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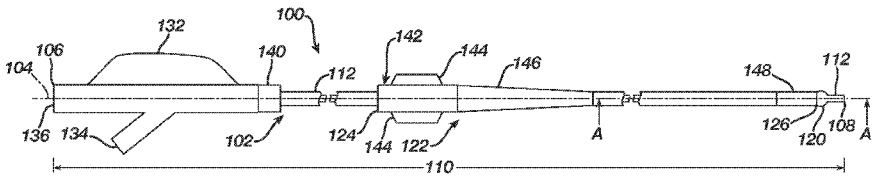


FIG. 1

(57) Abstract: A drug delivery system consistent with one aspect of the present invention is a balloon catheter having a drug coated balloon and an enlarged portion distal to the drug coated balloon, the enlarged portion having a diameter larger than the diameter of the pleated balloon when wrapped (aka folded) about the inner shaft of the balloon catheter, and a selectively retractable tubular member surrounding at least the pleated and wrapped balloon and having a distal end located in circumferential contact with the enlarged portion distal to the drug coated balloon to inhibit blood flow proximally into the distal end of the selectively retractable tubular member.

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# DRUG DELIVERY SYSTEM

[01]. RELATED APPLICATION

[02]. This application claims the benefit of priority to U.S. Provisional Patent Application Serial No. 61/908,171, filed November 24, 2013, which is incorporated in its entirety by reference herein.

[03]. BACKGROUND

[04]. 1. Technical Field

[05]. The invention relates to the field of medical devices, and more particularly medical devices suited for delivering agents to body lumen walls.

[06]. 2. Related Devices and Methods

[07]. Treatment of vascular disease may include delivery of therapeutic agents to the diseased tissue, and implantation of tissue supporting stents or prosthetic vasculature, e.g., grafts, stent-grafts, etc., which are delivered through the vasculature at a reduced dimension for ease of navigation in, and reduced chance of injury to, the tortuous vasculature from entry point to the diseased location. Such treatment may include angioplasty performed by expanding a compliant, semi-compliant, or non-compliant balloon in narrowed vessels to dilate them, which may be narrowed for one or more reasons including the presence of a calcified lesion. These treatments are delivered using a catheter designed to be advanced through the vasculature from a point of entry to the site where the treatment is needed. Such catheters typically include an elongated shaft with a distal end, which is the end furthest from the medical professional advancing the catheter. Such shafts may have variable designs as best suited to deliver the desired treatment from the point of entry to the vasculature to the intended implantation site. Some devices include additional features such as tips that taper from the outer diameter of the elongated shaft or distal balloon leg to a smaller diameter distal tip on the distal ends of the elongated shafts, sheaths or outer members disposed about much of the length of the elongated shaft and about the vascular implant, and various features on the proximal end, that is, the end closest to the medical professional to perform varied functions, e.g., release of dye or other visualization agent, valved access to a lumen running through the elongated shaft for inserting a guide wire, sealed attachment of a pressurized fluid to inflate balloons at the distal end, or other

mechanisms involved in the controlled delivery of the treatment to its intended site. This disclosure describes an agent delivery system having features on interfacing parts of the system.

[08]. Delivery of agents to localized sections of body lumen walls via selectively expandable and contractible devices, such as for example, balloons for angioplasty of arteries, is currently practiced in Europe. Commercially available drug delivery balloons are loaded with paclitaxel in dosages of two (2) to five (5) micrograms (μg) per square millimeter ($mm^2$), and said paclitaxel either covers the entire expanded cylindrical surface of such a balloon (360 degrees of the circular circumference, along the entire working length), or just in the folds of a pleated balloon, which balloon, when fully inflated to its nominal diameter, has paclitaxel on less than 360 degrees of the circular circumference of the balloon, along the entire working length. Said balloon catheters are introduced to the artery through a catheter sheath introducer and advanced over a previously placed guide wire that crosses the lesion to be treated with an agent. After exiting the distal end of the catheter sheath introducer, the balloon tracks along the guide wire until it crosses the lesion, at which time, it is inflated and once in contact with the lesion and/or vessel walls upon nominal expansion of the balloon, the paclitaxel in its excipient is pressed into the lesion and separates from the balloon outer surface. At least some of the loaded paclitaxel washes off or dissolves from the balloon into the blood stream during the tracking along the guide wire and during the effort to cross the lesion, which is often a stenosed section of artery, and which may require effort (and corresponding time) to safely cross. During this time, the drug continues to wash off or dissolve into the blood. Thus, the efficacy of the treatment depends on time to transfer the paclitaxel to the body lumen wall, as well as the initial concentration of paclitaxel, pre-insertion into the blood vessel. Paclitaxel has a local toxicity limit, which has been reported as 100 micromole per liter (100 μmol/l) tissue volume, and which chemotherapeutic level may be approached at the current commercial initial loadings with long balloons (20-30cm) having large diameters (e.g., 6 mm).

[09]. In some drug eluting balloons, paclitaxel is loaded directly onto the balloon surface, without any excipient. In other drug eluting balloon, paclitaxel is loaded along with an excipient onto the balloon surface. In most cases, a solvent used to assist in dispensing and/or dispersing the paclitaxel and/or excipient. Such solvent then evaporates leaving a solid layer on the balloon. Commercially used excipients include urea, Iopramid, shellac, butyryl-trihexyl-citrate (BTHC), and polyethyleneglycol (PEG), among others.

[10]. Non-commercialized devices, described in prior art patent publications, such as that described in USP 5,304,121 to Sahatjian, which describes the local delivery of drug from a hydrogel coated balloon, delivered to the lesion cite in a sheath, which "protects the coating and inhibits premature release of the coating." The sheath is proximally retracted and the balloon catheter held in place, or the device is advanced until the tip is proximal to the lesion and then the sheath is held in place and the balloon catheter is distally advanced to cross the lesion, and expanded to transfer the drug to the lesion and vessel surfaces. However, no more details about sheath are disclosed other than a partial illustration in FIG. 2.

[11]. USP 6,146,638 to Rowe describes another drug delivery balloon delivered to a coronary artery in an introducer catheter 18 of generally conventional design in 1989. However, no more details about the introducer catheter 18 are disclosed other than a partial illustration in FIG. 1.

[12]. USP 5,868,719 to Tsukernik describes a sheath for protecting the coating of a drug coated balloon and include modifications to help keep the balloon in the sheath during positioning of the balloon, like a collar with a smaller diameter than the rest of the sheath and indentations traverse to the longitudinal axis of the balloon distal to the balloon. The inner diameter of the sheath proximal to the collar is slightly larger than the outer diameter of the folded balloon. However, the collar terminates in an opening, and as depicted in FIG. 7 and the distal tip of the balloon is within the modified sheath and does not extend distal to it during delivery. The distal end of the sheath does not contact the much smaller distal tip of the catheter body, at any time.

[13]. More recently published, US 2010/0228333 A1 describes a retractable, thin walled tubular sheath with an inverted distal end, said tubular sheath terminating in an end proximal to the proximal end of the balloon. The sheath extends distally from the proximal end of the catheter and then inverts and extends proximally where it terminates proximal to the proximal end of the balloon. Variations of this arrangement are described, but in all embodiments the inner diameter of distal end of the sheath has a larger diameter than the outer diameter of the catheter (e.g., pleated and wrapped balloon and/or distal tip) within it such that blood flow therein is not inhibited. Also, in all embodiments, retraction of the sheath is designed to peel or roll (evert) proximally rather than slide proximally relative to the balloon.

[14]. In many cases, the balloon catheter is an elongated device, which includes one or more elongated tubular members. It may have an elongated balloon at or near its distal end. It may have a tubular member having a lumen through which the catheter follows the path of a previously placed guide wire in the vasculature. Such a tubular member is often referred to as a guide wire tube. The catheter may additionally have another tubular member having a proximal end and a distal end and a lumen therethrough, and surrounding a length of the guide wire tube, but having a different inner diameter than the outer diameter of the guide wire tube such that a roughly annular lumen remains between the guide wire tube and the other member. Such a tubular member is sometimes referred to as an outer member, and the guide wire tube may then alternately be referred to as an inner member. The guide wire tube or inner member may extend distally of the distal end of the outer member. An inflatable member may sealingly surround at its proximal end the external surface of the distal end of the outer member and the external surface of the distal end of the inner member at its (the inflatable member's) distal end. Such sealing may be accomplished by thermal bonding of bondable materials or through the use of a tie layer or adhesive between concentric surfaces. Such a fluid-tight attachment of the inflatable member to the inner and outer member places the interior of the inflatable member in fluid communication with the substantially annular lumen formed between the inner member and the outer member. A typically much shorter length (than either the inner or outer member's length) and separate tubular member having a proximal end and a distal end and a lumen therethrough may have a tapered outer surface and may be attached to the distal end of the elongated shaft, either through a butt joint with the annular surface of the distal end of the inner member or through a lap joint with the outer cylindrical surface of the distal end of the inner member. Alternate attachment constructions of distal tips to the distal end of the catheter are known in the art. For example, see U.S. Pat. Pub. No. 2003/0114794 A1 and U.S. Pat. No. 5964778 to Fugoso et al., which are expressly incorporated by reference to the extent not contradictory to the remainder of the present specification.

[15]. Rather than co-axial arrangement of a guide wire lumen and an inflation lumen in a balloon angioplasty catheter, it is known in the art to have two tubes with parallel axes, and such "side by side" construction is sometimes called a "bi-axial" catheter. Stated another way, an otherwise "outer'' surface of one tube is in contact with another otherwise "outer" surface of a second, parallel tube. One tube provides the lumen for the guide wire and the other for inflation

of the balloon. In bi-axial constructions, the proximal leg of the balloon seals to outer surfaces of both the guide wire tube and the inflation tube, and the distal end typically seals to the guide wire tube (only), because the distal end of the inflation tube terminates at the proximal portion of the balloon.

