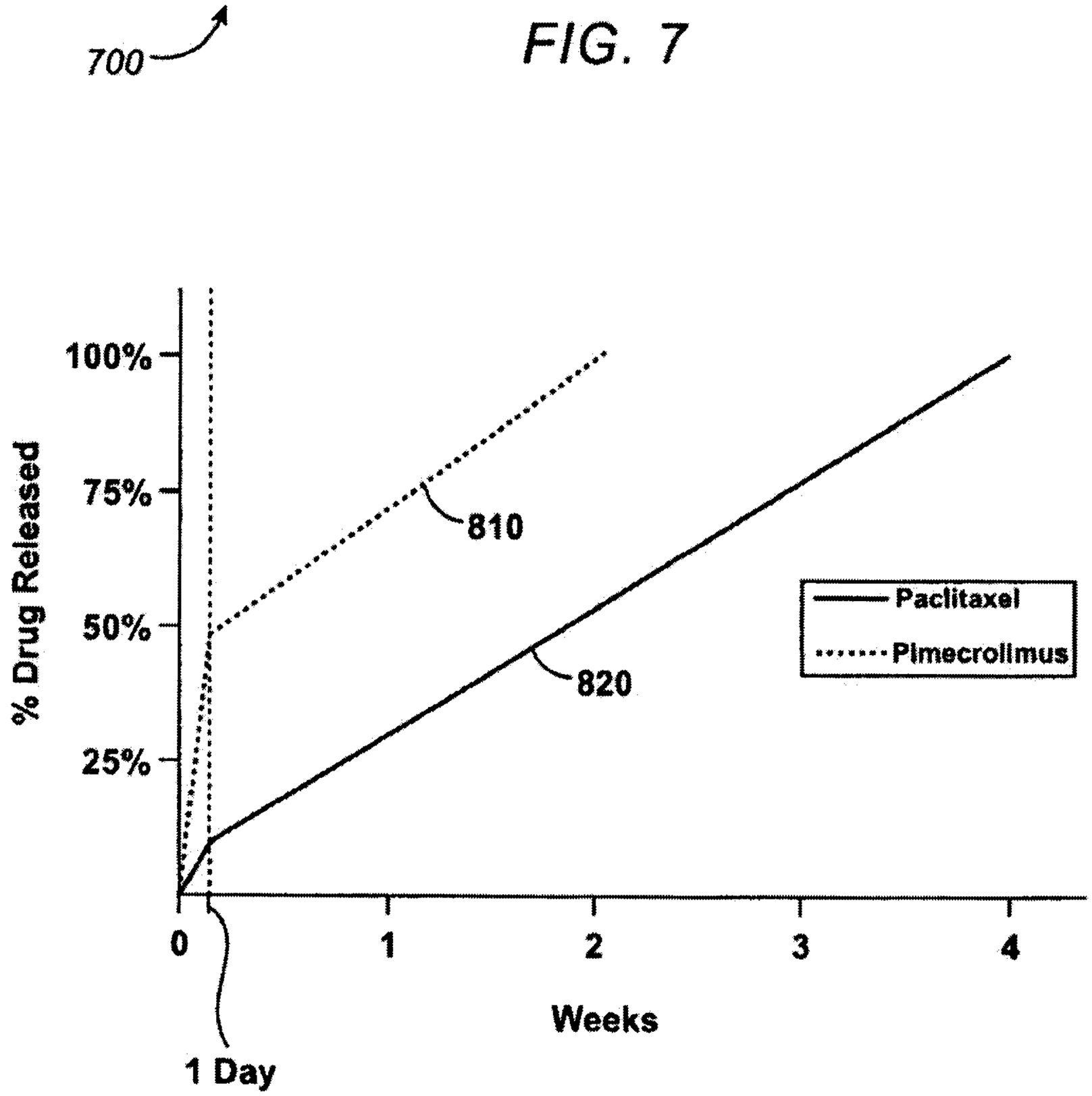

100%
75%
50%
25%
% Drug Released
810
820
Paclitaxel
Pimecrolimus
0
1
2
3
4
Weeks
1 Day

