(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
29 January 2009 (29.01.2009)

(10) International Publication Number
WO 2009/014692 A1

(51) International Patent Classification:
A61F 2/86 (2006.01)

(21) International Application Number:
PCT/US2008/008892

(22) International Filing Date: 22 July 2008 (22.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/951,551 24 July 2007 (24.07.2007) US

(71) Applicant *(for all designated States except US)*: **BOSTON SCIENTIFIC SCIMED, INC.** [US/US]; One Scimed Place, Maple Grove, MN 55311-1566 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KOKATE, Jaydeep, Y.** [IN/US]; 7322 Quantico Lane N., Maple Grove, MN 55311 (US). **IFTEKHAR, Arif, M.** [BD/US]; 1686 Waring Ct., Santa Rosa, CA 95403 (US). **WEBER, Jan** [NL/NL]; Holdaal 49, NL-6228GJ Maastricht (NL).

(74) Agents: **STERN, Gidon, D.** et al.; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, **AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC,** EE, **EG,** ES, **FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD,** SE, **SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW**

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** STENTS WITH POLYMER-FREE COATINGS FOR DELIVERING A THERAPEUTIC AGENT

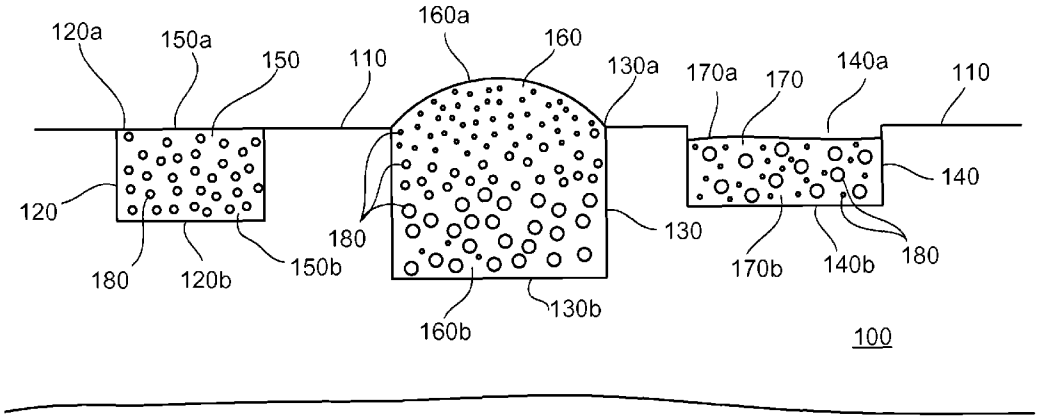

FIG. 1

(57) **Abstract:** Described, herein are implantable medical devices, such as intravascular stents, for delivering therapeutic agents to a- patient, and methods for making such medical devices. The medical devices comprise a substrate (100) having at least a cavity (120) therein and a pellet (150) disposed in the cavity (120). The pellet (150) comprises a non-polymeric material having a plurality of pores (180) therein. A therapeutic agent is disposed in at least some of the pores (180).

WO 2009/014692 A1

STENTS WITH POLYMER-FREE COATINGS FOR DELIVERING A THERAPEUTIC AGENT

This application claims priority to U.S. Provisional Application No. 60/951,551 filed on July 24, 2007, which is incorporated herein by reference in its entirety.

INTRODUCTION

[0001] Described herein are implantable medical devices, such as intravascular stents, for delivering therapeutic agents to a patient, and methods for making such medical devices. The medical devices comprise a substrate having at least a cavity therein and a pellet disposed in the cavity. The pellet comprises a non-polymeric material having a plurality of pores therein and a therapeutic agent disposed in at least some of the pores.

2.0 BACKGROUND

[0002] Medical devices have been used to deliver therapeutic agents locally to the body tissue of a patient. For example, stents having a coating containing a therapeutic agent, such as an anti-restenosis agent, have been used in treating or preventing restenosis. Currently, such medical device coatings include a therapeutic agent alone or a combination of a therapeutic agent and a polymer. Both of these types of coatings may have certain limitations.

[0003] Coatings containing a therapeutic agent without a polymer are generally ineffective in delivering the therapeutic agent since such coatings offer little or no control over the rate of release of the therapeutic agent. Specifically, the therapeutic agent is generally delivered in a burst release within a few hours. Therefore, many medical device coatings include a therapeutic agent and a polymer to provide sustained release of the therapeutic agent over time.

[0004] Though the use of polymers in coatings can provide control over the rate of release of the therapeutic agent therefrom, the use of such polymers in coatings may present certain other limitations. For example, the polymer in the coating may react adversely with the blood and cause thrombosis.

[0005] Moreover, some polymer coating compositions do not actually adhere to the surface of the medical device. In order to ensure that the coating compositions remain on the surface, the area of the medical device that is coated, such as a stent strut, is encapsulated with the coating composition. However, since the polymer does not adhere

to the medical device, the coating composition is susceptible to deformation and damage during loading, deployment and implantation of the medical device. Any damage to the polymer coating may alter the therapeutic agent release profile and can lead to an undesirable increase or decrease in the therapeutic agent release rate.

[0006] Also, surfaces coated with compositions comprising a polymer may be subject to undesired adhesion to other surfaces. For instance, balloon expandable stents must be put in an unexpanded or "crimped" state before being delivered to a body lumen. During the crimping process coated stent struts are placed in contact with each other and can possibly adhere to each other. When the stent is expanded or uncrimped, the coating on the struts that have adhered to each other can be damaged, torn-off or otherwise removed. Moreover, if the polymer coating is applied to the inner surface of the stent, it may stick or adhere to the balloon used to expand the stent when the balloon contacts the inner surface of the stent during expansion. Such adherence to the balloon may prevent a successful deployment of the medical device.

[0007] Similar to balloon-expandable stents, polymer coatings on self-expanding stents can also interfere with the delivery of the stent. Self-expanding stents are usually delivered using a pull-back sheath system. When the system is activated to deliver the stent, the sheath is pulled back, exposing the stent and allowing the stent to expand itself. As the sheath is pulled back it slides over the outer surface of the stent. Polymer coatings located on the outer or abluminal surface of the stent can adhere to the sheath as it is being pulled back and disrupt the delivery of the stent.

[0008] Accordingly, there is a need for medical devices that have little or no polymer and that can release an effective amount of a therapeutic agent in a controlled release manner while avoiding the disadvantages of current coatings for medical devices that include a polymer. Additionally, there is a need for methods of making such medical devices.

3.0 . SUMMARY

[0009] These and other objectives are addressed by the embodiments described herein. The embodiments described herein include medical devices that are capable of releasing a therapeutic agent in a controlled release manner as well as methods for making such devices.

[0010] In one embodiment, the medical device, which can be an implantable stent, comprises a stent sidewall structure having a surface and at least one cavity, having first

and second opposing ends, disposed within the stent sidewall structure. The first end of the cavity comprises an opening that is in fluid communication with the stent sidewall structure surface and the second end of the cavity comprises the bottom of the cavity. Also, at least one pellet is disposed within the cavity that comprises a non-polymeric material having a plurality of pores therein. A therapeutic agent is disposed in at least some of the pores of the pellet. The stent sidewall structure surface can be free of any coating. In some embodiments, the pellet has first and second opposing ends, in which the first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity.

[0011] Furthermore, at least some of the pores of the pellets can have different pore sizes. In some instances, the pores are arranged in a manner to form a pore size gradient in the pellet. The pore size gradient can extend from the first end of the pellet to the second end of the pellet. Also, the pores having the largest pore size can be disposed proximate the first end of the pellet.

[0012] Moreover, in some embodiments, the pellet can comprise one or more layers. For example, the pellet can include a first layer comprising pores having a first pore size and a second layer comprising pores having a second pore size that is different from the first pore size. Also, the layers can be arranged in a manner to form a pore size gradient in the pellet. In some instances, the pores having the largest pore size are disposed in the layer proximate the first end of the pellet.

[0013] In another embodiment, the medical device can be an implantable intravascular stent comprising a stent sidewall structure comprising a plurality of struts each having an abluminal surface and a luminal surface. There is at least one cavity, having first and second opposing ends, disposed within a strut wherein the first end of the cavity comprises an opening that is in fluid communication with the abluminal surface of the strut and the second end of the cavity comprises the bottom of the cavity. At least one pellet comprising a non-polymeric material, having a plurality of pores therein, is disposed in the cavity. The pellet has first and second opposing ends, and the first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity. Also, at least some of the pores have different pore sizes and the pores are arranged in a manner to form a pore size gradient in the pellet, in which the pores having the largest pore size are disposed proximate the first end of the pellet. An anti-restenosis agent is disposed within at least some of the pores of the pellet.

[0014] In yet another embodiment, the medical device can be an implantable intravascular stent comprising a stent sidewall structure comprising a plurality of struts each having an abluminal surface and a luminal surface. There is at least one cavity, having first and second opposing ends, disposed within a strut. The first end of the cavity comprises an opening that is in fluid communication with the abluminal surface of the strut and the second end of the cavity comprises the bottom of the cavity. Also, there is at least one pellet comprising a non-polymeric material, having a plurality of pores therein, disposed in the cavity. The pellet has first and second opposing ends, and the first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity. In addition, the pellet comprises a first layer comprising pores having a first pore size, a second layer comprising pores having a second pore size that is smaller than the first pore size, and a third layer comprising pores having a third pore size that is smaller than the second pore size. The first, second and third layers are arranged in a manner to form a pore size gradient in the pellet, in which the first layer is disposed proximate the first end of the pellet. An anti-restenosis agent is disposed within at least some of the pores of the pellet.

[0015] Also described herein are methods for making the medical device. In one embodiment, the method for making the medical device, which can be a stent, comprises providing a stent having a stent sidewall structure having a surface and at least one cavity, having first and second opposing ends, disposed within the stent sidewall structure. The first end of the cavity comprises an opening that is in fluid communication with the stent sidewall structure surface and the second end of the cavity comprises the bottom of the cavity. The method further comprises disposing at least one pellet into the cavity. The pellet comprises a non-polymeric material having a plurality of pores therein; as well as first and second opposing ends. The first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity. At least some of the pores have different pore sizes and the pores are arranged in a manner to form a pore size gradient in the pellet. The method also comprises disposing a therapeutic agent in at least some of the pores of the pellet.

[0016] In another embodiment, the method for making the medical device, such as an implantable stent, comprises providing a stent having a stent sidewall structure having a surface and at least one cavity, having first and second opposing ends, disposed within the stent sidewall structure. The first end of the cavity comprises an opening that is in fluid communication with the stent sidewall structure surface and the second end of the

cavity comprises the bottom of the cavity. The method further comprises forming a pellet in the cavity, wherein the pellet has a plurality of layers, and first and second opposing ends. The first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity. The step of forming the pellet comprises disposing a first solid, non-polymeric material into the cavity to form a first layer of the pellet, wherein the first layer has a plurality of pores having a first pore size. A second solid, non-polymeric material is disposed into the cavity to form a second layer of the pellet disposed over the first layer, wherein the second layer has a plurality of pores having a second pore size. The method further comprises disposing a therapeutic agent in at least some of the pores of the first and second layers.