[16]. Balloon catheters used to perform angioplasty in peripheral arteries are sometimes referred to as percutaneous transluminal angioplasty ("PTA") catheters. Balloon catheters used to perform angioplasty in coronary arteries are sometimes referred to as percutaneous transluminal coronary angioplasty ("PTCA") catheters. PTCA catheters are commercially available and sized to track over a 0.014" (outer) diameter guide wire. PTA catheters are commercially available and sized to track over one of three different (outer) diameter guide wires: 0.014", 0.018", and 0.035".

[17]. PTCA catheters are inserted at a point of entry in a peripheral artery, e.g., a radial or femoral artery, and advanced "upstream" through the arteries to the aorta and to the ostium of the specific coronary artery in need of treatment. PTA catheters are inserted at a point of entry in a peripheral artery, and advanced through that or other connected arteries to the specific arterial location in need of treatment. In either type of catheter, the force to advance the catheter is applied external to the patient on an external (proximal) portion of the catheter, and the force is transferred to the distal tip of the catheter as a result of the column strength or axial stiffness of the catheter. The stiffer the catheter, the easier to advance the distal tip and any therapeutic device or beneficial agent to the desired site. The quality of being able to push a proximal portion of the elongated shaft and have the distal tip move along an artery the same distance is commonly referred to as "pushability." However, a vascular balloon catheter also has the need to track closely to a guidewire that is resident in the arterial network and follows the tortuous path of the arteries. That quality is commonly called "trackability." Axial flexibility is needed to have high trackability, and therefore closely track a tortuously curved guidewire. Yet another desirable characteristic of a vascular balloon catheter designed to traverse a calcified lesion or other stenotic area in a coronary artery or other blood vessel is called "crossability," or, i.e., the catheter's ability to have the distal tip cross the stenosis by the medical professional pushing on the proximal end or some external (to the patient) portion of the catheter.

[18]. PTCA catheters that advance through the arteries by sliding over a previously placed guide wire have two commercially available variations, in terms of whether the entire (or almost

the entire) length of the catheter slides over the guide wire, or whether only a shorter length of the catheter, at its distal end, slides over the guide wire. With the use of radial arteries as the entry point for reduced complications and time to recover from catheter procedures, treating the peripheral vasculature in the legs will require even longer length catheters than PTCAs. Such PTAs may be up to one hundred and ninety (190) centimeters (cm) in length, and it is desirable to have only a shorter portion of the catheter run over the guide wire. Another way to express the difference between the two constructions is whether the guide wire lumen runs the entire length of the catheter and has a proximal port in the proximal end (or in one of the two ports present in the commonly used Y connectors) of the catheter, or whether the proximal port of the guide wire lumen is closer to the distal end of the catheter than the proximal end, and generally between 9 and 20 centimeters, for PTCAs, and between 10 and 60 centimeters, for PTAs, proximal of the distal end, or even closer, such as at the proximal end of the inflatable member. The case where the guide wire runs through the entire catheter, or i.e., the guide wire lumen runs through the entire length of the catheter is commonly called an "over-the-wire" ("OTW") catheter. The case where the guide wire runs through a shorter length of the catheter near the distal end, or i.e., the guide wire lumen has a proximal port closer to the distal end than the proximal end is commonly called a "rapid-exchange" or "Rx" catheter. Another known term for the second case is single-operator-exchange ("SOE") catheter.

[19]. It is common in either type of angioplasty catheter, OTW or Rx, to have a proximal portion with greater axial stiffness and a distal portion with a lower relative axial stiffness. This may be accomplished by a tapered support mandrel extending from the proximal end to a point proximal of the distal end, or selection of tubular segments with gradually decreasing column strength. In Rx catheters, it is common to use a relatively stiff proximal tubular member (shaft), such as a metal hypotube, and to attach a relatively less stiff (more flexible) polymer shaft to the distal segment of the hypotube. There may be additional metal or polymer members (e.g., stiffening wires, support tubes, reinforcing tubes, support mandrels, coils, patterned perforations in or "skived" sections of the hypotube, etc.) in Rx designs to provide a gradual transition in axial stiffness to the catheter as a whole from a relatively constant high stiffness proximal shaft to at least the proximal port of the guide wire lumen, which is present along side, or in the side of, the outer member. Without such a transition, the abrupt change in column strength between the end of the hypotube and the proximal port of the guidewire results in a tendency of the

catheter to close the inflation lumen when the catheter buckles or kinks in that section of the catheter as a result of the axial loading, which closure of the inflation lumen is undesirable. The distal shaft of an Rx PTCA catheter, as with the distal portion of an OTW PTCA catheter, is generally more flexible, as this is the part that follows the aortic arch and is advanced through small coronary arteries, which tend to be rather tortuous in addition to having a much smaller diameter.

[20]. PTAs that are designed to treat iliac, and arteries of the legs often do not require the same amount of flexibility as those to treat coronary arteries do to relatively less tortuosity of the vessels of the legs than those of the heart.

[21]. Two of the factors that influence the current angioplasty (PTCA or PTA) catheter crossability are flexibility and pushability of the distal shaft of an Rx catheter or of the distal portion of an OTW catheter. For example, the more flexible a distal shaft or distal portion is, the higher the crossability of a catheter given the same axial stiffness, or i.e., pushability. Mechanically, however, a shaft that is flexible enough to track through tortuous vessels may not have the column strength to transmit sufficient force axially, while a stiff shaft can transmit greater force axially, but not be flexible enough track along the guidewire through a tortuous vessel. The trade off with increasing flexibility is the reduction of pushability and vice versa.

[22]. SUMMARY

[23]. A drug delivery system consistent with one aspect of the present invention is a balloon catheter having a drug coated balloon and an enlarged portion distal to the drug coated balloon, the enlarged portion having a diameter larger than the diameter of the pleated balloon when wrapped (aka folded) about the inner shaft of the balloon catheter, and a selectively retractable tubular member surrounding at least the pleated and wrapped balloon and having a distal end located in circumferential contact with the enlarged portion distal to the drug coated balloon to inhibit blood flow proximally into the distal end of the selectively retractable tubular member.

[24]. An agent delivery system consistent with one aspect of the present invention has a balloon angioplasty catheter having a longitudinal axis having a catheter shaft having proximal end, a distal end, and a length inbetween, an inflatable balloon pleated and wrapped about a distal portion of the catheter shaft, the pleated and wrapped inflatable balloon with therapeutic agent disposed thereon having a first circumference transverse to the longitudinal axis, an enlarged portion with a circumference transverse to the longitudinal axis greater than the first

circumference of the pleated and wrapped inflatable balloon, the enlarged portion located distal to the pleated and wrapped inflatable balloon on the catheter shaft, and an elongated tubular member having a proximal end and a distal end and a lumen therebetween, wherein the balloon angioplasty catheter is located within the lumen therebetween, the distal end of the tubular member is proximal to the distal end of the distal tip of the balloon angioplasty catheter, and the distal end of the tubular member is in contact with a circumference of the enlarged portion transverse to the longitudinal axis.

[25]. These and other features, benefits, and advantages of the present invention will be made apparent with reference to the following detailed description, appended claims, and accompanying figures, wherein like reference numerals refer to structures that are either the same structures, or perform the same functions as other structures, across the several views.

[26]. BRIEF DESCRIPTION OF THE FIGURES:

[27]. The figures are merely exemplary and are not meant to limit the present invention.

[28]. FIG. 1 illustrates a first embodiment of a drug delivery system with the retractable tubular member in the protective position in contact with an enlarged region distal to the balloon.

[29]. FIG. 2 illustrates the embodiment of FIG. 1 with the retractable tubular member retracted to a position for inflating the balloon.

[30]. FIG. 3 illustrates a retractable tubular member of drug delivery system.

[31]. FIG. 4. illustrates a simplified cross-section along section A-A in FIG. 1.

[32]. FIG. 5 illustrates a cross-section of a retractable tubular member with an annular gap between its inner surface and a pleated and wrapped uninflated balloon with therapeutic agent disposed thereon (the inner member and other parts of the catheter shaft are not shown for simplicity).

[33]. FIGS. 6A, 6B, & 6C illustrate three variations in the arrangement of the wall of the retractable tubular member,

[34]. FIGS. 7A, 7B, & 7C illustrate a first embodiment of a distal tip for assembly over an inner member distal to a balloon to create an enlarged portion for circumferential contact with the retractable tubular member and a distal tip.

[35]. FIGS. 8A, 8B, and 8C illustrate a second embodiment of a distal tip for assembly over an inner member distal to a balloon to create an enlarged portion for circumferential contact with the retractable tubular member and a distal tip.

[36]. FIGS. 9A, 9B, and 9C illustrate a third embodiment of a distal tip for assembly over an inner member distal to a balloon to create an enlarged portion for circumferential contact with the retractable tubular member and a distal tip.

[37]. DETAILED DESCRIPTION

[38]. The terms "tube" and "tubular" are used in their broadest sense, that is, any object which is arranged at a radial distance about a longitudinal axis. Accordingly, the terms "tube" or "tubular" include any structure that is (i) cylindrical or not, such as for example having an elliptical or polygonal transverse cross-section, or any other regular or irregular cross-section; (ii) has a changing or different cross-section along its length; (iii) is arranged around a straight, curved, bent, or discontinuous axis; (iv) has an imperforate, or a periodic or other perforate, irregular, or gapped surface or cross-section; (v) is spaced uniformly or irregularly, including being spaced varying radial distances from the longitudinal axis; or (vi) has any desired length or cross-sectional size.

[39]. A drug delivery system consistent with one aspect of the present invention is a balloon catheter having a drug coated balloon and an enlarged region distal to the drug coated balloon, the enlarged region having a diameter larger than the diameter of the pleated balloon when wrapped (aka folded) about the inner shaft of the balloon catheter, and a selectively retractable tubular member surrounding at least the pleated and wrapped balloon and having a distal end located in circumferential contact with the enlarged region distal to the drug coated balloon to inhibit blood flow proximally into the distal end of the selectively retractable tubular member.