FIG. 8

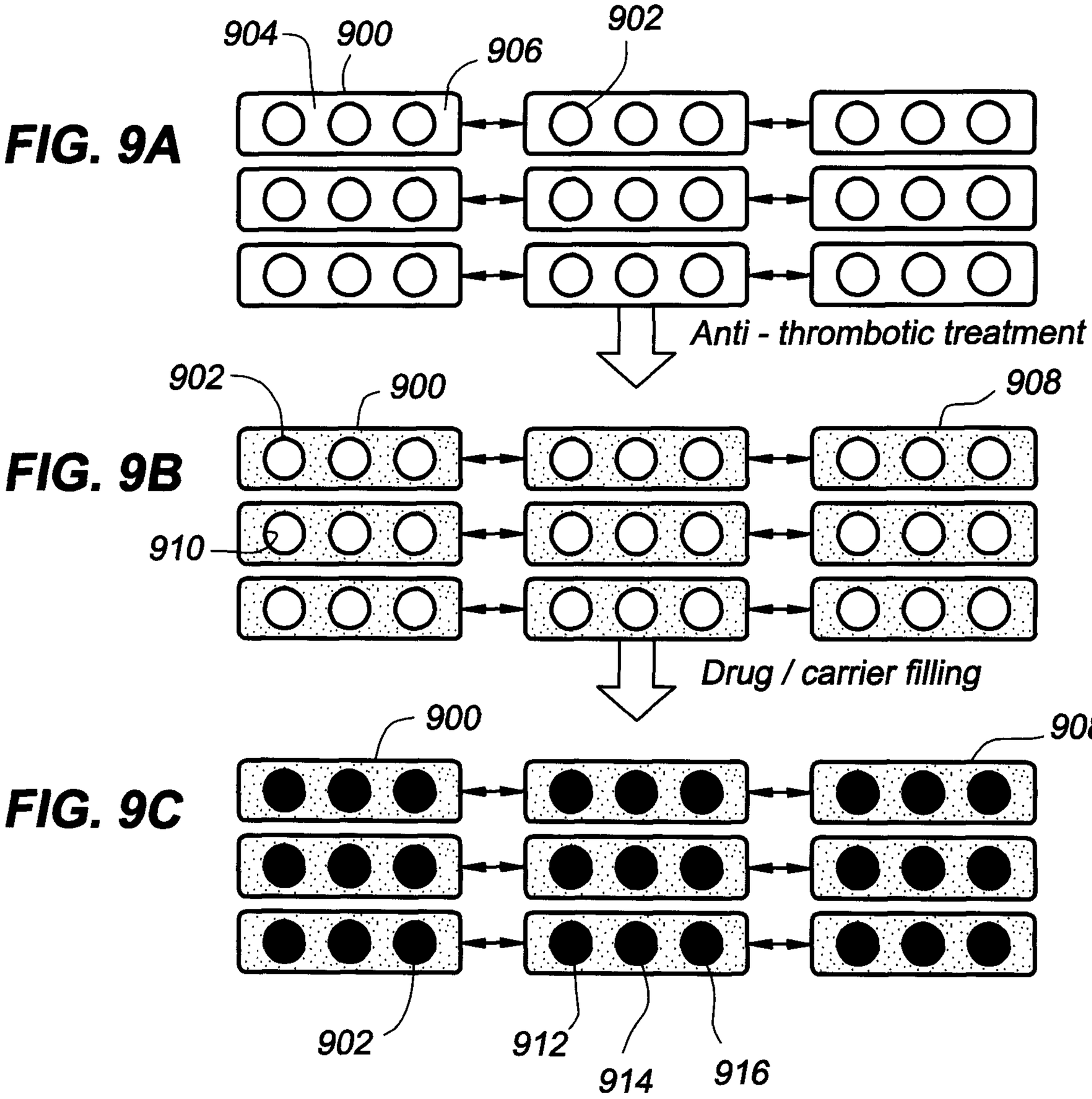


FIG. 9A

FIG. 9B

FIG. 9C

FIG. 10

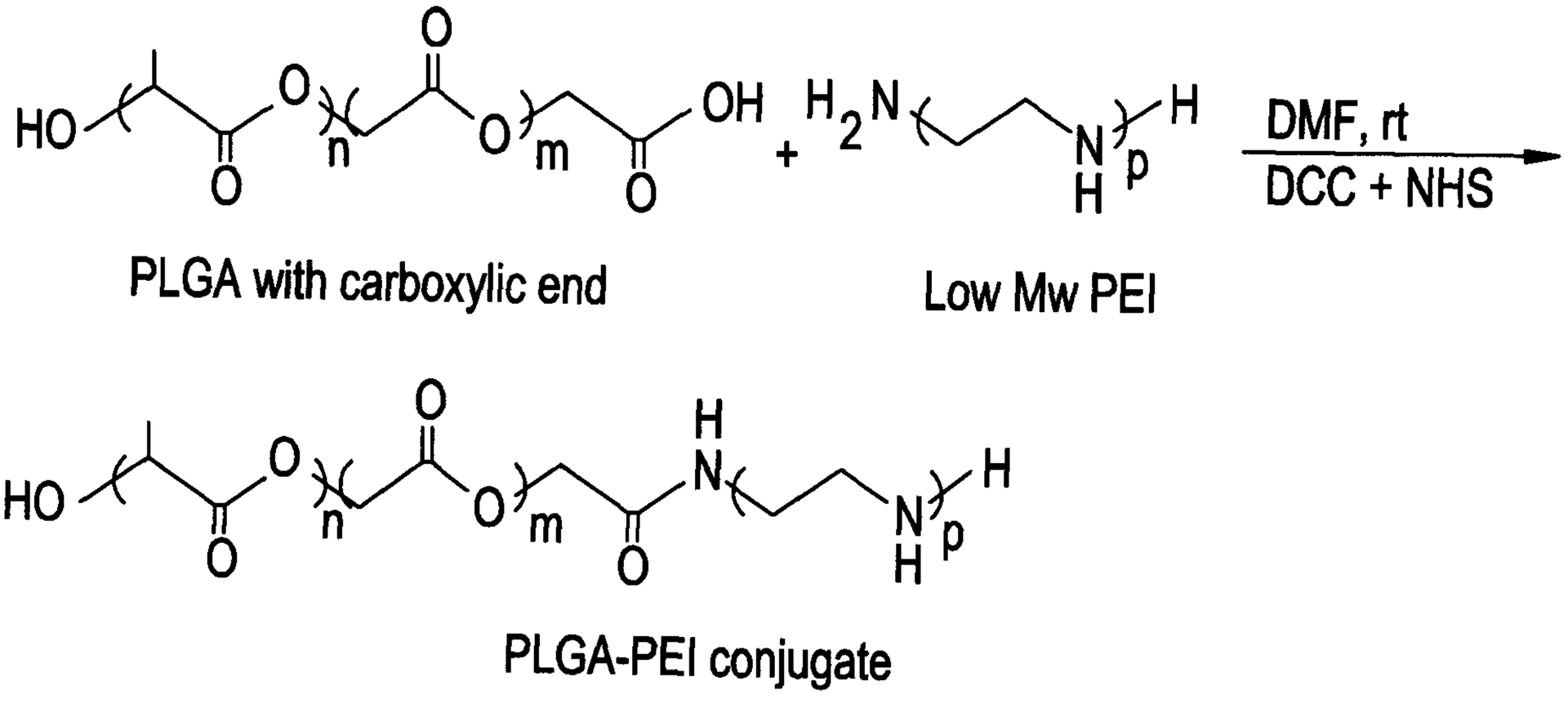