4.0 BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Certain embodiments will be explained with reference to the following drawings.

[0018] **Figure 1** shows a cross-sectional view of an example of a medical device substrate having cavities therein and pellets, having a plurality of pores, disposed in the cavities.

[0019] **Figure 2** shows a cross-sectional view of another example of a medical device substrate having cavities therein and pellets, having a plurality of pores, disposed in the cavities, in which a pore size gradient is present in the pellets.

[0020] **Figure** 3 shows a cross-sectional view of another example of a medical device substrate having cavities therein and pellets, having a plurality of pores and layers, disposed in the cavities, in which a pore size gradient is present in the pellets.

[0021] **Figure 4A** shows a cross-sectional view of another embodiment of the medical device comprising cavities and pellets disposed in the cavities.

[0022] **Figure 4B** shows a cross-sectional view of yet another embodiment of the medical device comprising cavities and pellets disposed in the cavities.

[0023] **Figure 5** shows a peripheral view of an embodiment of an intravascular stent.

[0024] **Figures 6A-6C** show a method of preparing a medical device comprising cavities and pellets disposed in the cavities.

[0025] **Figures 7A-7C** show another method of preparing a medical device comprising cavities and pellets disposed in the cavities.

5.0 DETAILED DESCRIPTION

5.1 THE MEDICAL DEVICE

[0026] The medical devices described herein generally include a substrate having at least one surface. For instance, in the case where the medical device is an intravascular stent, the substrate is the stent sidewall structure and the surface is the abluminal surface of the stent. A cavity is disposed in the substrate and a pellet comprising a non-polymeric material having a plurality of pores therein is disposed in the cavity. A therapeutic agent is disposed in at least some of the pores for delivery to a patient.

[0027] **Figure 1** shows one embodiment of the medical device, which can be a stent. The medical device comprises a substrate **100** having a surface **110.** In this embodiment, the surface **110** is free of any coating, *i.e.,* is not covered by a coating. In other embodiments, a coating may be disposed on at least a portion of the surface **110.** As shown in the figure, there are three cavities 120, **130** and **140** disposed in the substrate **100.** Each cavity comprises two opposing ends **120a** and **120b, 130a** and 130b, and **140a** and **140b.** Each first end 120a, **130a** and **140a** comprises an opening that is in fluid communication with the surface **110.** Each second end 120b, **130b** and **140b** comprises the bottom of the cavity. In this embodiment, since the cavity has a bottom, the cavity does not extend through the entire substrate. In other embodiments the cavity can extend through the entire substrate. For instance, if the cavity is disposed in a stent strut the cavity can extend through the strut. Also, as shown in **Figure** 1, the cavities in a single substrate can have different sizes or geometries or cross-sectional shapes.

[0028] Pellets 150, **160** and **170** are disposed in each of the cavities 120, **130** and **140.** The pellets comprise a non-polymeric material. In some embodiments, the pellet is substantially free of any polymer, *i.e.* no polymer is intentionally included. Also, the pellets, 150, **160** and **170** each comprise two opposing ends **150a** and 150b, **160a** and 160b, and **170a** and **170b.** Each first end 150a, **160a** and **170a** of the pellets 150, **160** and **170** faces toward the opening of a cavity. Each second end 150b, **160b** and **170b** of the pellets 150, **160** and **170** faces toward the bottom of a cavity.

[0029] In certain embodiments, the pellet does not extend beyond the opening of the cavity in which the pellet is disposed. In **Figure** 1, pellets **150** and **170** are examples of such pellets. Pellet **150** extends up to the opening **120a** and pellet **170** does not

extend beyond the opening **140a.** In other embodiments, the pellet does extend beyond the opening of the cavity in which it is disposed. Pellet **160** is an example of such a pellet where the first end **160a** of the pellet **160** extends past the opening **130a** of the cavity **130.**

[0030] Furthermore, as shown in **Figure** 1, the pellets are comprised of a material having a plurality of pores **180** therein. A therapeutic agent (not shown) is disposed in at least some of the pores **180.** The pores of the pellet can be of a generally uniform pore size such as the pores of pellet **150.** Alternatively, the pores can have varying pore sizes throughout the pellet as shown in pellets **160** and **170.** In pellet 160, the pores **180** are arranged in a manner such that a pore size gradient is formed. The pores **180** at the second end **160b** of the pellet **160** are the largest and the pores **180** at the first end **160a** of the pellet **160** are the smallest, while the pores in the middle of the pellet have pore sizes that lie between the smallest and largest sizes. In pellet 170, pores **180** having small and large sizes are dispersed among each other.

[0031] Porosity and surface area of porous pellets can be measured by various techniques such as, but not limited to, physical gas absorption, helium pycnometry and mercury porosimetry. Physical gas absorption uses inert gas such as argon, nitrogen, krypton or carbon dioxide to determine surface area or total pore volume of the porous material. Helium pycnometry is a technique used to obtain information on the true density of solids using helium, which can enter even the smallest voids or pores. Mercury porosimetry uses the non-wetting properties of mercury to gain information of the porous characteristics of solid materials.

[0032] **Figure 2** shows another embodiment of a medical device having a substrate 200, a surface **210** and cavities 220, **230** disposed in the substrate. Each cavity comprises two opposing ends **220a** and **220b,** and **230a** and **230b.** Each first end **220a** and **230a** comprises an opening that is in fluid communication with the surface **210.** Each second end **220b** and **230b** of the cavities **220** and **230** comprises the bottom of the cavity.

[0033] Pellets **250** and **260** each comprise two opposing ends **250a** and 250b, and **260a** and **260b.** Each first end **250a** and **260a** faces toward an opening of a cavity. Each second end **250b** and **260b** of the pellets 250, **260** faces toward the bottom of a cavity. Similar to the pellets shown in **Figure** 1, the pellets are comprised of a material having a plurality of pores 280a, **280b** and **280c** therein. **A** therapeutic agent (not

shown) is disposed in at least some of the pores. In this embodiment, the pores are arranged in a manner such that a pore size gradient is formed. In pellet 250, the pores **280a** that are proximate the second end **250b** of the pellet **250** are generally the largest in pore size and the pores **280c** that are proximate first end **250a** of the pellet **250** are generally the smallest in pore size. The pores **280b** in the middle of the pellet **250** have pore sizes that are generally between the smallest and largest pore sizes. In pellet 260, the pores **280a** that are proximate the first end **260a** of the pellet **260** are generally the largest" in pore size and the pores **280c** that are proximate the second end **260b** of the pellet **260** are generally the smallest in pore size. The pores **280b** in the middle of the pellet **260** generally have pore sizes that are between the smallest and largest pore sizes. The advantages of having a pore size gradient include creating a variety of drug release profiles

[0034] **Figure 3** shows another embodiment of a medical device having a substrate **300,** a surface **310** and cavities **320** and **330** disposed in the substrate. Each cavity comprises two opposing ends **320a** and 320b, and **330a** and **330b.** Each first end 320a and **330a** comprises an opening that is in fluid communication with the surface **310.** Each second end **320b** and **330b** of the cavities **320** and **330** comprises the bottom of the cavity.

[0035] Like the pellets described above, pellets **350** and **360** each comprise two opposing ends **350a** and **350b,** and **360a** and **360b.** Each first end **350a** and **360a** faces toward an opening of a cavity. Each second end **350b** and **360b** of the pellets **350** and **360** faces toward the bottom of a cavity. The pellets 350, **360** are comprised of layers **355a, 355b** and 355c, and 365a, **365b** and **365c** of materials having a plurality of pores 380a, **380b** and **380c** therein. A therapeutic agent (not shown) is disposed in at least some of the pores. The layers can have various thicknesses.

[0036] In this embodiment, each layer of a pellet has pores of different pore sizes. For example, with respect to pellet 350, the first layer **355a** has pores **380a** that have a first pore size, *i.e.* the pores predominantly have this pore size but there may be some pores having different pore sizes. The second layer 355b, which is disposed on the first layer **355a,** has pores **380b** having a second pore size that is smaller than the first pore size. The third layer **355c** of pellet 350, which is disposed on the second layer 355b, has pores **380c** having a third pore size that is smaller than the second pore size. In this pellet 350, the layers **355a, 355b** and **355c** are arranged in a manner to form a pore size gradient in the pellet, which in this case extends from the first end **350a** of the

pellet to the second end **350b.** Also, in this pellet 350, the pores **380c** having the smallest pore size are disposed in the layer proximate the first end of the pellet **350a.**

[0037] The other pellet **360** of the medical device shown in **Figure 3** also comprises three layers **365a,** 365b, and **365c.** Each layer of this pellet **360** also has pores of different pore sizes. The first layer **365a** has pores **380c** having a first pore size. The second layer 365b, which is disposed on the first layer 365a, has pores **380b** having a second pore size that is larger than the first pore size. The third layer **365c** of pellet 360, which is disposed on the second layer 365b, has pores **380a** having a third pore size that is larger than the second pore size. In this pellet 360, the layers **365a, 365b** and **365c** are also arranged in a manner to form a pore size gradient in the pellet, which in this case extends from the first end **360a** of the pellet to the second end **360b.** Moreover, in this pellet **360,** the pores **380a** having the largest pore size are disposed in the layer proximate the first end of the pellet **360a.**

[0038] **Figure 4A** shows a medical device having a substrate 400, a surface **410** and three cavities **420, 430** and **440** disposed in the substrate **400.** Each cavity comprises two opposing ends **420a** and 420b, **430a** and 430b, and **440a** and **440b.** Each first end 420a, **430a** and **440a** comprises an opening that is in fluid communication with the surface **410.** Each second end 420b, **430b** and **440b** of the cavities 420, **430** and **440** comprises a bottom of a cavity. The three cavities have different geometries with different cross-sectional shapes. Specifically, cavity **420** has a U-shaped cross-section, cavity **430** has a V-shaped or triangular cross-section and cavity **440** has a modified-U-shaped cross-section. In other embodiments, such as those shown in **Figure** 4B, the cavities can have other geometries and cross-sections.