[40]. In some embodiments, the retractable protective tubular member can have the same construction as a guide catheter. In some embodiments, the retractable protective tubular member can have the same construction as a diagnostic catheter. In some embodiments, the retractable protective tubular member can be a single material extrusion tubing. In some embodiments, the retractable protective tubular member can have a composite tubular structure.

[41]. In some embodiments, the retractable protective tubular member comprises a multiple co-axial layer construction, with a lubricious inner layer and a nylon or nylon copolymer outer layer either bonded directly together chemically or mechanically via an intermediate "tie" layer.

In some embodiments, the retractable protective tubular member comprises a multiple co-axial layer construction, with a lubricious innermost layer and a nylon or nylon copolymer outermost layer and an intermediate reinforcing layer. Examples of the inner most lubricious layer include HDPE, anhydride modified HDPE, PTFE, carbon loaded nylon, carbon loaded PEBAX® brand polyether block amide copolymer. Examples of the intermediate reinforcing layer may be braided metal or alloy wires or a spiral cut metal or alloy tube or coil. In some embodiments, the retractable protective tubular member comprises a single layer extrusion of nylon tubing, such as nylon 12, a polyamide homopolymer.

[42]. The length of the retractable, protective sheath may be between 90-150 cm. In some embodiments, perhaps for treatment of arteries in the leg from an entry point in the radial artery, the retractable, protective tubular member may be about 190 cm from hub to distal tip. In some embodiments, the sheath is shorter than the balloon catheter that it is disposed about by an amount at least equal to the length of the hub and or Y connector plus the working length of the balloon plus the distal leg of the balloon, so that when retracted, the proximal end of the sheath is distal to the proximal end of the balloon catheter and the distal end of the sheath is proximal to the proximal end of the working length of the balloon of the balloon catheter. Thus, in a certain embodiment, if the balloon catheter is 190 cm long and has a 30 cm balloon, for example, the retractable, protective tubular member would be about 155 cm long.

[43]. In some embodiments, a retractable, protective tubular member may be coated internally and externally with a lubricious or low friction compound, and thereby have a lubricious coating or a low friction coating on the surface that was coated. In some embodiments, a retractable, protective tubular member may be coated internally with a lubricious or low friction compound, and thereby have a lubricious coating or a low friction coating on the surface that was coated. In some embodiments, a retractable, protective tubular member may be coated externally with a lubricious or low friction compound and thereby have a lubricious coating or a low friction coating on the surface that was coated. In some embodiments, a retractable protective tubular member may be coated only on an internal surface with a lubricious or low friction compound and thereby have a lubricious coating or a low friction coating on only the surface that was coated. In some embodiments, a retractable protective tubular member may be coated only an external surface with a lubricious or low

friction compound, and thereby have a lubricious coating or a low friction coating only the surface that was coated.

[44]. In some embodiments, the drug delivery system includes a distal tip on the balloon catheter that has a lubricious coating or is made of intrinsically lubricious material to exhibit low friction or slick properties and a retractable, protective tubular member with a lubricious coating on at least the outer surface of the distal portion.

[45]. In some embodiments, the retractable sheath terminates at its proximal end distal to the proximal end of balloon catheter. In some embodiments, the sheath may comprise a hub with which to grip the proximal end, a luer lock to tighten the valve and seal between the sheath and the outer diameter of the balloon catheter outer member, a length of nylon tubing joined to a radiopaque tip at the distal end, and a strain relief co-axially surrounding the nylon tubing adjacent the proximal attachment to the hub and luer lock.

[46]. In some embodiments, the sheath has a radiopaque distal tip. Being able to see the distal tip on a fluoroscopic screen in a catheter laboratory permits an operator to know when the distal tip of the sheath has been retracted (moved proximally) sufficiently to clear the proximal skirt or proximal cone or proximal shoulder of the balloon. This judgment of "clearing" the proximal end of the expandable portion of the balloon is made by seeing a gap of recommended distance between a marker aligned with the proximal end of the working length of the balloon. In some embodiments, the radiopaque distal tip is five (5) millimeters (mm) long. In some embodiments, the length of the radiopaque distal tip is shorter than five mm, and in some it is longer than five mm. In some embodiments, the radiopaque distal tip is constructed of polyurethane with a radiopaque material, such as, for example, bismuth stearate. In some embodiments, the radiopaque distal tip of the sheath is constructed of a nylon copolymer, such as, for example, Grilamid ELG 5930, with radiopaque material, such as, for example, bismuth stearate. In some embodiments, the radiopaque distal tip is constructed of material having a Shore hardness value of 80A. In some embodiments, the sheath has a 5 mm long, radiopaque distal tip comprising polyurethane and bismuth stearate, having a Shore hardness value of 80A.

[47]. In some embodiments, the catheter tip may be made from a nylon copolymer, such as PEBAX®, with a hardness on the Shore D scale from 25 to 75. In some embodiments the enlarged portion may consist of a nylon copolymer, such as PEBAX®, with a hardness on the Shore D scale from 25 to 75.

[48]. In some embodiments, the enlarged portion is a tubular member between 2 and 10 millimeters long. In some embodiments the enlarged portion is between 2.5 mm and 5.0 mm long.

[49]. The interface between the distal end of the retractable, protective tubular member and the enlarged portion provides a seal to prevent significant blood flow from entering the lumen of the retractable, protective tubular member. In some embodiments, the interface is circumferential contact of just the distal end against a plane orthogonal to the longitudinal axis of the balloon catheter. In some embodiments, the interface is cylindrical contact between the inner circumference of the retractable, protective tubular member and an outer cylindrical surface of the enlarged portion. In some embodiments, the distal tip of the retractable, protective tubular member stretches beyond its free (unstressed) dimensions to conform to the outer surface of the enlarged portion, forming a conical section or a spherical section. Because of the relative sizing and contact between the inner circumference of the retractable, protective tubular member and the enlarged portion, the retractable, protective tubular member does not distort (aka fishmouth) when tracking over curves in the guide wire. In some embodiments, the maximum outer dimension of the retractable protective tubular member is less than the maximum diameter of the enlarged portion, which assists the distal end to stay in contact with the enlarged portion when crossing lesions or other stenosed sections of the vasculature.

[50]. A1. An agent delivery system comprising a balloon angioplasty catheter having a longitudinal axis comprising a catheter shaft having proximal end, a distal end, and a length inbetween; an inflatable balloon pleated and wrapped about a distal portion of the catheter shaft, the pleated and wrapped inflatable balloon with therapeutic agent disposed thereon having a first circumference transverse to the longitudinal axis; an enlarged portion with a circumference transverse to the longitudinal axis greater than the first circumference of the pleated and wrapped inflatable balloon, the enlarged portion located distal to the pleated and wrapped inflatable balloon on the catheter shaft; and an elongated tubular member having a proximal end and a distal end and a lumen therebetween, wherein the balloon angioplasty catheter is located within the lumen therebetween, the distal end of the tubular member is proximal to the distal end of the distal tip of the balloon angioplasty catheter, and the distal end of the tubular member is in contact with a circumference of the enlarged portion transverse to the longitudinal axis.

[51]. A2. The agent delivery system of the previous paragraph A1, wherein a distal end of the enlarged portion and the distal end of the catheter shaft are in one plane transverse to the longitudinal axis.

[52]. A3. The agent delivery system of the previous paragraph A1, wherein the distal end of the enlarged portion and the distal end of the catheter shaft are one and the same.

[53]. A4. The agent delivery system of paragraph A1, wherein a distal end of the enlarged portion and the distal end of the catheter shaft are located in different transverse planes to the longitudinal axis.

[54]. A5. The agent delivery system of any of paragraphs A1 through the previous paragraph, wherein the catheter shaft comprises: a first tubular member having a proximal end and a distal end and lumen therebetween; a second tubular member having a proximal end and a distal end and a lumen therebetween, disposed about at least a portion of the first tubular member, such that the first tubular member is located within the lumen of the second tubular member and an annular inflation lumen is formed between the first and second tubular members; wherein the inflatable balloon has a proximal leg, a distal leg, and a working length, the proximal leg is sealably connected to a distal portion of the second tubular member and the distal leg is disposed about a distal portion of the first tubular member and the annular inflation lumen is in fluid communication with an interior of the inflatable balloon.

[55]. A6. The agent delivery system of any of paragraphs A1 to A4, wherein the catheter shaft comprises: a first tubular member having a length, a proximal end and a distal end, and lumen therebetween; a second tubular member having a length, a proximal end and a distal end, and a lumen therebetween, disposed alongside at least a portion of the first tubular member, such that the first tubular member and the second tubular member are substantially parallel and connected to each other for at least a portion of their respective lengths; wherein the inflatable balloon has a proximal leg, a distal leg, and a working length, the proximal leg is sealably connected to a distal portion of the second tubular member and a portion of the first tubular member, and the distal leg is disposed about a distal portion of the first tubular member and the lumen of the second tubular member is in fluid communication with an interior of the inflatable balloon.

[56]. A7. The agent delivery system of any of the previous paragraphs A1-A6, wherein an inner diameter of a distal portion of the elongated tubular member multiplied by pi

(π) is greater than the first circumference of the pleated and wrapped inflatable balloon with therapeutic agent disposed thereon and is constant or increasing proximally from the distal tip of the elongate tubular member to a point proximal to the proximal end of the working length of the inflatable balloon.

[57]. A8. The agent delivery system of paragraph A7, wherein the inner diameter of the elongated tubular member is constant over the length disposed about the inflatable balloon to the distal end of the elongated tubular member.

[58]. A9. The agent delivery system of paragraph A8, wherein the inner circumference of the elongated tubular member is equal to the transverse circumference of the pleated and wrapped inflatable balloon.

[59]. A10. The agent delivery system of paragraph A8, wherein the inner circumference of the elongated tubular member is greater than the transverse circumference of the pleated and wrapped inflatable balloon.