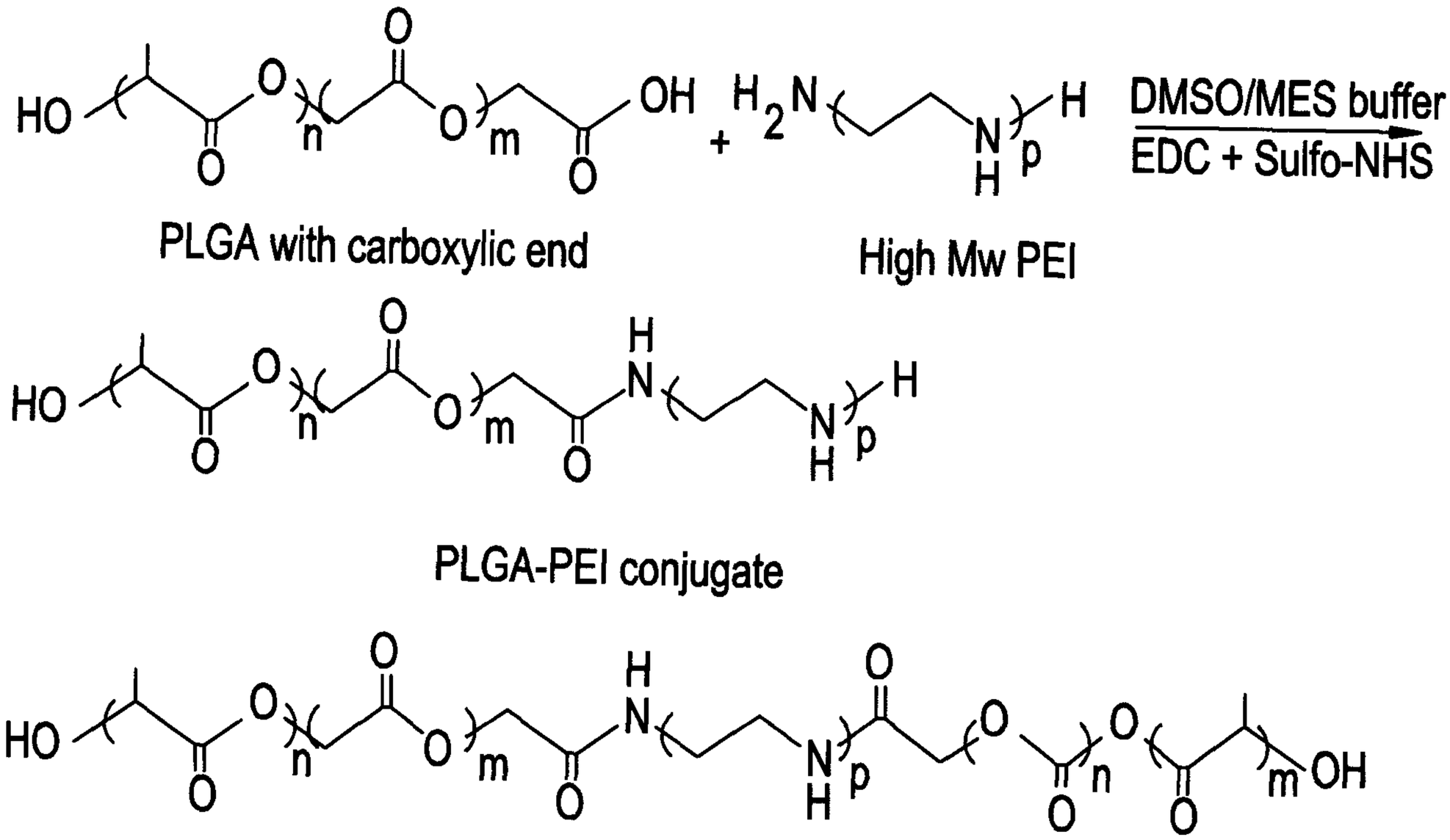
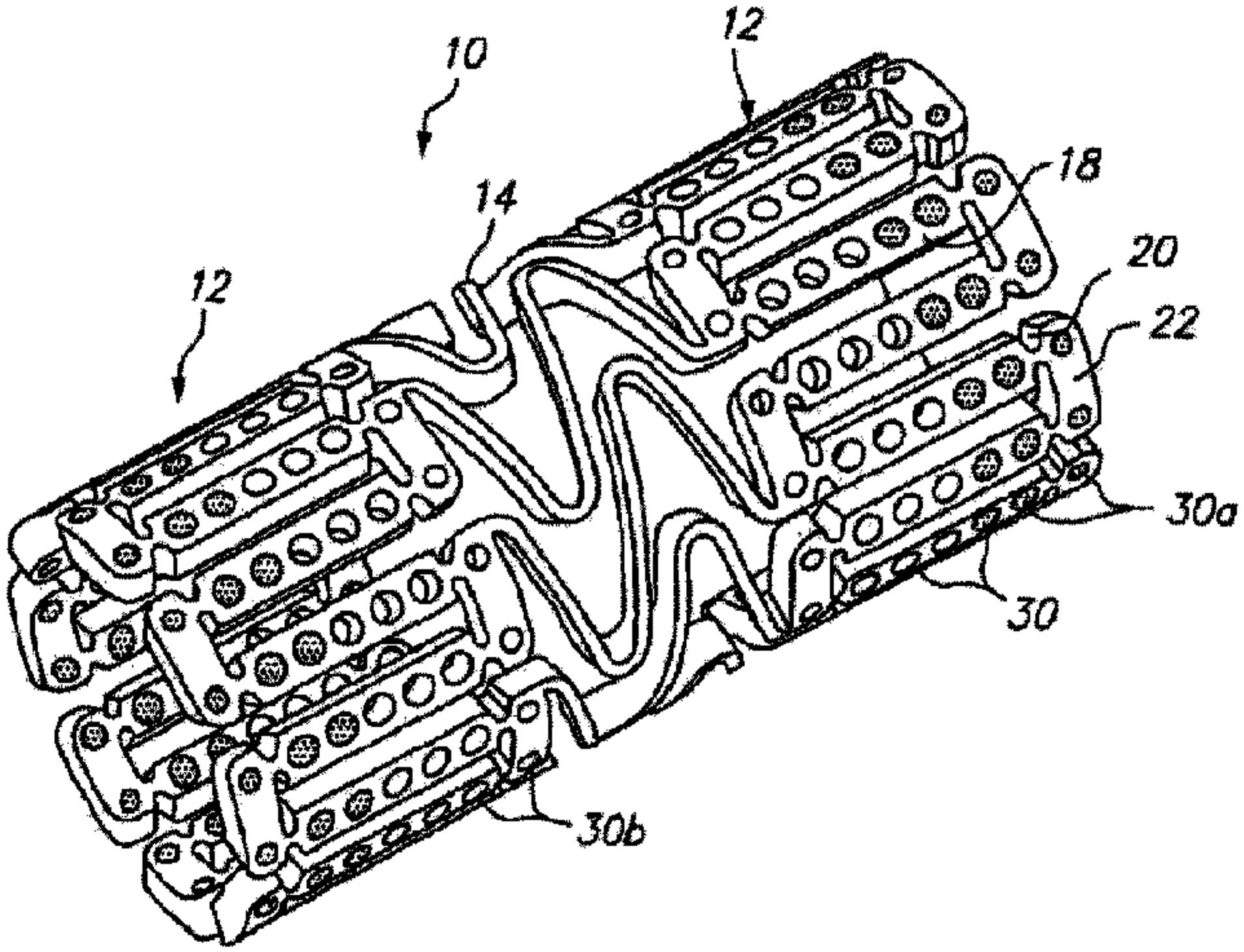

HO
O
n
O
m
OH
O
+
H_2N
N
H
p
H
DMF, rt
DCC + NHS
PLGA with carboxylic end
Low Mw PEI
HO
O
n
O
m
H
N
N
H
p
H
PLGA-PEI conjugate

FIG. 11


HO
O
n
O
m
OH
O
+
H_2N
N
H
p
H
DMSO/MES buffer
EDC + Sulfo-NHS
PLGA with carboxylic end
High Mw PEI
HO
O
n
O
m
H
N
N
H
p
H
PLGA-PEI conjugate
HO
O
n
O
m
H
N
O
N
H
p
O
O
n
O
O
m
OH
PLGA-PEI-PLGA conjugate


10
12
12
14
18
20
22
30a
30
30b