[0039] Also, as shown in **Figure** 4A, the pellets, which have a plurality of pores 480, disposed in the cavities do not necessarily have to conform to the geometry or shape of the cavities, or be confined within the cavity. For instance, pellet 450, which has first and second ends 450a, 450b, conforms to the cavity but then extends beyond the opening **420a** of the cavity **420.** Pellet 460, which has first and second ends 460a, **460b,** is contained in cavity **430** but does not fill or completely conform to cavity **430.** Pellet 470, which has first and second ends 470a, 470b, extends beyond opening **440a** of the cavity **440** but does not completely conform to the entire cavity **440.**

[0040] **Figure 4B** shows a medical device, such as a stent strut, having a substrate 400, with an abluminal surface **412** and a luminal surface **414.** The abluminal surface is the surface of the medical device that faces away from a body lumen and the

luminal surface is the surface of the medical device that faces towards a body lumen. As shown in **Figure** 4B, the medical device substrate **400** has two cavities **481** and **482** disposed in the substrate **400.** Each cavity comprises two opposing ends **484a** and **484b** and **486a** and **486b.** The first end **484a** of cavity **481** comprises an opening that is in fluid communication with the abluminal surface **412.** The second end **484b** comprises an opening that is in fluid communication with luminal surface **414.** Also, cavity **481** has a portion **481a** that gives the cavity a T-shaped cross-section. With respect to cavity **482,** the first end **486a** comprises two openings that are in fluid communication with the abluminal surface **412** and the second end **486b** of cavity **481** comprises the bottom of the cavity. **As** shown in **Figure 4B,** cavity **482** has a Y-shaped cross-section.

[0041] **As** shown in **Figure** 4B, pellets **491** and 492, which have a plurality of pores **493,** are disposed in the cavities. The shapes of the pellets and cavities prevent the pellets from easily being removed from the cavities. Moreover, if the pellets shrink or otherwise change shape such pellet and cavity shapes will prevent the pellets from unintentionally falling out of the cavity.

[0042] Additionally, as shown in the embodiment of **Figure** 4B, pellets **491** and **492** each include a different therapeutic agent. As shown in **Figure 4B,** pellet **491** includes therapeutic agent **494** disposed in at least some of the pores **493** and pellet **492** includes therapeutic agent **495** disposed in at least some of the pores **493.** However, in other embodiments described herein, all pellets disposed in cavities of a medical substrate can include the same therapeutic agent.

5.1.1 Types Of Medical Devices

[0043] The medical devices described herein can be implanted or inserted into the body of a patient. Suitable medical devices include, but are not limited to, stents, surgical staples, catheters, such as balloon catheters, central venous catheters, and arterial catheters, guide wires, cannulas, cardiac pacemaker leads or lead tips, cardiac defibrillator leads or lead tips, implantable vascular access ports, blood storage bags, blood tubing, vascular or other grafts, intra aortic balloon pumps, heart valves, cardiovascular sutures, total artificial hearts and ventricular assist pumps, and extra coφ oreal devices such as blood oxygenators, blood filters, septal defect devices, hemodialysis units, hemoperfusion units and plasmapheresis units.

[0044) Suitable medical devices include, but are not limited to, those that have a tubular or cylindrical like portion. For example, the tubular portion of the medical

device need not be completely cylindrical. The cross-section of the tubular portion can be any shape, such as rectangle, a triangle, etc., not just a circle. Such devices include, but are not limited to, stents, balloon catheters, and grafts. A bifurcated stent is also included among the medical devices which can be fabricated by the methods described herein.

[0045] In addition, the tubular portion of the medical device may be a sidewall that may comprise a plurality of struts defining a plurality of openings. The sidewall defines a lumen. The struts may be arranged in any suitable configuration. Also, the struts do not all have to have the same shape or geometric configuration. When the medical device is a stent comprising a plurality of struts, the surface is located on the struts. Each individual strut has an outer surface adapted for exposure to the body tissue of the patient, an inner surface, and at least one side surface between the outer surface and the inner surface.

[0046] Medical devices that are particularly suitable for the embodiments described herein include any kind of stent for medical purposes which is known to the skilled artisan. Preferably, the stents are intravascular stents that are designed for permanent implantation in a blood vessel of a patient. In certain embodiments, the stent comprises an open lattice sidewall stent structure. In preferred embodiments, the stent is a coronary stent. Other suitable stents include, for example, vascular stents such as self-expanding stents and balloon expandable stents. Examples of self-expanding stents useful in the embodiments described herein are illustrated in United States Patent Nos. 4,655,771 and 4,954,126 issued to Wallsten and 5,061,275 issued to Wallsten *et al.* Examples of appropriate balloon-expandable stents are shown in United States Patent No. 5,449,373 issued to Pinchasik *et al.*

[0047] **Figure 5** shows an example of a medical device that is suitable for use in the embodiments described herein. This figure shows a peripheral view of an implantable intravascular stent **510.** As shown in **Figure 5,** the intravascular stent **510** is generally cylindrical in shape. Stent **510** includes a sidewall **520** which comprises a plurality of struts **530** and at least one opening **540** in the sidewall **520.** Generally, the opening **540** is disposed between adjacent struts **530.** Also, the sidewall **520** may have a first sidewall surface **522** and an opposing second sidewall surface, which is not shown in **Figure 5.** The first sidewall surface **522** can be an outer or abluminal sidewall surface, which faces a body lumen wall when the stent is implanted, or an inner or luminal sidewall surface, which faces away from the body lumen surface. Likewise, the second sidewall surface

can be an abluminal sidewall surface or a luminal sidewall surface. In certain embodiments, at least one strut comprises an abluminal surface, which forms part of the abluminal surface of the stent, and at least one strut comprises a luminal surface opposite the abluminal surface of the strut, which forms part of the luminal surface of the stent.

[0048] In some embodiments, the abluminal surface of the stent sidewall structure comprises at least one cavity and the luminal surface is free of cavities. In other embodiments, the cavity or cavities can be located on a low-stress bearing part of the stent sidewall structure.

[0049] When the coatings described herein are applied to a stent having openings in the stent sidewall structure, in certain embodiments, it is preferable that the coatings conform to the surface of the stent so that the openings in the sidewall stent structure are preserved, *e.g.* the openings are not entirely or partially occluded with coating material.

[0050] The framework of suitable stents may be formed through various methods known in the art. The framework may be welded, molded, laser cut, electro-formed, or consist of filaments or fibers which are wound or braided together in order to form a continuous structure.

[0051] Suitable substrates of the medical device *(e.g.,* stents) described herein may be fabricated from a metallic material, ceramic material, polymeric or non-polymeric material, or a combination thereof *(see* Sections 5.1.1.1 to 5.1.1.3 *infra.).* Preferably, the materials are biocompatible. The material may be porous or non-porous, and the porous structural elements can be microporous or nanoporous.

5.1.1.1. Metallic Materials for Medical Devices

[0052] In certain embodiments, the medical devices described herein can comprise a substrate which is metallic. Suitable metallic materials useful for making the substrate include, but are not limited to, metals and alloys based on titanium (such as nitinol, nickel titanium alloys, thermo memory alloy materials), stainless steel, gold, iron, magnesium, platinum, iridium, molybdenum, niobium, palladium, chromium, tantalum, nickel chrome, or certain cobalt alloys including cobalt chromium nickel alloys such as Elgiloy® and Phynox®, or a combination thereof. Other metallic materials that can be used to make the medical device include clad composite filaments, such as those disclosed in WO 94/16646.

[0053] In some embodiments, the metal is a radiopaque material that makes the medical device visible under X-ray or fluoroscopy. Suitable materials that are

radiopaque include, but are not limited to, gold, tantalum, platinum, bismuth, iridium, zirconium, iodine, titanium, barium, silver, tin, alloys of these metals, or a combination thereof.

[0054] Furthermore, although the embodiments described herein can be practiced by using a single type of metal to form the substrate, various combinations of metals can also be employed. The appropriate mixture of metals can be coordinated to produce desired effects when incorporated into a substrate.

5.1.1.2. Ceramic Materials for Medical Devices

[0055] In certain embodiments, the medical devices described herein can comprise a substrate which is ceramic. Suitable ceramic materials used for making the substrate include, but are not limited to, oxides, carbides, or nitrides of transition elements such as titanium oxides, hafnium oxides, iridium oxides, chromium oxides, aluminum oxides, zirconium oxides, transition metal oxides, platinum oxides, tantalum oxides, niobium oxides, tungsten oxides, rhodium oxides, or a combination thereof. Silicon based materials, such as silica, may also be used. Furthermore, although certain embodiments described herein can be practiced by using a single type of ceramic to form the substrate, various combinations of ceramics can also be employed. The appropriate mixture of ceramics can be coordinated to produce desired effects when incorporated into a substrate.

5.1.1.3. Polymeric Materials for Medical Devices

[0056] In certain embodiments, the medical devices described herein can comprise a substrate which is polymeric. In other embodiments, the material can be a non-polymeric material. The polymer(s) useful for forming the components of the medical devices should be ones that are biocompatible and avoid irritation to body tissue. The polymers can be biostable or bioabsorbable. Suitable polymeric materials useful for making the substrate include, but are not limited to, isobutylene-based polymers, polystyrene-based polymers, polyacrylates, and polyacrylate derivatives, vinyl acetate-based polymers and its copolymers, polyurethane and its copolymers, silicone and its copolymers, ethylene vinyl-acetate, polyethylene terephtalate, thermoplastic elastomers, polyvinyl chloride, polyolefins, cellulosics, polyamides, polyesters, polysulfones, polytetrafluorethylenes, polycarbonates, acrylonitrile butadiene styrene copolymers, acrylics, polylactic acid, polyglycolic acid, polycaprolactone, polylactic

acid-polyethylene oxide copolymers, cellulose, collagens, chitins, or a combination thereof.

[0057] Other polymers that are useful as materials for making the substrate include, but are not limited to, dacron polyester, poly(ethylene terephthalate), polycarbonate, polymethylmethacrylate, polypropylene, polyalkylene oxalates, polyvinylchloride, polysiloxanes, nylons, poly(dimethyl siloxane), polycyanoacrylates, polyphosphazenes, poly(amino acids), ethylene glycol I dimethacrylate, poly(methyl methacrylate), poly(2-hydroxyethyl methacrylate), polytetrafluoroethylene poly(HEMA), polyhydroxyalkanoates, poly(glycolide-lactide) co-polymer, poly(β-hydroxybutyrate), polydioxanone, poly(γ-ethyl glutamate), polyiminocarbonates, poly(ortho ester), polyanhydrides, styrene isobutylene styrene, polyetheroxides, polyvinyl alcohol, poly-2-hydroxy-butyrate, polycaprolactone, poly(lactic-co-clycolic)acid, Teflon, alginate, dextran, cotton, derivatized versions thereof, *(i.e.*, polymers which have been modified to include, for example, attachment sites or cross-linking groups, *e.g.*, arginine-glycine-aspartic acid RGD, in which the polymers retain their structural integrity while allowing for attachment of cells and molecules, such as proteins and/or nucleic acids), or a combination thereof.

[0058] The polymers may be dried to increase their mechanical strength. The polymers may then be used as the base material to form a whole or part of the substrate.

[0059] Furthermore, although the embodiments described herein can be practiced by using a single type of polymer to form the substrate, various combinations of polymers can also be employed. The appropriate mixture of polymers can be coordinated to produce desired effects when incorporated into a substrate.

5.1.2 Non-Polymeric Materials For Making The Pellets

[0060] The non-polymeric materials that can be used to form the pellets include without limitation the metal and metal oxides described above that can be used to make the medical devices. Preferred metals and metal oxides that can be used to form the pellets include, without limitation, titanium dioxide, in anatase or rutile form; silica; hydroxyl-apatite; stainless steel or gold.