[60]. A11. The agent delivery system of paragraph A10, wherein a substantially annular gap between the inner circumference of the portion of elongated tubular member that is disposed about the pleased and wrapped inflatable balloon and the transverse circumference of the pleated and wrapped inflatable balloon is greater than 0.0000 inches and less than 0.050 inches.

[61]. A12. The agent delivery system of paragraph A11, wherein the substantially annular gap is between 0.002 inches and 0.003 inches.

[62]. A13. The agent delivery system of paragraph A7, wherein the lumen of the elongated tubular member is tapered from the distal end of the elongated tubular member and increases proximally.

[63]. A14. The agent delivery system of paragraph A13, wherein a substantially annular gap between the inner circumference of the elongated tubular member and a circumference of the balloon catheter transverse to the longitudinal axis of the balloon catheter is greater than 0.0000 inches and less than 0.050 inches.

[64]. A15. The agent delivery system of paragraph A14, wherein the substantially annular gap between the inner circumference of the portion of elongated tubular member that is disposed about the pleased and wrapped inflatable balloon and the transverse circumference of the pleated and wrapped inflatable balloon is between 0.002 inches and 0.003 inches.

[65]. A16. The agent delivery system of any of the previous paragraphs A1 –A15, wherein a wall thickness of the elongated tubular member is constant.

[66]. A17. The agent delivery system of any of the previous paragraphs A1 –A16, wherein a wall thickness of the elongated tubular member is between 0.0005 inches and 0.050 inches.

[67]. A18. The agent delivery system of any of the previous paragraphs A1 –A17, wherein the distal end of the elongated tubular member is radiopaque.

[68]. A19.The agent delivery system of any of the previous paragraphs A1 –A18, further comprising lubricious coating on the outer surface of a distal portion of the tubular member terminating at the distal end.

[69]. A20. The agent delivery system of any of the previous paragraphs A1 –A19, further comprising lubricious coating on the inner surface of a distal portion of the tubular member terminating at the distal end.

[70]. A21. The agent delivery system of any of the previous paragraphs A1 –A20, wherein the tubular member includes a metal reinforcing layer.

[71]. A22.The agent delivery system of any of the previous paragraphs A1 –A21, wherein the tubular member is free of a metal reinforcing layer.

[72]. A23. The agent delivery system of any of the previous paragraphs A1 –A22, wherein the therapeutic agent is paclitaxel or sirolimus or their analogs.

[73]. A24. The agent delivery system of any of the previous paragraphs A1 –A23, wherein the therapeutic agent is present in an excipient.

[74]. A25. The agent delivery system of any of the previous paragraphs A1 –A24, wherein the excipient is selected from the group consisting of urea, polyethyleneglycol, a terpenoid, Iopramid, butyryl-trihexyl-citrate (BTHC) and any compound disclosed in a patent application assigned to SurModics.

[75]. A26. The agent delivery system of any of the previous paragraphs A1 –A25, wherein the enlarged portion comprises a conical distal portion.

[76]. A27. The agent delivery system of any of the previous paragraphs A1 –A26, wherein the enlarged portion comprises a maximum diameter proximal to the conical distal portion.

[77]. A28. The agent delivery system of paragraph A27, wherein the enlarged portion comprises a portion proximal to the maximum diameter that tapers from the maximum diameter to a smaller diameter.

[78]. A29. The agent delivery system of paragraph A28, wherein the enlarged portion comprises a portion proximal to the maximum diameter that tapers proximally from the maximum diameter to a smaller diameter.

[79]. A30.The agent delivery system of paragraph A29, wherein the taper of the portion proximal to the maximum diameter is constant.

[80]. A31. The agent delivery system of paragraph A30, wherein the portion proximal to the maximum diameter is now the first proximal portion and the enlarged portion comprises a second proximal portion proximal to the first proximal portion.

[81]. A32. The agent delivery system of paragraph A31, wherein the second proximal portion has a constant outer diameter.

[82]. A33. The agent delivery system of paragraph A31, wherein the second proximal portion has a radiused cross section, forming a section of a sphere.

[83]. A34.The agent delivery system of any of paragraphs A1 to A25, wherein the enlarged portion comprises a sphere having a diameter on the longitudinal axis and a cylindrical lumen co-axial with the longitudinal axis.

[84]. A35. The agent delivery system of any of the previous paragraphs A1-A34, wherein the enlarged portion has a cylindrical lumen co-axial with the longitudinal axis, which is a part of the lumen of the catheter shaft.

[85]. A36. The agent delivery system of any of the paragraphs A5 to A35, wherein the distal leg of the balloon is sealably connected to the distal end of the first tubular member of the catheter shaft.

[86]. A37. The agent delivery system of any of paragraphs A5 to A36, wherein the enlarged portion comprises a distal tip sealably connected to the distal end of the first tubular member of the catheter shaft.

[87]. A38. The agent delivery system of any of the previous paragraphs A1-A37, wherein a bare metal expandable stent is disposed about the pleated and wrapped inflatable balloon, over the therapeutic agent disposed on the balloon.

[88]. A39. The agent delivery system of any of the previous paragraphs A1 to A37, wherein the system is free of a stent disposed about the pleated and wrapped inflatable balloon, over the therapeutic agent disposed on the balloon, when the elongated tubular member is disposed about the balloon.

[89]. Detailed Description of the Figures

[90]. FIG. 1 illustrates a first embodiment of a drug delivery system. As illustrated, drug delivery system 100 has a balloon angioplasty catheter 102 having a longitudinal axis 104 and a proximal end 106, a distal end 108, a length 110 inbetween. Balloon angioplasty catheter 102 has catheter shaft 112 and a pleated inflatable balloon 114 (seen in FIGS. 2, 4, and 5) wrapped around an inner member 116 (seen in FIG. 4) of catheter shaft 112. Pleated inflatable balloon 114 has an initial loading of therapeutic agent 118 (seen in FIG. 5) disposed thereon. Balloon angioplasty catheter 102 has an enlarged portion 120 distal to the pleated and wrapped inflatable balloon 114. Drug delivery system 100 has a retractable tubular member 122 with a proximal end 124, a distal end 126, and a lumen 128 therebetween (seen best in FIGS. 4, 6A, 6B, and 6C) and a length 130. Distal end 126 of retractable tubular member 122 is distal to pleated and wrapped inflatable balloon 114 (seen best in FIG. 4) and is in contact with enlarged portion 120 of balloon catheter 102. Balloon catheter 102 has a hub 132 that includes two lumens 134, 136, one (134) for inflating the balloon and one (136) for receiving a guide wire, in a standard Y connector configuration. As illustrated in FIG. 1, balloon catheter 102 may also have a strain relief 140. Retractable tubular member 122 has a hub 142 with flanges 144 for ease of gripping and twisting the proximal end. Retractable tubular member 122 has a strain relief 146. Retractable tubular member 122 has a radiopaque tip 148. The circumference, here a diameter, of distal end 126 of retractable tubular member 122 (which is the distal end of radiopaque tip 148) is in contact with a matching circumference 150, as seen in FIG. 4, of enlarged portion 120 of balloon catheter 102. Retractable tubular member 122 is selectively retractable from a position surrounding pleated and wrapped inflatable balloon 114, as shown in FIG. 2. Retractable tubular member 122 may be selectively secured in place to prevent unintentional translation or rotation of retractable tubular member with respect to balloon catheter 102. Such selective securing device may also provide sealing contact between retractable tubular member 122 and balloon catheter shaft 112.

[91]. FIG. 2 illustrates drug delivery system 100 of FIG. 1 with retractable tubular member 122 in a (fully) retracted position with proximal end 124 in mechanical contact with strain relief 140 of balloon catheter 102. If retractable tubular member 122 was secured to balloon catheter shaft 112 when in the protective position, the selective securing device was released permitting at least proximal translation of retractable tubular member 122 with respect to balloon catheter

102 or, additionally or alternatively, the distal translation of balloon catheter102 with respect to retractable tubular member 122. When retractable tubular member 122 and the pleated and wrapped inflatable balloon 114 are no longer co-axial (i.e., retractable tubular member 122 no longer surrounds balloon 114), balloon 114 may be inflated to bring its working surface in contact with the lesion surface to dilate the stenosis and transfer at least some of the initially loaded therapeutic agent 118 to the vessel wall.

[92]. In FIG. 2, enlarged portion 120 may be fully seen in side view, showing its radiused longitudinal profile both proximal and distal to its maximum dimension, and its location distal to the pleated and wrapped balloon 114.

[93]. FIG. 3 illustrates an embodiment of a retractable tubular member 122 which has a proximal end 124, a distal end 126, a length 130, and a lumen (128) therebetween. Retractable tubular member 122, which is elongated, has a hub 142 with flanges 144, and a strain relief 146. A distal section 156 of retractable tubular member 122 is radiopaque. Such radiopaque material may be a band embedded in a polymer tube or may be dispersed in a polymeric tubular member (148) of the same wall thickness as the remainder of the tubular member.

[94]. FIG. 4 illustrates a cross-section in the same plane as the longitudinal axis 104 of balloon catheter 102, along the section A-A of FIG. 1. Here, retractable tubular member 122 is shown with its distal end 126 in circumferential contact with enlarged portion 120. In embodiments where the distal section 156 of tubular member 122 is elastomeric polymer, it may stretch to increase in diameter and conform to the outer surface of enlarged portion 120, creating a greater area of contact between the two. A first shaft or tubular member 116 of catheter shaft 112 is surrounded by distal balloon leg 162, which is sealed around it. First tubular member 116 is illustrated with a lumen 164 therethrough, which is intended to receive a guide wire (aka guide wire lumen). A second shaft or tubular member 166 of catheter shaft 112 surrounds at least a portion of first tubular member 116, and the two create an annular lumen 168 therebetween, which is intended to serve as an inflation lumen for the fluid used to inflate balloon 114 (aka inflation lumen). Proximal balloon leg 170 is sealed to a distal portion of second tubular member 166. Inflation lumen 168 is in fluid communication with the interior 172 of inflatable balloon 114. Pleated and wrapped balloon 114 has an effective diameter, which is the diameter of the smallest circle which can enclose the shape in the cross-section transverse to the longitudinal axis 104 (like shown in FIG. 5).