5.1.3 Therapeutic Agents

[0061] The phrase "therapeutic agent" as used herein encompasses drugs, genetic materials, and biological materials and can be used interchangeably with "biologically

active material". The term "genetic materials" means DNA or RNA, including, without limitation, DNA/RNA encoding a useful protein stated below, intended to be inserted into a human body including viral vectors and non-viral vectors.

[0062] The term "biological materials" include cells, yeasts, bacteria, proteins, peptides, cytokines and hormones. Examples for peptides and proteins include vascular endothelial growth factor (VEGF), transforming growth factor (TGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), cartilage growth factor (CGF), nerve growth factor (NGF), keratinocyte growth factor (KGF), skeletal growth factor (SGF), osteoblast-derived growth factor (BDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), cytokine growth factors (CGF), platelet-derived growth factor (PDGF), hypoxia inducible factor- 1 (HIF-I), stem cell derived factor (SDF), stem cell factor (SCF), endothelial cell growth supplement (ECGS), granulocyte macrophage colony stimulating factor (GM-CSF), growth differentiation factor (GDF), integrin modulating factor (IMF), calmodulin (CaM), thymidine kinase (TK), tumor necrosis factor (TNF), growth hormone (GH), bone morphogenic protein (BMP) *(e.g.*, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (PO-I), BMP-8, BMP-9, BMP-IO, BMP-1 1, BMP- 12, BMP- 14, BMP-1 5, BMP- 16, etc.), matrix metalloproteinase (MMP), tissue inhibitor of matrix metalloproteinase (TIMP), cytokines, interleukin *(e.g.*, IL-I, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-IO, IL-1 1, IL-12, IL-15, etc.), lymphokines, interferon, integrin, collagen (all types), elastin, fibrillins, fibronectin, vitronectin, laminin, glycosaminoglycans, proteoglycans, transferrin, cytotactin, cell binding domains *(e.g.*, RGD), and tenascin. Currently preferred BMP's are BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered, if desired, to deliver proteins of interest at the transplant site. The delivery media can be formulated as needed to maintain cell function and viability. Cells include progenitor cells *(e.g.*, endothelial progenitor cells), stem cells *(e.g.*, mesenchymal, hematopoietic, neuronal), stromal cells, parenchymal cells, undifferentiated cells, fibroblasts, macrophage, and satellite cells.

[0063] Other suitable therapeutic agents include:

- anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone);

- anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, acetylsalicylic acid, tacrolimus, everolimus, pimecrolimus, sirolimus, zotarolimus, amlodipine and doxazosin;
- anti-inflammatory agents such as glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, rosiglitazone, mycophenolic acid and mesalamine;
- anti-neoplastic/anti-proliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, methotrexate, azathioprine, adriamycin and mutamycin; endostatin, angiostatin and thymidine kinase inhibitors, cladribine, taxol and its analogs or derivatives, paclitaxel as well as its derivatives, analogs or paclitaxel bound to proteins, *e.g.* Abraxane™;
- anesthetic agents such as lidocaine, bupivacaine, and ropivacaine;
- anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, aspirin (aspirin is also classified as an analgesic, antipyretic and anti-inflammatory drug), dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors, antiplatelet agents such as trapidil or liprostin and tick antiplatelet peptides;
- DNA demethylating drugs such as 5-azacytidine, which is also categorized as a RNA or DNA metabolite that inhibit cell growth and induce apoptosis in certain cancer cells;
- vascular cell growth promoters such as growth factors, vascular endothelial growth factors (VEGF, all types including VEGF-2), growth factor receptors, transcriptional activators, and translational promoters;
- vascular cell growth inhibitors such as anti-proliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin;

- cholesterol-lowering agents, vasodilating agents, and agents which interfere with endogenous vasoactive mechanisms;
- anti-oxidants, such as probucol;
- antibiotic agents, such as penicillin, cefoxitin, oxacillin, tobranycin, daunomycin, mitocycin;
- angiogenic substances, such as acidic and basic fibroblast growth factors, estrogen including estradiol (E2), estriol (E3) and 17-beta estradiol;
- drugs for heart failure, such as digoxin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors including captopril and enalopril, statins and related compounds;
- macrolides such as sirolimus (rapamycin) or everolimus; and
- AGE-breakers including alagebrium chloride (ALT-71 1).

[0064] Other therapeutic agents include nitroglycerin, nitrous oxides, nitric oxides, antibiotics, aspirins, digitalis, estrogen, estradiol and glycosides. Preferred therapeutic agents include antiproliferative drugs such as steroids, vitamins, and restenosis-inhibiting agents. Preferred restenosis-inhibiting agents include microtubule stabilizing agents such as Taxol®, paclitaxel *(i.e.*, paclitaxel, paclitaxel analogs, or paclitaxel derivatives, and mixtures thereof). For example, derivatives suitable for use in the embodiments described herein include 2'-succinyl-taxol, 2'-succinyl-taxol triethanolamine, 2'-glutaryl-taxol, 2'-glutaryl-taxol triethanolamine salt, 2'-O-ester with N-(dimethylaminoethyl) glutamine, and 2'-O-ester with N-(dimethylaminoethyl) glutamide hydrochloride salt.

[0065] Other preferred therapeutic agents include tacrolimus; halofuginone; inhibitors of HSP90 heat shock proteins such as geldanamycin; microtubule stabilizing agents such as epothilone D; phosphodiesterase inhibitors such as cliostazole; Barkct inhibitors; phospholamban inhibitors; and Serca 2 gene/proteins. In yet another preferred embodiment, the therapeutic agent is an antibiotic such as erythromycin, amphotericin, rapamycin, adriamycin, etc.

[0066] In preferred embodiments, the therapeutic agent comprises daunomycin, mitocycin, dexamethasone, everolimus, tacrolimus, zotarolimus, heparin, aspirin, warfarin, ticlopidine, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, prioxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin, celcoxib, alagebrium chloride or a combination thereof.

(0067J The therapeutic agents can be synthesized by methods well known to one skilled in the art. Alternatively, the therapeutic agents can be purchased from chemical and pharmaceutical companies.

5.2. METHODS OF MAKING THE MEDICAL DEVICES

[0068] In one method for making the medical devices described herein, the method comprises the step of providing a medical device having a substrate and at least one cavity disposed therein. The method further comprises disposing or forming a pellet in the cavity. Therapeutic agents can be disposed in at least some pores of the pellet.

[0069] For instance, **Figures 6A-6C** show an example of a method for making the medical devices described herein. In this method, a medical device having a substrate 600, such as stent having a stent sidewall structure is provided **(Figure 6A).** The substrate **600** has a surface **610** and at least one cavity disposed within the substrate **600.** In this case, there are four cavities shown **620, 630, 640** and 650. Each of the cavities **620, 630, 640** and **650** has a first end **620a, 630a, 640a** and **650a** and a second end **620b, 630b, 640b** and **650b** opposing the first end. Each first end **620a, 630a, 640a** and **650a** comprises an opening that is in fluid communication with the stent sidewall structure surface **610** and each second end **620b, 630b, 640b** and **650b** comprises the bottom of a cavity.

[0070] **As** shown in **Figure** 6B, pellets **660, 670** comprising a non-polymeric material having a plurality of pores **680** therein are formed. The pellets have a first end **660a** and **670a** and a second end **660b** and **670b** opposing the first end. Also, at least some of the pores have different pore sizes and the pores are arranged in a manner to form a pore size gradient in the pellet. Pellet **660** is made up of different layers each of which have varying pore sizes.

[0071] **As** shown in **Figure** 6C, two pellets are disposed in cavities **620** and **640** in a manner so that first ends **660a** and **670a** face toward the openings **620a** and **640a** of cavities **620** and 640, respectively, and second ends **660b** and **670b** face toward the second ends **620b** and **640b** or bottoms of cavities **620** and 640, respectively. The two remaining pellets are disposed in the cavities **630** and **650** in a manner so that second ends **660b** and **670b** face toward the openings **630a** and **650a** of cavities **630** and 650, respectively, and first ends **660a** and **670a** face toward the second ends **630b** and **650b** or bottoms of cavities **630** and 650, respectively. A therapeutic agent can be disposed in at least some of the pores of the pellets before or after the pellets are disposed in the

cavities. In alternative embodiments, the pores in the non-polymeric material can be formed after the material has been disposed in the cavity.

[0072] **Figures 7A-C** show another embodiment of a method for making the devices described herein. This method comprises the step of providing a medical device having a substrate **700** and at least one cavity **710** disposed therein. As shown in **Figure** 7A, a pellet is formed in the cavity by disposing a first solid, non-polymeric material to form a first layer of the pellet **720.** The first solid, non-polymeric material comprises a plurality of pores therein. At least some of the pores of the first layer **720** have a first pore size **720a.** The pores can be formed in the first solid, non-polymeric material before or after it is disposed in the cavity **710.**

[0073] Thereafter, as shown in **Figure** 7B, a second solid, non-polymeric material is disposed over the first layer **720** to form a second layer **730** of the pellet. The second solid, non-polymeric material comprises a plurality of pores therein. At least some of the pores of the second layer have a second pore size **730a** that is different from the first pore size **720a.** The pores can be formed in the second solid, non-polymeric material before or after it is disposed in the cavity **710.**

[0074] **Figure 7C** shows that a third solid, non-polymeric material is disposed over the second layer **730** to form a third layer **740** of the pellet **750.** The third solid, non-polymeric material comprises a plurality of pores therein. At least some of the pores of the third layer have a third pore size **740a** that is different from the first and second pore sizes **720a, 730a.** In this embodiment, the third pore size **740a** is smaller than the second pore size 730a, which is smaller than the first pore size **720a.** The pores can be formed in the third solid, non-polymeric material before or after it is disposed in the cavity **710.** As shown in **Figure** 7C, the pellet **750** comprises three layers **720, 730** and 740, and first and second opposing ends **750a** and **750b.** The first end of the pellet **750a** faces toward the opening of the cavity and the second end of the pellet **750b** faces toward the bottom of the cavity. A therapeutic agent can be disposed in at least some of the pores of the layers before or after the layers are formed in the cavity. Additionally, each layer can have the same or a different therapeutic agent.

5.2.1. Preparing Cavities In The Substrate

[0075] The cavities in the substrate can be created by any method known to one skilled in the art including, but not limited to, sintering, co-deposition, micro-roughing, laser ablation, drilling, chemical etching or a combination thereof. For example, the

cavities can be made by a deposition process such as sputtering with adjustments to the deposition condition, by micro-roughening using reactive plasmas, by ion bombardment electrolyte etching, or a combination thereof. Other methods include, but are not limited to, alloy plating, physical vapor deposition, chemical vapor deposition, sintering, or a combination thereof. Still another suitable method that can be used to form the cavities involves the use of colloid crystals as templates to form porous materials. In such methods, colloid crystals are assembled to serve as a template. Voids between the crystals are filled with a material such as a sol-gel solution or suspension of metal nanoparticles. The material between the crystals is allowed to solidify and then the colloid crystals are removed. Examples of such processes are described in, O. Velev, *et al., Colloidal crystals as templates for porous materials,* Current Opinion in Colloid & Interface Sciences 5, 56-63, (2000), (hereinafter "Velev") hereby incorporated by reference in its entirety.

[0076] Additionally, the cavities can be formed by removing a secondary material such as a spacer group from the material used to form the substrate. In particular, the substrate is formed from a composition containing the substrate material and the secondary material. The secondary material is then removed. Techniques for removing a secondary material include, but are not limited to, dealloying or anodization processes, or by baking or heating to remove the secondary material. The secondary material can be any material so long as it can be removed from the substrate material. For example, the secondary material can be more electrochemically active than the substrate material. Examples of a method for removing a secondary material are described in U.S. Publication No. 2005/0266040, which is incorporated by reference herein in its entirety.

5.2.2. Preparing The Pellets

[0077] The pellets described herein can be formed inside a cavity of a medical device substrate or, alternatively, the pellets can be formed prior to being disposed in a cavity of a medical deivce substrate. When forming pellets prior to disposing them in a cavity of a medical device substrate, the pellets described herein can be prepared by obtaining a non-polymeric material and shaping the material into pellets of desired sizes and shapes.

[0078] Other methods that can be used to form pellets include embossing techniques. An example of an embossing technique is described in C. Goh, *et al, Nanostructuring Titania by Embossing with Polymer Molds Made from Anodic Alumina Templates,* Nano

Letters 5:8, 1545-1549 (2005), hereby incorporated by reference in its entirety. By using embossing techniques, large quantities of pellets can be formed using porous pellet molds made out of polymethyl methacrylate (PMMA). The molds can be used to emboss titanium oxide sol-gel solutions applied to a surface by spin coating. Once the sol-gel solution has dried the polymethyl methacrylate mold can be removed with acetonitrile. Also, the PMMA mold can be designed so that it can stamp out individual pellets.

[0079] Additionally, porous pellets can be formed in the cavities of the medical device substrate. In certain embodiments, individual porous layers that comprise a pellet can be each individually disposed in the cavity as shown in Figures 7A-7C. Ih the embodiments where the pellet comprises layers of material, the layers can be joined to each other by using an adhesive.

[0080] In other embodiments, sol-gel processes can be used to form porous pellets in the cavities of the medical device substrate. For example, sol-gel solutions containing polyethylene glycol (PEG) spacing elements can be disposed in a cavity. The PEG spacing elements can then be removed, leaving behind a porous pellet. Sol-gel solutions containing polyethylene glycol (PEG) spacing elements are discussed in B. Guo, *et al*, *Sol gel derived photocatalytic porous TiOy thin films,* Surface & Coatings Technology 198, 24-29 (2005) hereby incorporated by reference in its entirety. Layers of the sol-gel solutions comprising different molecular weight PEG spacing elements can be disposed in the cavities of the medical device substrate. The PEG spacing elements can then be removed, leaving behind a layered pellet having various sized pores in the pellet.

[0081] In certain embodiments of the methods described herein, pores are formed after the pellets have been formed and after the pellets have been disposed in the cavities. In alternative embodiments of the methods described herein, the pores in the pellets can be formed in the material used to make the pellets or the pores can be formed after the pellets are formed but prior to disposing the pellets in the cavities. The pores in the pellets or the material used to make the pellets can be formed using any of the techniques described above for making the cavities.

[0082] In embodiments where a therapeutic agent is disposed in pores, the therapeutic agent can be dispersed in the pores by any method known to one skilled in the art including, but not limited to, dipping, spray coating, spin coating, plasma deposition, condensation, electrochemically, electrostatically, evaporation, plasma vapor deposition, cathodic arc deposition, sputtering, ion implantation, use of a fluidized bed,

or a combination thereof. Methods suitable for dispersing the therapeutic agent into the pores preferably do not alter or adversely impact the therapeutic properties of the therapeutic agent. In medical devices containing a plurality of pellets each pellet can include the same or a different therapeutic agent.

[0083] To facilitate the disposition of the therapeutic agent into the pores, the therapeutic agent can be placed into a solution or suspension containing a solvent or carrier. For instance, a solution containing the therapeutic agent can be formed and the pellet or non-polymeric material can be dipped into the solution to allow the therapeutic agent to be disposed in the pores. Furthermore, forming porous pellets that include a therapeutic agent prior to disposing the pellets in the cavities have many advantages. For example, the pellets can be formed and exposed to high temperatures without affecting the medical device. Additionally, disposing the drug in the pellets before disposing the pellets in the cavities of the medical device substrate prevents excess therapeutic agent from being disposed on the medical deivce substrate.

[0084] Once the pellets have been made, the pellets can be disposed in the cavities of the medical device substrate by, for example, piezo-driven positioning devices. A piezo-driven positioning device can be used to grip a pre-formed and in certain embodiments a drug-filled pellet, dispose the pellet in a cavity and using a gripper, squeeze the area around the cavity, for example a stent strut, in which the cavity is located on and secure the pellet in the cavity. Alternatively, an adhesive or other material can be used to affix the pellets in the cavities.

[0085] The description provided herein is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of certain embodiments. The methods, compositions and devices described herein can comprise any feature described herein either alone or in combination with any other feature(s) described herein. Indeed, various modifications, in addition to those shown and described herein, will become apparent to those skilled in the art from the foregoing description and accompanying drawings using no more than routine experimentation. Such modifications and equivalents are intended to fall within the scope of the appended claims.

[0086] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference in their entirety into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. Citation

or discussion of a reference herein shall not be construed as an admission that such is prior art.

WHAT IS CLAIMED IS:

1. An implantable stent comprising:

a. a stent sidewall structure having a surface;

b. at least one cavity, having first and second opposing ends, disposed within the stent sidewall structure wherein the first end of the cavity comprises an opening that is in fluid communication with the stent sidewall structure surface and the second end of the cavity comprises the bottom of the cavity;

c. at least one pellet disposed within the cavity comprising a non-polymeric material having a plurality of pores therein; and

d. a therapeutic agent disposed in at least some of the pores of the pellet.

2. The stent of claim 1, wherein the pellet has first and second opposing ends and wherein the first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity.

3. The stent of claim 2, wherein at least some of the pores have different pore sizes.

4. The stent of claim 3, wherein the pores are arranged in a manner to form a pore size gradient in the pellet.

5. The stent of claim 4, wherein the pores having the largest pore size are disposed proximate the first end of the pellet.

6. The stent of claim 4, wherein the pore size gradient extends from the first end of the pellet to the second end of the pellet.

7. The stent of claim 2, wherein the pellet comprises one or more layers.

8. The stent of claim 7, wherein a first layer comprises pores having a first pore size and wherein a second layer comprises pores having a second pore size that is different from the first pore size.

9. The stent of claim 8, wherein the layers are arranged in a manner to form a pore size gradient in the pellet.

10. The stent of claim 9, wherein the pores having the largest pore size are disposed in the layer proximate the first end of the pellet.

11. The stent of claim 1, wherein the therapeutic agent comprises an anti-thrombogenic agent, anti-angiogenesis agent, anti-proliferative agent, antibiotic, anti-restenosis agent, growth factor, immunosuppressant or radiochemical.

12. The stent of claim 1, wherein the therapeutic agent comprises an agent that inhibits smooth muscle cell proliferation.

13. The stent of claim 1, wherein the therapeutic agent comprises paclitaxel.

14. The stent of claim 1, wherein the therapeutic agent comprises sirolimus, tacrolimus, pimecrolimus, everolimus or zotarolimus.

15. The stent of claim 1, wherein the stent sidewall structure surface is free of any coating.

16. An implantable intravascular stent comprising:

a. a stent sidewall structure comprising a plurality of struts each having an abluminal surface and a luminal surface;

b. at least one cavity, having first and second opposing ends, disposed within a strut, wherein the first end of the cavity comprises an opening that is in fluid communication with the abluminal surface of the strut and the second end of the cavity comprises the bottom of the cavity;

c. at least one pellet comprising a non-polymeric material, having a plurality of pores therein, disposed within the cavity; wherein the pellet has first and second opposing ends and wherein the first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity; and wherein at least some of the pores have different pore sizes and the pores are arranged in

a manner to form a pore size gradient in the pellet in which the pores having the largest pore size are disposed proximate the first end of the pellet; and

d. an anti-restenosis agent disposed within at least some of the pores of the pellet.

17. An implantable intravascular stent comprising:

a. a stent sidewall structure comprising a plurality of struts each having an abluminal surface and a luminal surface;

b. at least one cavity, having first and second opposing ends, disposed within a strut, wherein the first end of the cavity comprises an opening that is in fluid communication with the abluminal surface of the strut and the second end of the cavity comprises the bottom of the cavity;

c. at least one pellet comprising a non-polymeric material, having a plurality of pores therein, disposed within the cavity; wherein the pellet has first and second opposing ends and wherein the first end of the pellet faces toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity; and wherein the pellet comprises a first layer comprising pores having a first pore size, a second layer comprising pores having a second pore size that is smaller than the first pore size, and a third layer comprising pores having a third pore size that is smaller than the second pore size; and wherein the first, second and third layers are arranged in a manner to form a pore size gradient in the pellet in which the first layer is disposed proximate the first end of the pellet; and

d. an anti-restenosis agent disposed within at least some of the pores of the pellet.

18. A method for making an implantable stent comprising:

a. providing a stent having a stent sidewall structure having a surface and at least one cavity, having first and second opposing ends, disposed within the stent sidewall structure, wherein the first end of the cavity comprises an opening that is in fluid communication with the stent sidewall structure surface and the second end of the cavity comprises the bottom of the cavity;

b. disposing at least one pellet into the cavity, wherein the pellet comprises a non-polymeric material having a plurality of pores therein; and wherein the pellet has first and second opposing ends, and the first end of the pellet faces toward the

first end of the cavity and the second end of the pellet faces toward the second end of the cavity; and wherein at least some of the pores have different pore sizes and the pores are arranged in a manner to form a pore size gradient in the pellet; and

c. disposing a therapeutic agent in at least some of the pores of the pellet.

19. The method of claim 18, wherein the pores having the largest pore size are disposed proximate the first end of the pellet.

20. The method of claim 18, wherein the pellet comprises one or more layers.

21. The method of claim 20, wherein a first layer comprises pores having a first pore size and wherein a second layer comprises pores have a second pore size that is different from the first pore size.

22. The method of claim 21, wherein the layers are arranged in a manner to form a pore size gradient in the pellet.

23. The method of claim 22, wherein the pores having the largest pore size are disposed in the layer proximate the first end of the pellet.

24. The method of claim 18, wherein the pores are formed in the pellet before the pellet is disposed in the cavity.

25. The method of claim 18, wherein the therapeutic agent is disposed in the pores before the pellet is disposed in the cavity.