[95]. FIG. 4 also illustrates the gap 174 between the pleated and wrapped balloon 114 and the inner surface176 of the retractable tubular member 122. It is noted that the actual gap on the opposite side of a pleated and wrapped balloon may not be the same dimension, due to the number of pleats and/or the non-circular circumference of a pleated and wrapped balloon. However, if the gap 174 is calculated assuming a circle having the effective diameter of the pleated and wrapped balloon 114 is co-axial with the circle on the inner surface 176 of tubular member 122, then the gap 174 on either side will be equal to one half of the inner diameter 178 of the tubular member 122 and the effective diameter 180 of the pleated and wrapped balloon 114. In FIG. 4, the gap 174 is constant along the entire working length of balloon 114.

[96]. FIG. 4 also illustrates an enlarged portion 120 having a spherical shape 182 with maximum cross-sectional (transverse to the longitudinal axis 104) diameter $D_{MAX}$, labeled as 152. Enlarged portion 120 may be constructed of a separate piece bonded to, by heat or adhesive, the first tubular member 116 and/or to the previously sealed distal balloon leg 162 and first tubular member 116. FIG. 4 shows a constant taper tapered portion 184 distal to the spherical portion 182.

[97]. FIG. 5 illustrates a cross-section taken transverse to the longitudinal axis of the balloon catheter. The retractable tubular member 122 can be seen with a circular cross section and balloon 114 has three pleats which have been wrapped clockwise about first tubular member (not shown for simplicity, but co-axial with retractable tubular member 122). FIG. 5 illustrates with "x" the initially loaded therapeutic agent, optionally in a carrier or excipient. FIG. 5 illustrates the annular gap 174 between the circle with the effective diameter 180 of the pleated and wrapped balloon 114 and the inner surface 176 of retractable tubular member 122

[98]. FIG. 6A illustrates a constant wall thickness retractable tubular member 186 that tapers from a larger proximal end 190 to a smaller distal end 188 with a lumen 128 therethrough. While illustrated with a single tubular composition, alternate embodiments have a composite construction as described earlier.

[99]. FIG. 6B illustrates a proximally increasing wall thickness retractable tubular member 192 that has a constant inner diameter, $d_{ID}$, a distal outer diameter, $d_{DOD}$, and a proximal outer diameter, $d_{POD}$, and lumen 128 therethrough. While illustrated with a single tubular composition, alternate embodiments have a composite construction as described earlier.

[100]. FIG. 6C illustrates a constant wall thickness retractable tubular member 194 that has a constant inner diameter and a constant outer diameter and a lumen 128 therethrough. While illustrated with a single tubular composition, alternate embodiments have a composite construction as described earlier.

[101]. FIG. 7A illustrates a side view of a first distal tip 196 that may be assembled to first tubular member 116 of balloon catheter and/or to distal leg 162 of balloon 114 to provide a second embodiment 198 of enlarged portion. First distal tip 196 has a proximal end 200 and a distal end 202 and a maximum dimension portion 204 in between the proximal and distal end. Proximal to the maximum dimension portion 204 is a proximally tapering proximal tapered section 206. Distal to the maximum dimension portion 204 is a distally tapering proximal tapered section 208, with reduced angle and greater length than the proximal tapered portion. Proximal to the proximal tapered section 206 is a constant diameter portion 210 having an outer diameter equal to the minimum diameter in the proximal tapered portion 206. The maximum dimension portion 204 has a length and is of constant diameter. Maximum dimension portion has a glue port 212, which is a hole from the outer surface to the proximal lumen through which adhesive may be injected to the annular space between the distal tip and the tubular member to which is it to be sealed. Glue ports are optional, and may be omitted if heat bonding is to be used for sealing. Enlarged portions that are integral to the first tubular member will have the same outer dimensions and shape as the distal tip illustrated here (but will have material instead of the glue port).

[102]. FIG. 7B illustrates a cross-section along view lines A-A of FIG. 7A. Lumen 214 between the proximal and distal ends may be seen. Lumen 214 includes a proximal lumen 216 and distal lumen 218 in fluid communication. The diameter of distal lumen 218 matches the inner diameter of the distal end of first tubular member 116. The diameter of proximal lumen 216 matched the outer diameter of the first tubular member 116, or if being sealed to the distal leg 162 of the balloon 114, the outer diameter of the distal leg 162 of the balloon 114.

[103]. FIG. 7C is a perspective view of the distal tip of FIGS. 7A and 7B, showing the conical shape of the proximal and distal tapered portions, and the cylindrical shape of the maximum dimension portion and the second proximal portion.

[104]. FIG. 8A illustrates a side view of a second distal tip 222 that may be assembled to first tubular member 116 of balloon catheter or to distal leg 162 of balloon 114 to provide a third

embodiment 224 of enlarged portion. Second distal tip 222 has a proximal end 226 and a distal end 228 and a maximum dimension portion 230 in between the proximal and distal end. Proximal to the maximum dimension portion 230 is a proximally tapering first proximal tapered portion 232. The length of the proximal tapered section is very short compared to the first distal tip, on the order of one-fourth the length. Proximal to the first proximal tapered portion 232 is a proximally tapering second tapered portion 234. The proximal taper of the second tapered portion is not constant but follows a radius from the larger diameter to the terminating smaller diameter. The maximum dimension portion 230 has a length and is of constant diameter. Maximum dimension portion has a glue port 236 , which is a hole from the outer surface to the proximal lumen through which adhesive may be injected to the annular space between the distal tip and the tubular member to which is it to be sealed. Glue ports are optional, and may be omitted if heat bonding is to be used for sealing. Distal to the maximum dimension portion is a distally tapering proximal tapered section 238, with reduced angle and greater length than the first proximal tapered portion 232. Enlarged portions that are integral to the first tubular member will have the same outer dimensions and shape as the distal tip illustrated here (but will have material instead of the glue port).

[105]. FIG. 8B illustrates a cross-section along view lines A-A of FIG. 8A. Lumen 242 between the proximal and distal ends may be seen. Lumen 242 includes a proximal lumen 244 and distal lumen 246 in fluid communication. The diameter of distal lumen 246 matches the inner diameter of first tubular member 116. The diameter of proximal lumen 244 matches the outer diameter of the first tubular member 116, or if being sealed to the distal leg 162 of the balloon 114, the outer diameter of the distal leg 162 of the balloon 144.

[106]. FIG. 8C is a perspective view of the distal tip of FIGS. 8A and 8B, showing the conical shape of the first proximal tapered portion and distal tapered portion, and the cylindrical shape of the maximum dimension portion, and the spherical taper of the second proximal tapered portion.

[107]. FIG. 9A illustrates a side view of a third distal tip 248 that may be assembled to first tubular member 116 of balloon catheter or to distal leg 162 of balloon 114 to provide a fourth embodiment 250 of enlarged portion. Distal tip 248 has a proximal end 252 and a distal end 254, a length 256 and a lumen therethrough. Distal tip 248 has a maximum dimension portion 260 and a first proximal tapered portion proximal 261 to maximum dimension portion 260.

Proximal to the first proximal tapered portion 261 is a cylindrical section 262 of length 264 and distal tip terminates at the proximal end with a beveled proximal tip 264. Distal to maximum dimension portion 260 is a first distally tapering distal tapered portion 266. Distal to first distal tapered portion 266 is a second distally tapering distal tapered portion 268. The angle of the second distal tapered portion 268 is less than that of the first distal tapered portion 266 and its length is longer. Distal to the second distal tapered portion 268 is a constant outer diameter section 270 over a length greater than the length of the second distal tapered portion. The distal tip 248 terminates with a rounded portion that is a third distal tapered portion 272, where the taper follows a radius from the constant outer section's diameter to the diameter of the lumen.

[108]. FIG. 9B illustrates a cross-section along view lines A-A of FIG. 9A. Lumen 274 between the proximal and distal ends may be seen. Lumen 274 includes a proximal lumen 276 and distal lumen 278 in fluid communication. The diameter of distal lumen 278 matches the inner diameter of the distal end of first tubular member 116. The diameter of proximal lumen 276 matches the outer diameter of the first tubular member 116, or if being sealed to the distal leg 162 of the balloon 114, the outer diameter of the distal leg 162 of the balloon 144.

[109]. FIG. 9C is a perspective view of the distal tip of FIGS. 9A and 9B, showing the conical shape of the proximal tapered portion and first and second distal tapered portions, and the cylindrical shape of the maximum dimension portion, and the third distal portion and second proximal portion, and the spherical taper of the third tapered portion.

[110]. Aspects of the present invention have been described herein with reference to certain exemplary or preferred embodiments. These embodiments are offered as merely illustrative, not limiting, of the scope of the present invention. Certain alterations or modifications which are possible include the substitution of selected features from one embodiment to another, the combination of selected features from more than one embodiment, and the elimination of certain features of described embodiments. Other alterations or modifications may be apparent to those skilled in the art in light of instant disclosure without departing from the spirit or scope of the present invention, which is defined solely with reference to the following appended claims.

CLAIMS

1. An agent delivery system comprising:

a balloon angioplasty catheter having a longitudinal axis comprising

a catheter shaft having proximal end, a distal end, and a length inbetween;

an inflatable balloon pleated and wrapped about a distal portion of the catheter shaft, the pleated and wrapped inflatable balloon with therapeutic agent disposed thereon having a first circumference transverse to the longitudinal axis;

an enlarged portion with a circumference transverse to the longitudinal axis greater than the first circumference of the pleated and wrapped inflatable balloon, the enlarged portion located distal to the pleated and wrapped inflatable balloon on the catheter shaft; and

an elongated tubular member having a proximal end and a distal end and a lumen therebetween, wherein the balloon angioplasty catheter is located within the lumen therebetween, the distal end of the tubular member is proximal to the distal end of the distal tip of the balloon angioplasty catheter, and the distal end of the tubular member is in contact with a circumference of the enlarged portion transverse to the longitudinal axis.

2. The agent delivery system of claim 1, wherein a distal end of the enlarged portion and the distal end of the catheter shaft are in one plane transverse to the longitudinal axis.

3. The agent delivery system of claim 2, wherein the distal end of the enlarged portion and the distal end of the catheter shaft are one and the same.

4. The agent delivery system of claim 1, wherein a distal end of the enlarged portion and the distal end of the catheter shaft are located in different transverse planes to the longitudinal axis.

5. The agent delivery system of any of the previous claims, wherein the catheter shaft comprises:

a first tubular member having a proximal end and a distal end and lumen therebetween;

a second tubular member having a proximal end and a distal end and a lumen therebetween, disposed about at least a portion of the first tubular member, such that the first tubular member is

located within the lumen of the second tubular member and an annular inflation lumen is formed between the first and second tubular members;

wherein the inflatable balloon has a proximal leg, a distal leg, and a working length, the proximal leg is sealably connected to a distal portion of the second tubular member and the distal leg is disposed about a distal portion of the first tubular member and the annular inflation lumen is in fluid communication with an interior of the inflatable balloon.

6. The agent delivery system of any of claims 1 to 4, wherein the catheter shaft comprises:

a first tubular member having a length, a proximal end and a distal end, and lumen therebetween;

a second tubular member having a length, a proximal end and a distal end, and a lumen therebetween, disposed alongside at least a portion of the first tubular member, such that the first tubular member and the second tubular member are substantially parallel and connected to each other for at least a portion of their respective lengths;

wherein the inflatable balloon has a proximal leg, a distal leg, and a working length, the proximal leg is sealably connected to a distal portion of the second tubular member and a portion of the first tubular member, and the distal leg is disposed about a distal portion of the first tubular member and the lumen of the second tubular member is in fluid communication with an interior of the inflatable balloon.

7. The agent delivery system of any of the previous claims, wherein an inner diameter of a distal portion of the elongated tubular member multiplied by pi ($\pi$) is greater than the first circumference of the pleated and wrapped inflatable balloon with therapeutic agent disposed thereon and is constant or increasing proximally from the distal tip of the elongate tubular member to a point proximal to the proximal end of the working length of the inflatable balloon.

8. The agent delivery system of claim 7, wherein the inner diameter of the elongated tubular member is constant over the length disposed about the inflatable balloon to the distal end of the elongated tubular member.

9. The agent delivery system of claim 8, wherein the inner circumference of the elongated tubular member is equal to the transverse circumference of the pleated and wrapped inflatable balloon.

10. The agent delivery system of claim 8, wherein the inner circumference of the elongated tubular member is greater than the transverse circumference of the pleated and wrapped inflatable balloon.

11. The agent delivery system of claim 10, wherein a substantially annular gap between the inner circumference of the portion of elongated tubular member that is disposed about the pleased and wrapped inflatable balloon and the transverse circumference of the pleated and wrapped inflatable balloon is greater than 0.0000 inches and less than 0.050 inches.

12. The agent delivery system of claim 11, wherein the substantially annular gap is between 0.002 inches and 0.003 inches.

13. The agent delivery system of claim 7, wherein the lumen of the elongated tubular member is tapered from the distal end of the elongated tubular member and increases proximally.

14. The agent delivery system of claim 13, wherein a substantially annular gap between the inner circumference of the elongated tubular member and a circumference of the balloon catheter transverse to the longitudinal axis of the balloon catheter is greater than 0.0000 inches and less than 0.050 inches.

15. The agent delivery system of claim 14, wherein the substantially annular gap between the inner circumference of the portion of elongated tubular member that is disposed about the pleased and wrapped inflatable balloon and the transverse circumference of the pleated and wrapped inflatable balloon is between 0.002 inches and 0.003 inches.

16. The agent delivery system of any of the previous claims, wherein a wall thickness of the elongated tubular member is constant.

17. The agent delivery system of any of the previous claims, wherein a wall thickness of the elongated tubular member is between 0.0005 inches and 0.050 inches.

18. The agent delivery system of any of the previous claims, wherein the distal end of the elongated tubular member is radiopaque.

19. The agent delivery system of any of the previous claims, further comprising lubricious coating on the outer surface of a distal portion of the tubular member terminating at the distal end.

20. The agent delivery system of any of the previous claims, further comprising lubricious coating on the inner surface of a distal portion of the tubular member terminating at the distal end.

21. The agent delivery system of any of the previous claims wherein the tubular member includes a metal reinforcing layer.

22. The agent delivery system of any of the previous claims, wherein the tubular member is free of a metal reinforcing layer.

23. The agent delivery system of any of the previous claims, wherein the therapeutic agent is paclitaxel or sirolimus or their analogs.

24. The agent delivery system of any of the previous claims, wherein the therapeutic agent is present in an excipient.

25. The agent delivery system of any of the previous claims, wherein the excipient is selected from the group consisting of urea, polyethyleneglycol, a terpenoid, lopramid, butyryl-trihexyl-citrate (BTHC).

26. The agent delivery system of any of the previous claims, wherein the enlarged portion comprises a conical distal portion.

27. The agent delivery system of any of the previous claims, wherein the enlarged portion comprises a maximum diameter proximal to the conical distal portion.

28. The agent delivery system of claim 27, wherein the enlarged portion comprises a portion proximal to the maximum diameter that tapers from the maximum diameter to a smaller diameter.

29. The agent delivery system of claim 28, wherein the enlarged portion comprises a portion proximal to the maximum diameter that tapers proximally from the maximum diameter to a smaller diameter.

30. The agent delivery system of claim 29, wherein the taper of the portion proximal to the maximum diameter is constant.

31. The agent delivery system of claim 30, wherein the portion proximal to the maximum diameter is now the first proximal portion and the enlarged portion comprises a second proximal portion proximal to the first proximal portion.

32. The agent delivery system of claim 31, wherein the second proximal portion has a constant outer diameter.

33. The agent delivery system of claim 31, wherein the second proximal portion has a radiused cross section, forming a section of a sphere.

34. The agent delivery system of any of claims 1 to 25, wherein the enlarged portion comprises a sphere having a diameter on the longitudinal axis and a cylindrical lumen co-axial with the longitudinal axis.

35. The agent delivery system of any of the previous claims, wherein the enlarged portion has a cylindrical lumen co-axial with the longitudinal axis, which is a part of the lumen of the catheter shaft.

36. The agent delivery system of any of the claims 5 to 35, wherein the distal leg of the balloon is sealably connected to the distal end of the first tubular member of the catheter shaft.

37. The agent delivery system of any of claims 5 to 36, wherein the enlarged portion comprises a distal tip sealably connected to the distal end of the first tubular member of the catheter shaft.

38. The agent delivery system of any of the previous claims, wherein a bare metal expandable stent is disposed about the pleated and wrapped inflatable balloon, over the therapeutic agent disposed on the balloon.

39. The agent delivery system of any of the previous claims 1 to 37, wherein the system is free of a stent disposed about the pleated and wrapped inflatable balloon, over the therapeutic agent disposed on the balloon, when the elongated tubular member is disposed about the balloon.

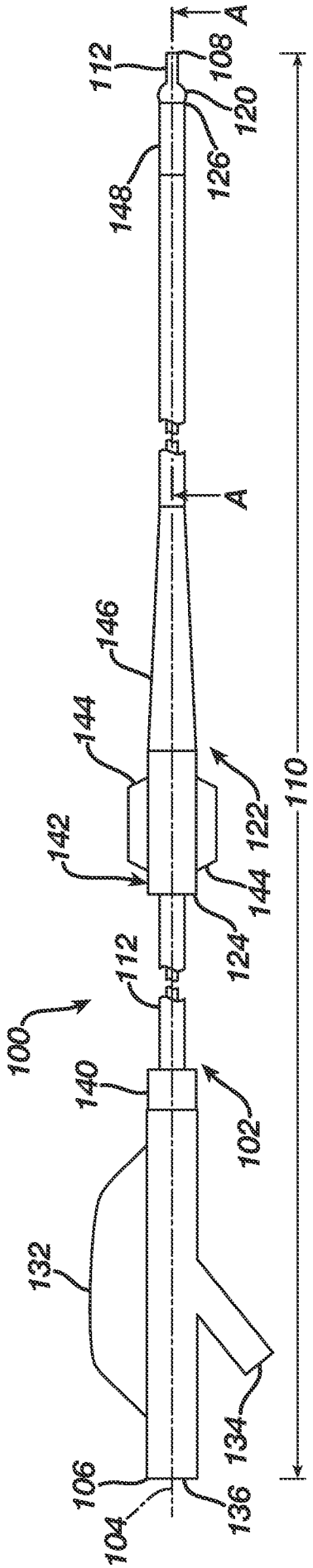
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FIG. 1