26. A method for making an implantable stent comprising:

a. providing a stent having a stent sidewall structure having a surface and at least one cavity, having first and second opposing ends, disposed within the stent sidewall structure wherein the first end of the cavity comprises an opening that is in fluid communication with the stent sidewall structure surface and the second end of the cavity comprises the bottom of the cavity;

b. forming a pellet in the cavity, wherein the pellet has a plurality of layers and first and second opposing ends, in which the first end of the pellet faces

toward the first end of the cavity and the second end of the pellet faces toward the second end of the cavity, comprising:

(1) disposing a first solid, non-polymeric material into the cavity to form a first layer of the pellet, wherein the first layer has a plurality of pores having a first pore size; and

(2) disposing a second solid, non-polymeric material into the cavity to form a second layer of the pellet disposed over the first layer, wherein the second layer has a plurality of pores having a second pore size; and

c. disposing a therapeutic agent in at least some of the pores of the first and second layers.

27. The method of claim 26, wherein the step of forming the pellet further comprises disposing a third solid, non-polymeric material into the cavity to form a third layer of the pellet over the second layer, wherein the third layer has a plurality of pores having a third pore size that is different from the first pore size and the second pore size.

28. The method of claim 27, wherein the layers are arranged in a manner to form a pore size gradient in the pellet.

29. The method of claim 27, wherein the third pore size is greater than the second pore size and the second pore size is greater than the first pore size.

30. The method of claim 26, wherein the therapeutic agent is disposed in the pores of the first, second or third layer before the layer is formed.

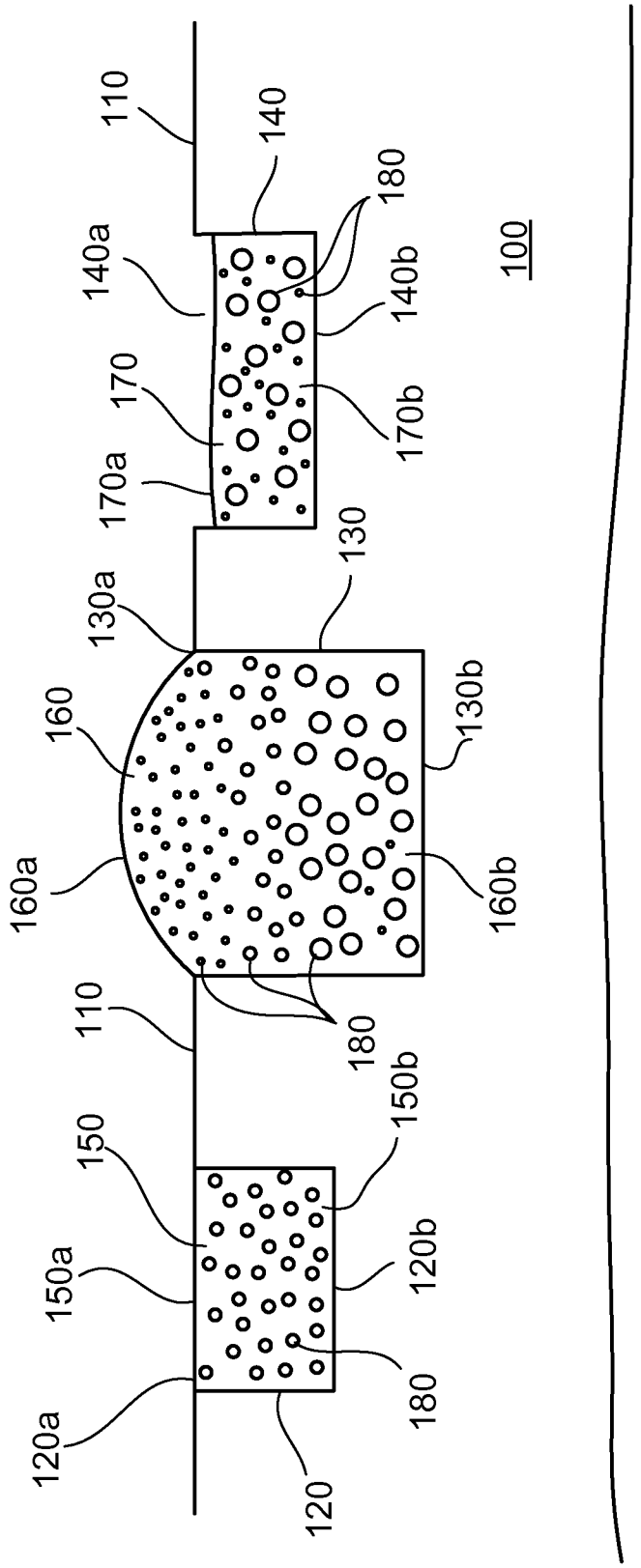
110
140
180
140a
140b
100
170
170b
170a
130
130a
160
130b
160a
160b
110
180
150b
150
150a
120b
180
120a
120

FIG. 1

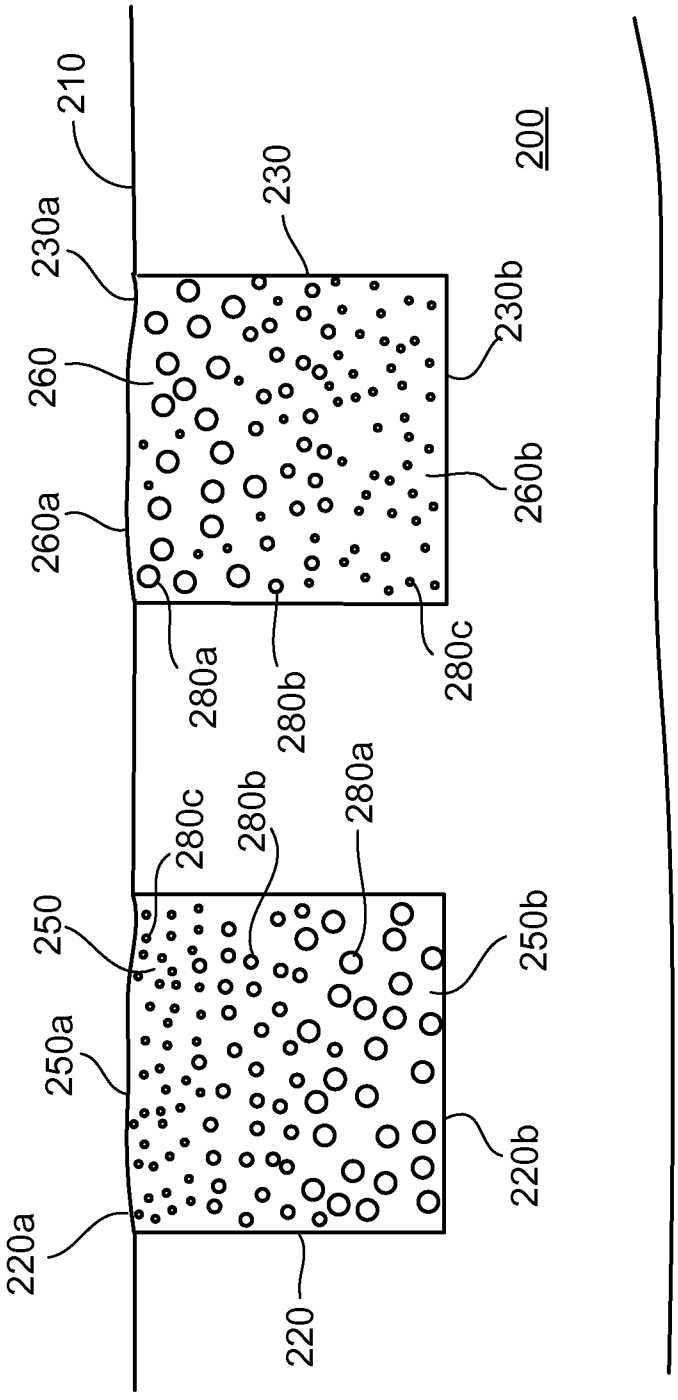
210
200
230
230a
230b
260
260a
260b
280a
280b
280c
250
250a
250b
220a
220
220b

FIG. 2

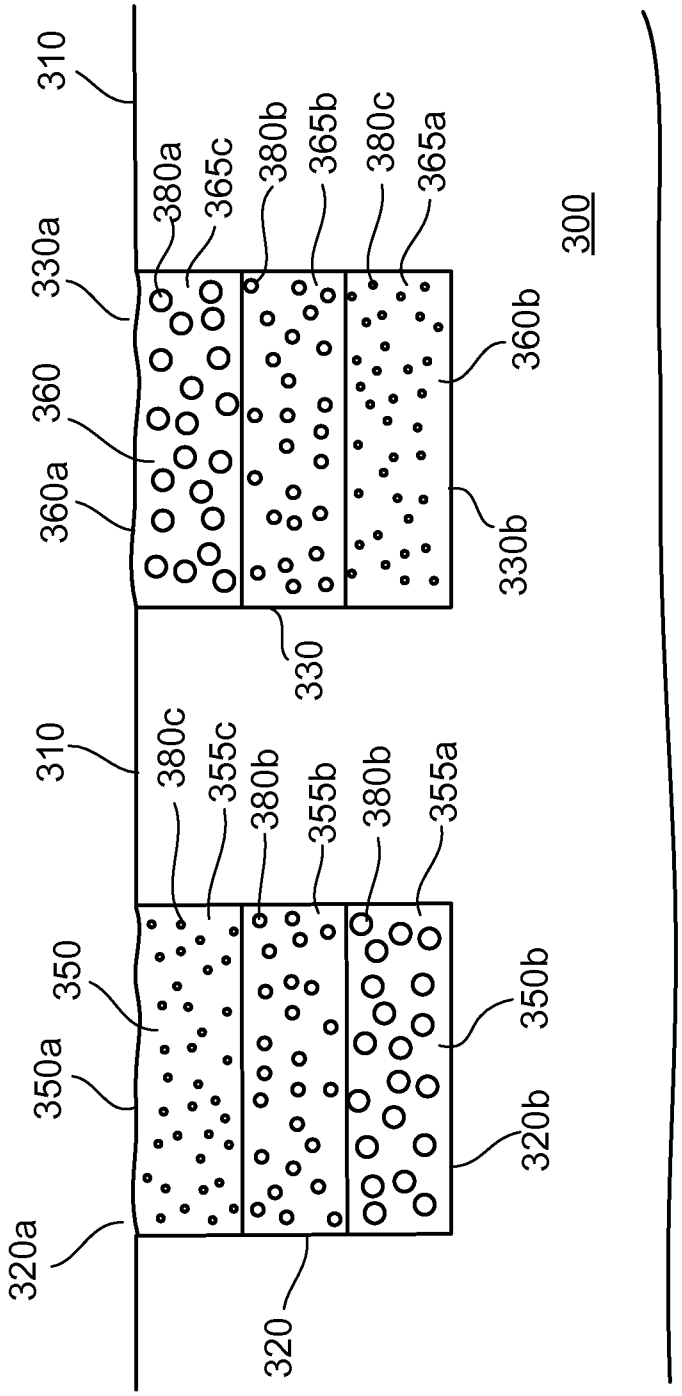
310
380a
365c
380b
365b
380c
365a
330a
300
360b
360
360a
330b
330
310
380c
355c
380b
355b
380b
355a
350
350b
350a
320b
320a
320