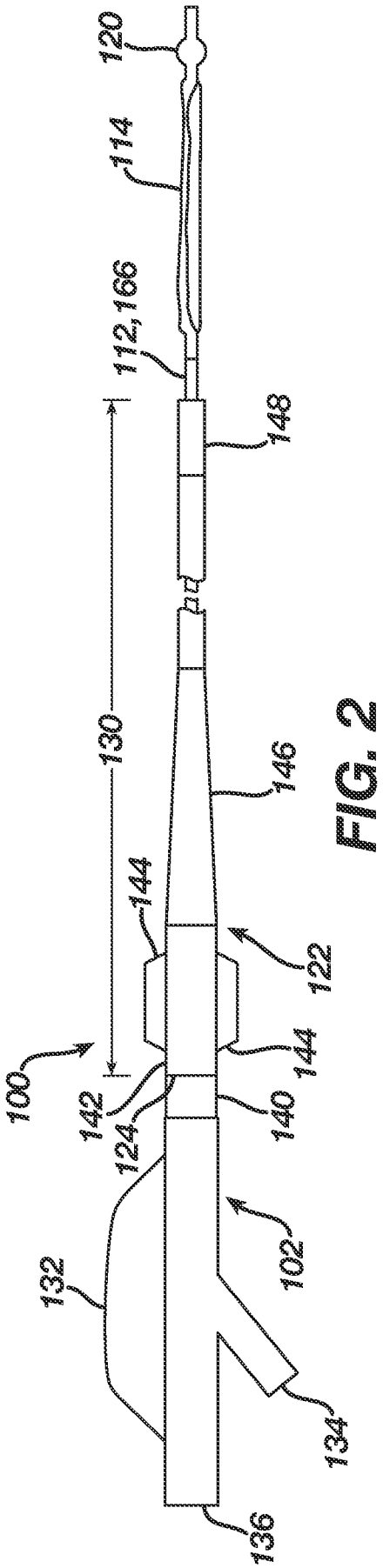
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FIG. 2

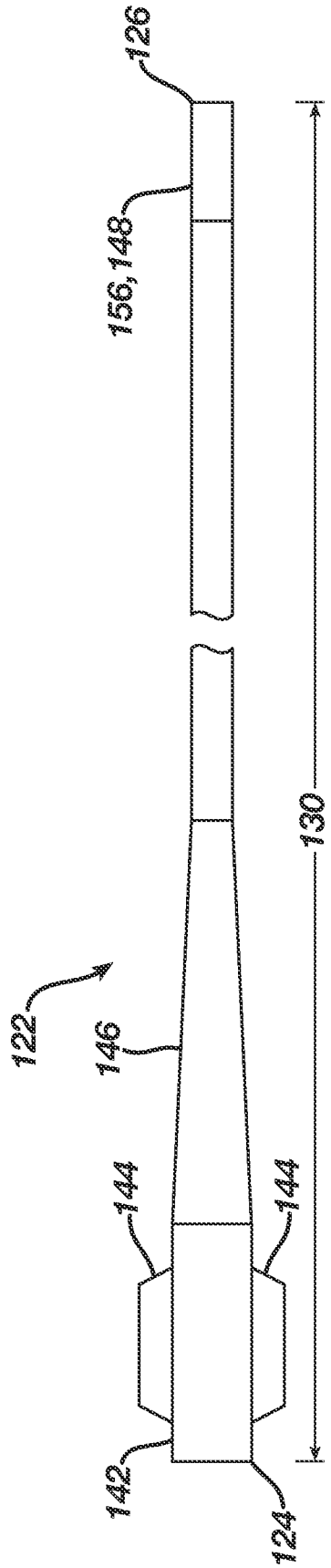
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FIG. 3

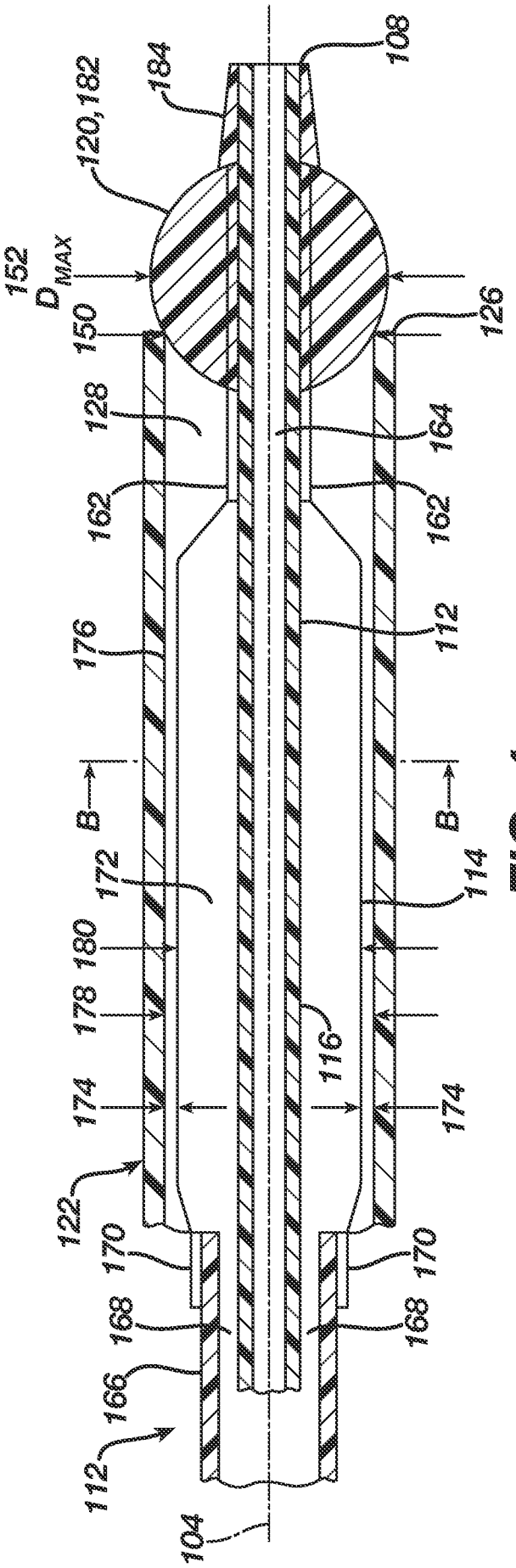
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FIG. 4