FIG. 3

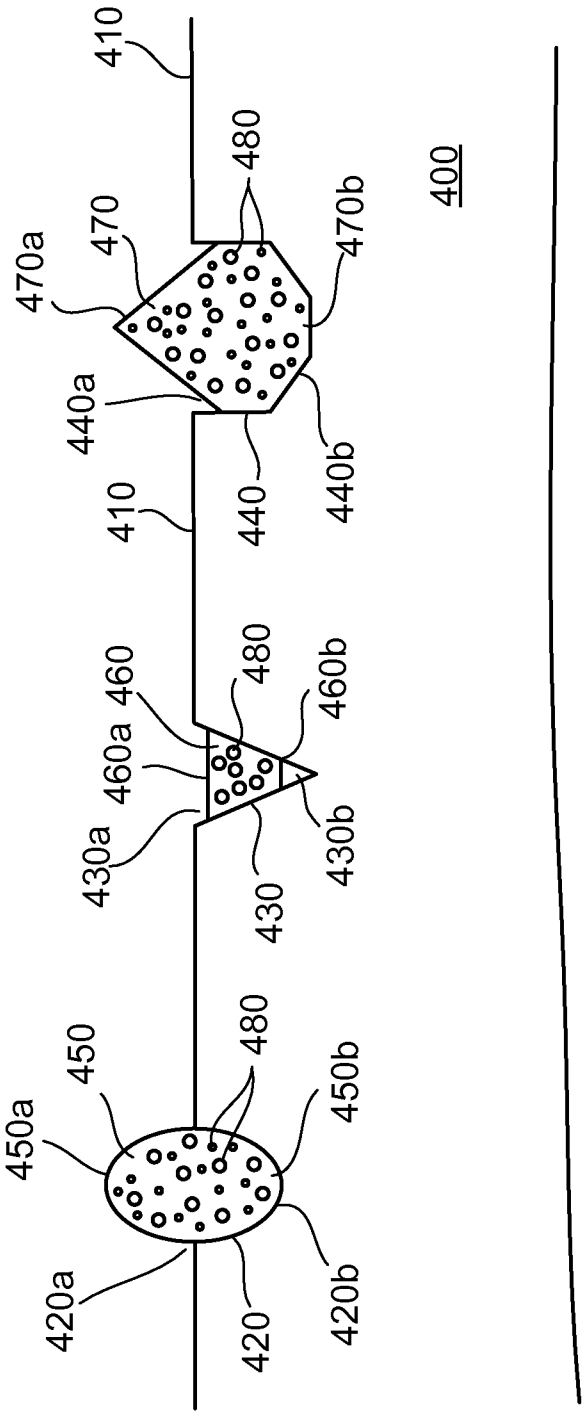
410
480
470
470a
470b
400
440a
440
440b
410
460
480
460b
460a
430a
430
430b
450
480
450b
450a
420a
420
420b

FIG. 4A

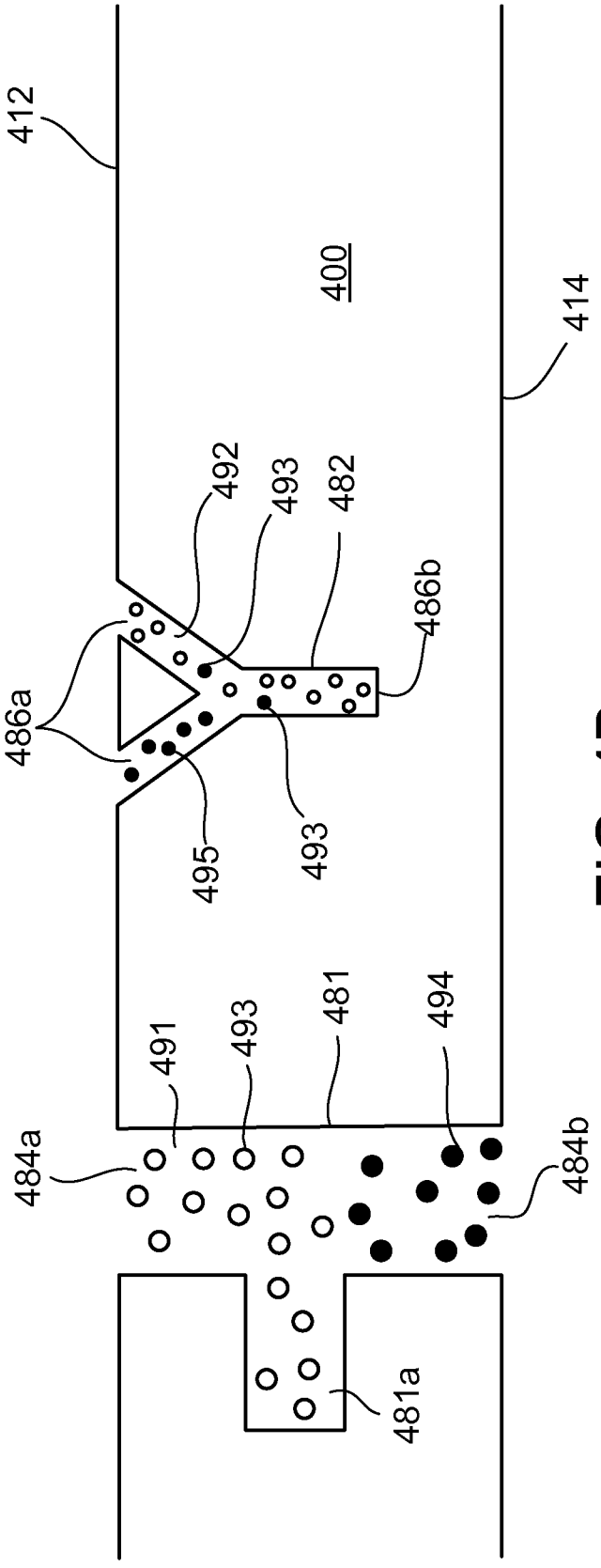
412
400
414
492
493
482
486b
486a
495
493
491
493
481
494
484a
484b
481a

FIG. 4B

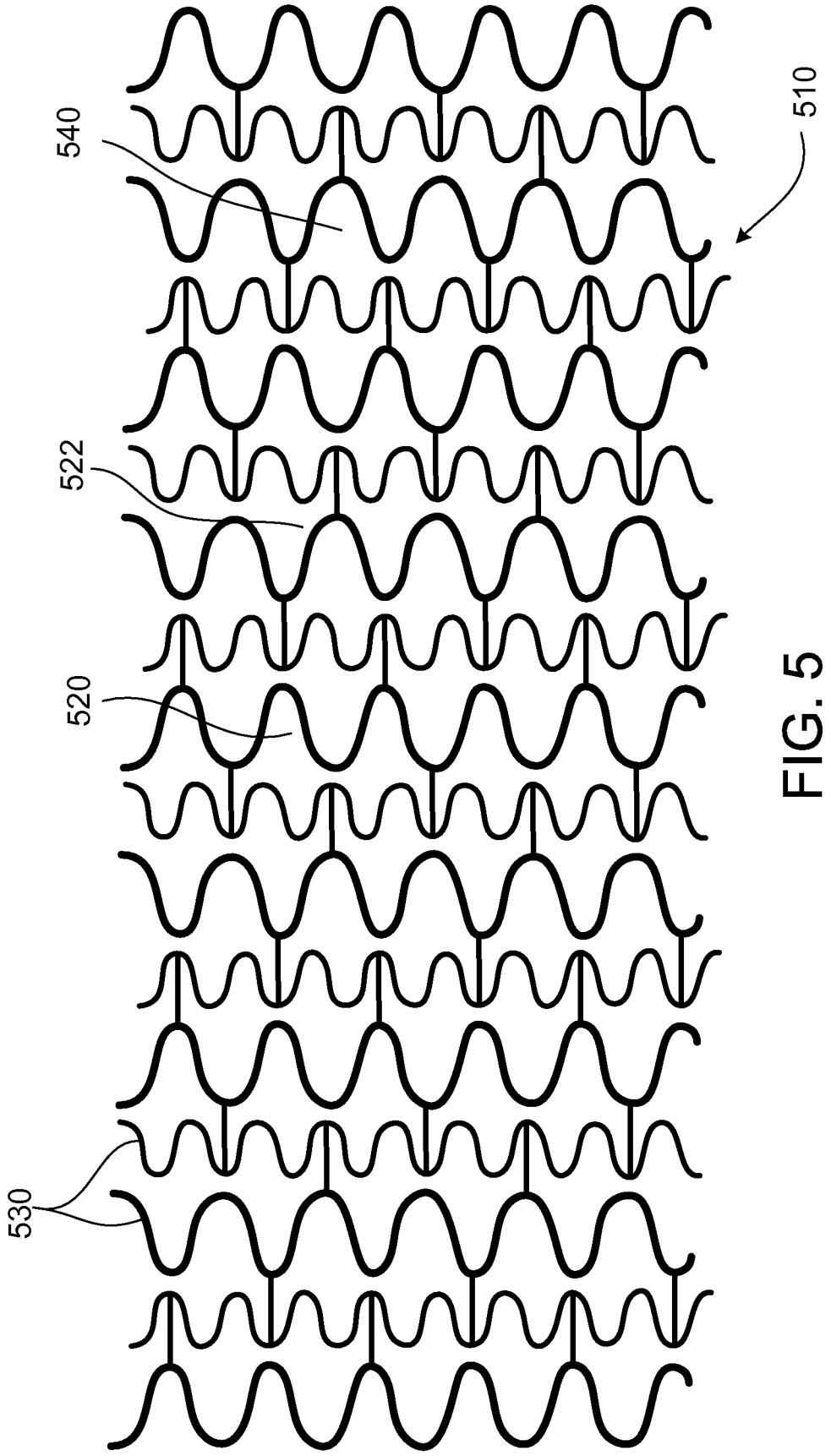

FIG. 5

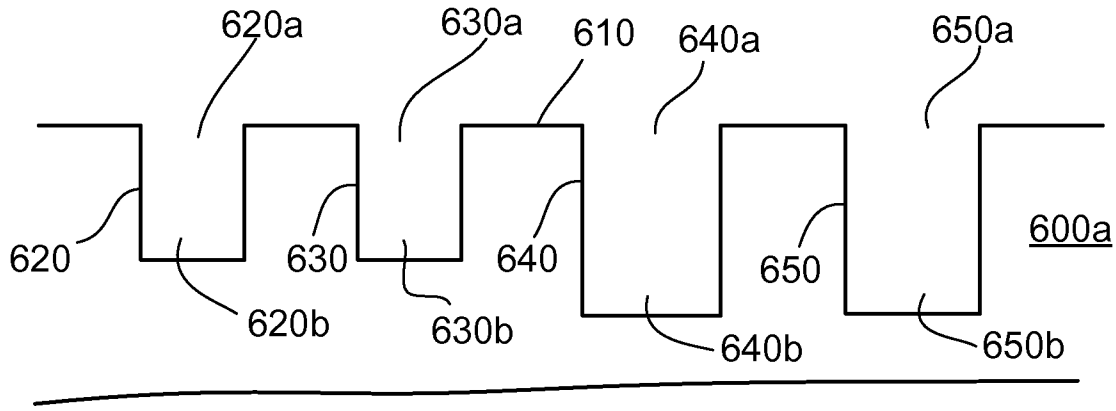

FIG. 6A

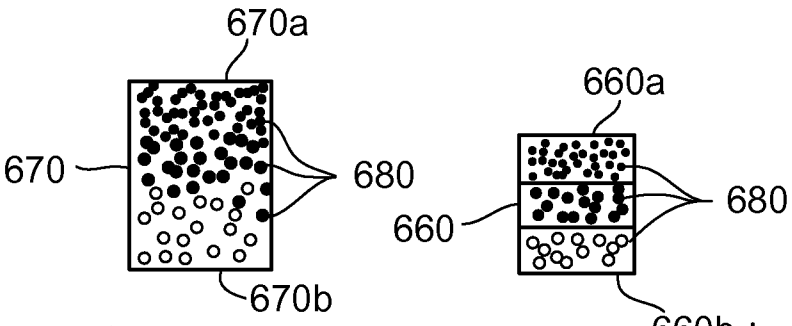

FIG. 6B

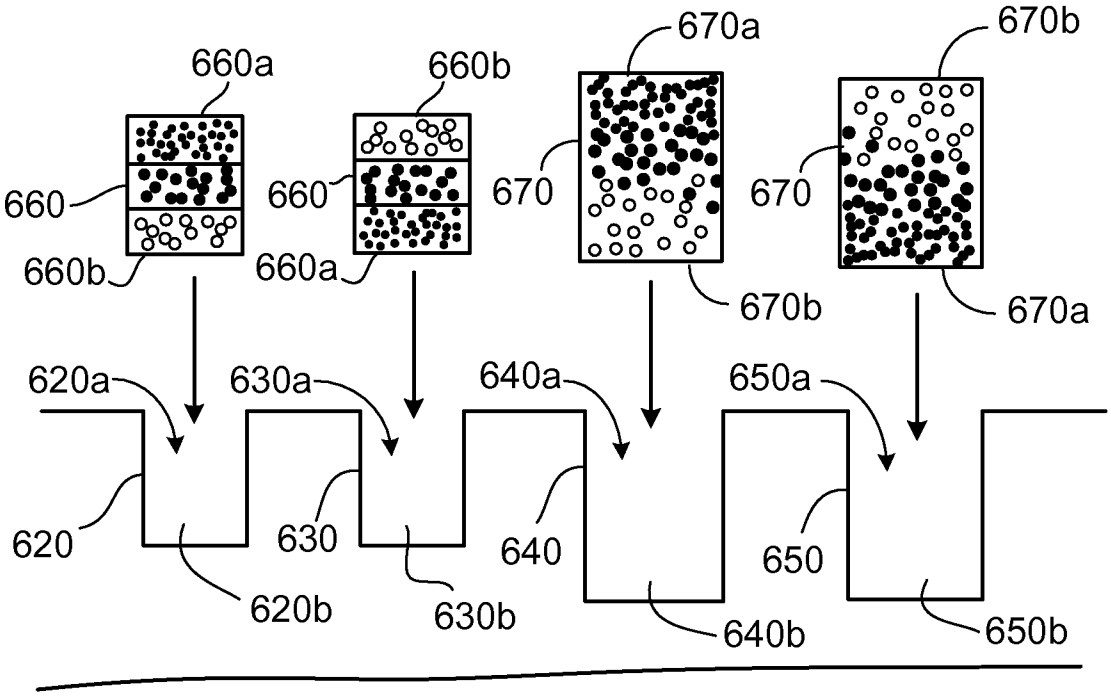

FIG. 6C

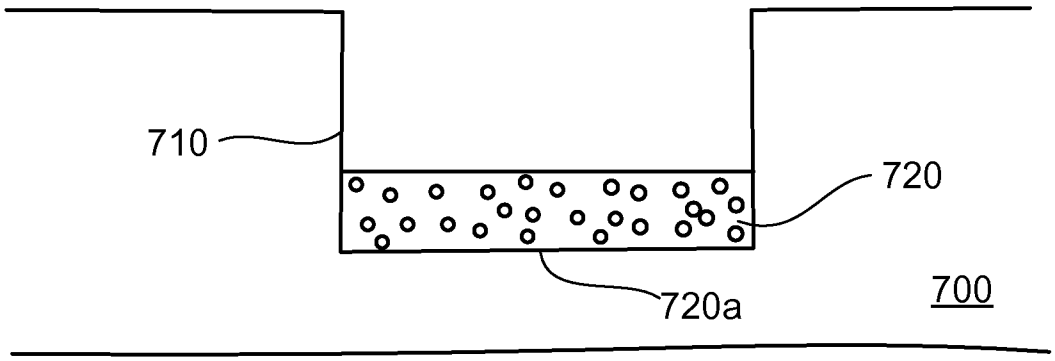

FIG. 7A

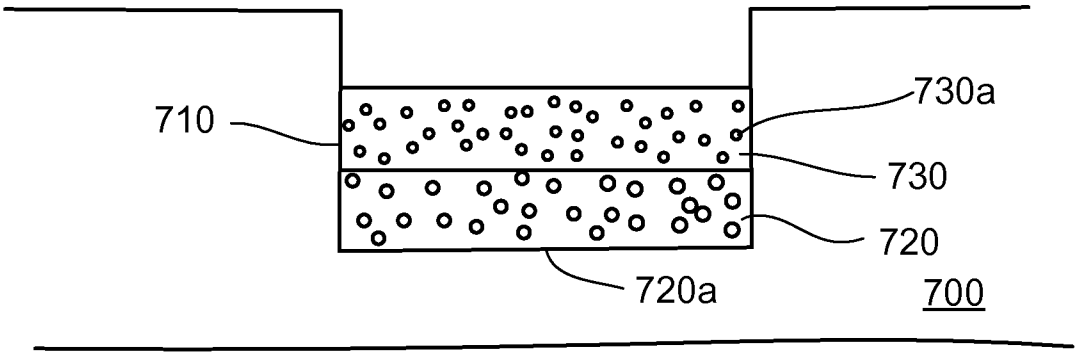

FIG. 7B

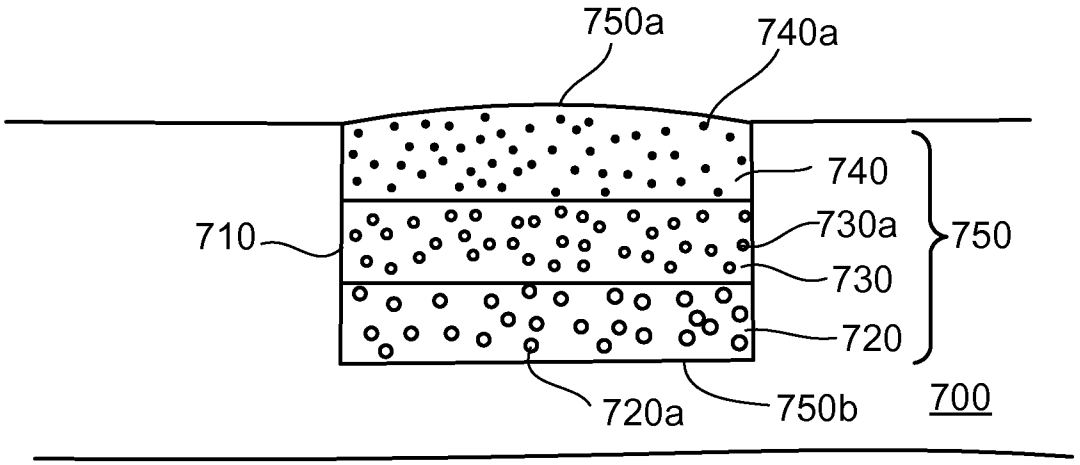

FIG. 7C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/008892

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/86
ADD. A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate of the relevant passages	Relevant to claim No
P,X	WO 2008/036549 A (BOSTON SCIENT SCIMED INC [US]; ATANASOSKA LILIANA [US]; WEBER JAN [NL]) 27 March 2008 (2008-03-27) page 6, line 25 - page 7, line 14 page 11, lines 5-28 page 17, lines 13-30 page 18, lines 5-9 figures 2-7	1,2,7,8, 11-15, 18,20, 24,25
X	US 2004/254635 A1 (SHANLEY JOHN F [US] ET AL) 16 December 2004 (2004-12-16) paragraphs [0051], [0052], [0059], [0063] - [0065], [0072], [0074], [0075], [0089], [0092], [0102], [0110], [0112], [0129], [0132]; figures 1-22	1-30

-/-

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art

"S" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2008	10/11/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040 Fax (+31-70) 340-3016	Portoni, Luisa

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/008892

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/229713 Al (SHANLEY JOHN F [US] ET AL) 12 October 2006 (2006-10-12) paragraphs [0026] - [0028], [0031], [0032], [0044] - [0048], [0088] - [0093]; figures 1,2,6	1,2,7, 11-14
X	US 2005/100577 Al (PARKER THEODORE L [US] ET AL) 12 May 2005 (2005-05-12) paragraphs [0030], [0031], [0045], [0069], [0070], [0082] - [0085], [0117]; figures 1-6	1,2,7, 11-14
A	WO 2006/104976 A (LABCOAT LTD [IE]; ROSENTHAL ARTHUR [US]) 5 October 2006 (2006-10-05) paragraphs [0046], [0137], [0138]; figures l-13d	1-30
A	US 2003/069631 Al (STOLL HANS-PETER [DE]) 10 April 2003 (2003-04-10) paragraphs [0035] - [0038], [0052], [0104] - [0106]; figures 1-9	1,2,7,11
A	WO 99/16386 A (SCIMED LIFE SYSTEMS INC [US]) 8 April 1999 (1999-04-08) page 4, lines 10,11 page 6, line 9 - page 7, line 12	3-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/008892

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008036549 A	27-03-2008	US 2008071349 Al	20-03-2008
US 2004254635 Al	16-12-2004	NONE	
us 2006229713 Al ,	12-10-2006	NONE	
us 2005100577 Al	12-05-2005	NONE	
WO 2006104976 A	05-10-2006	EP 1874372 A2	09-01-2008
us 2003069631 Al	10-04-2003	AT 359040 T	15-05-2007
		DE 10150995 Al	10-04-2003
		EP 1314405 A2	28-05-2003
WO 9916386 A	08-04-1999	US 6253443 Bl	03-07-2001
		US 5972027 A	26-10-1999