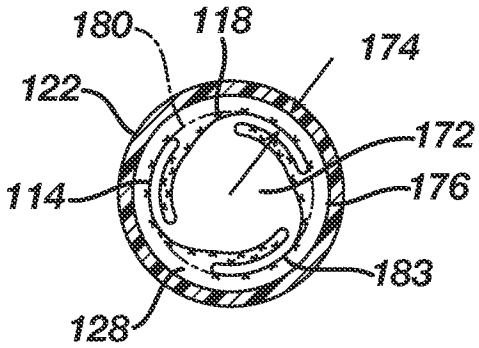


FIG. 5

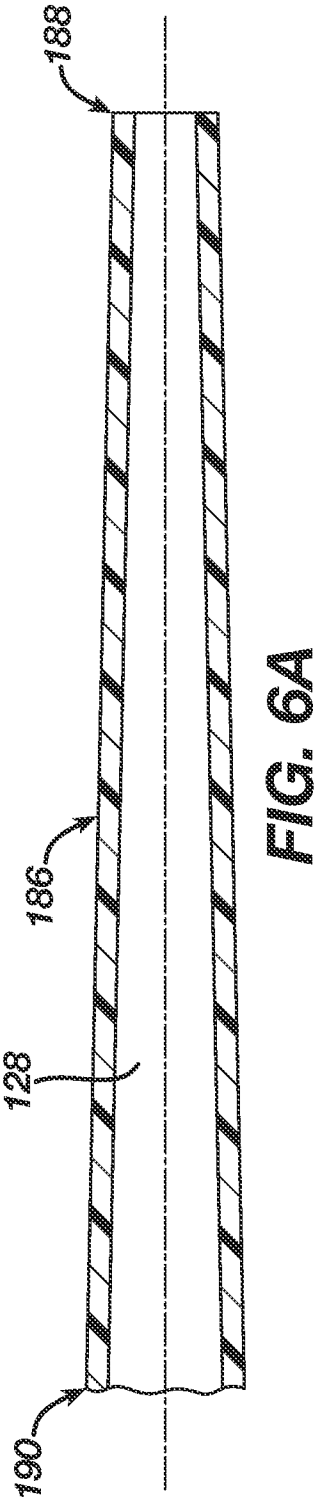


FIG. 6A

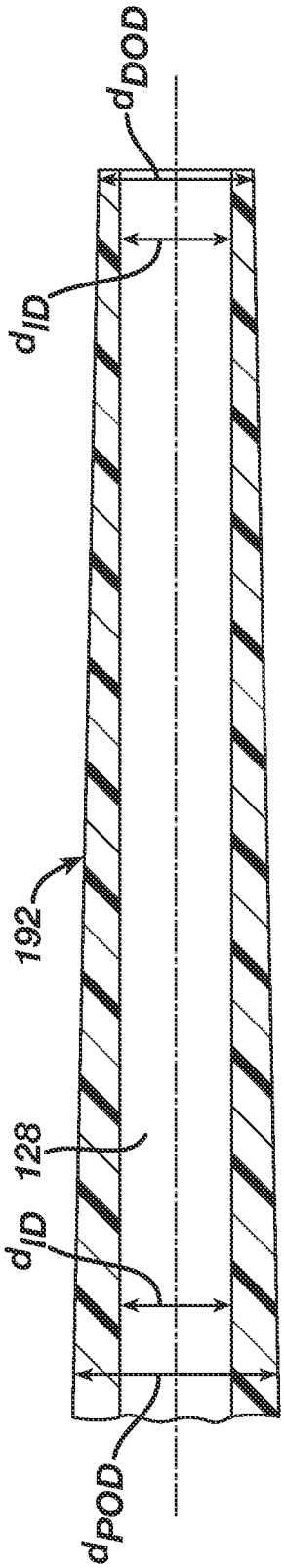


FIG. 6B

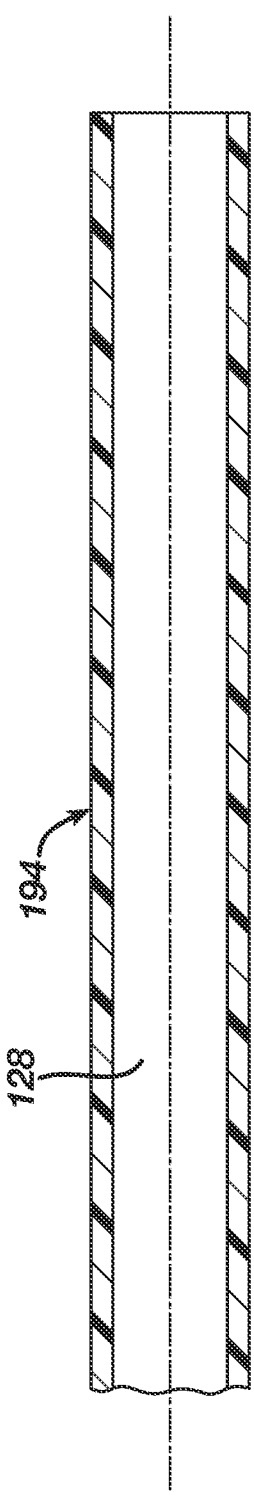


FIG. 6C

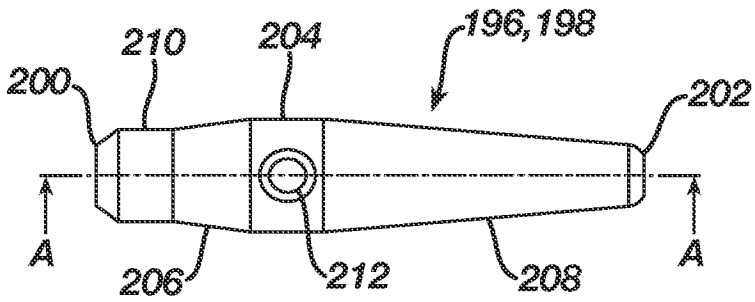


FIG. 7A

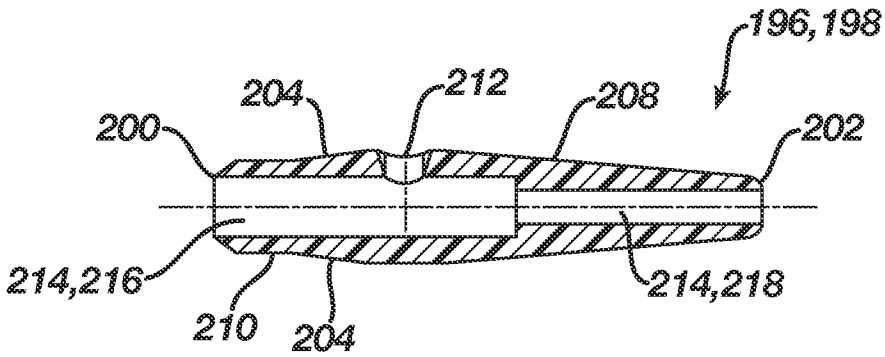


FIG. 7B

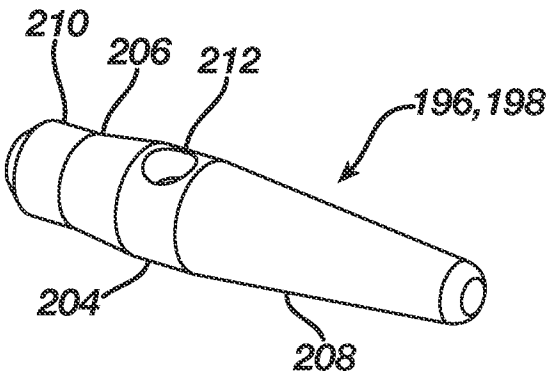


FIG. 7C

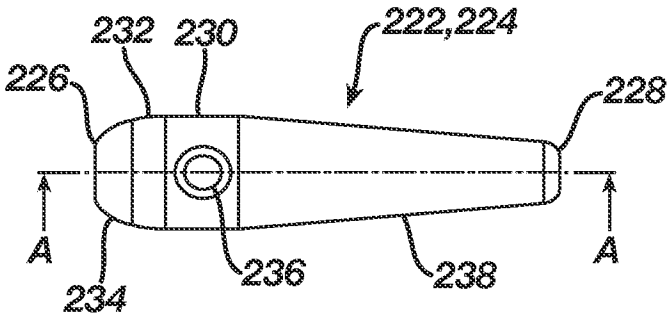


FIG. 8A

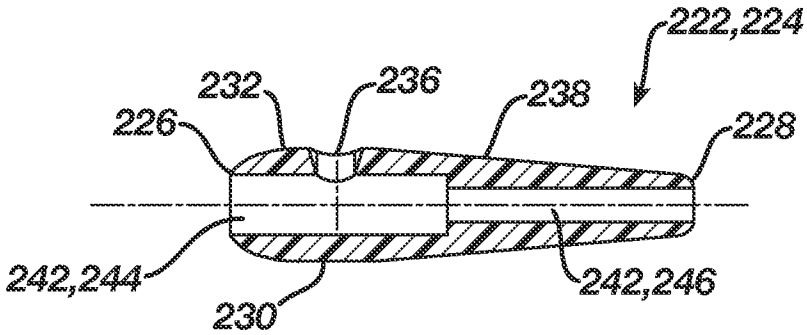


FIG. 8B

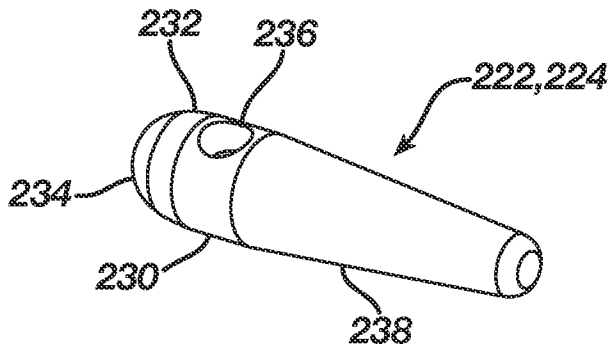


FIG. 8C

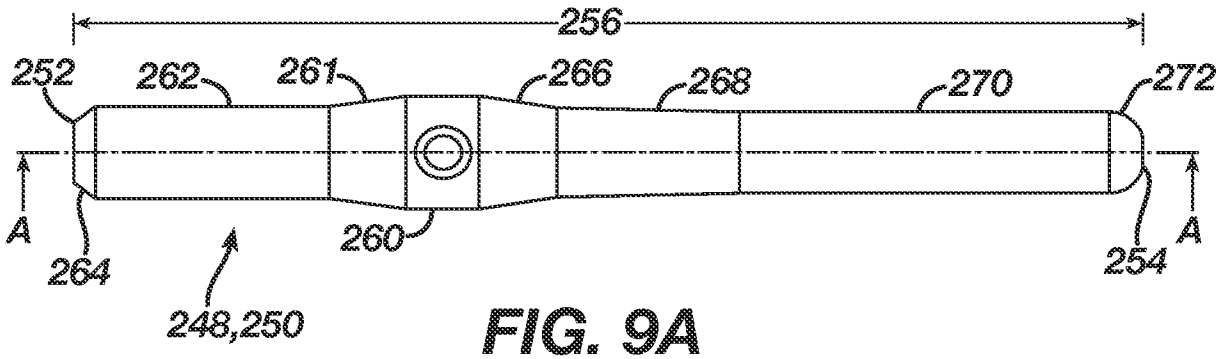


FIG. 9A

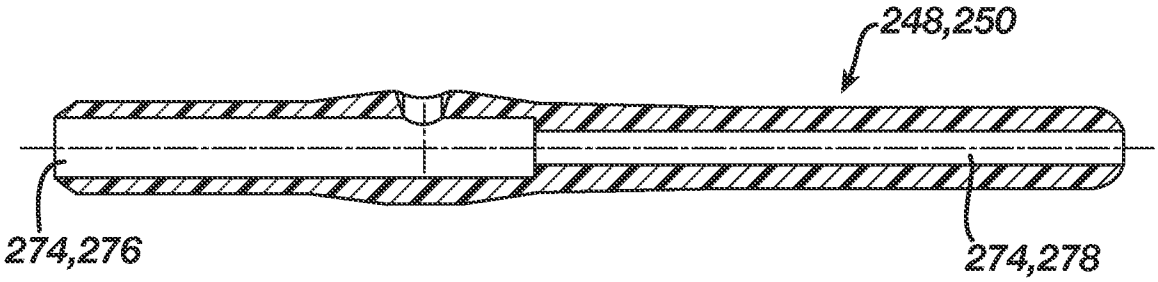


FIG. 9B

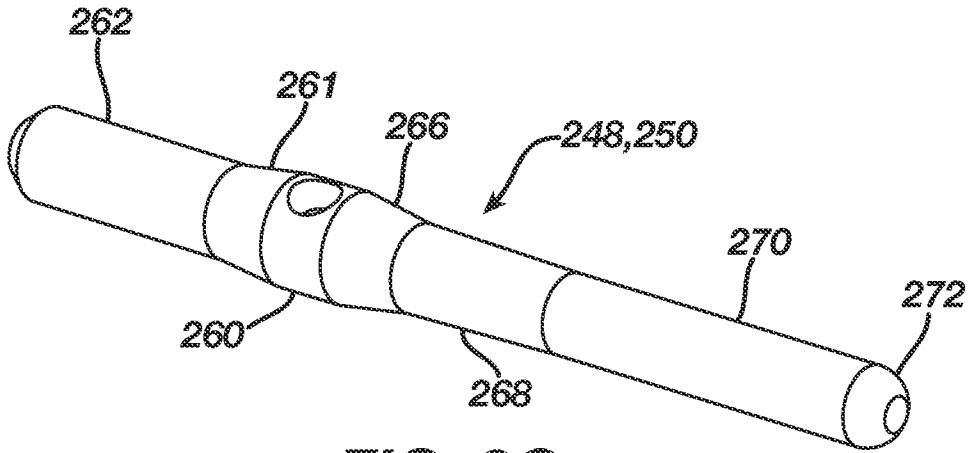


FIG. 9C

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/066788

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M25/10
ADD.

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)
A61M

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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2013/237950 A1 (GIANOTTI MARC [CH] ET AL) 12 September 2013 (2013-09-12)<br><br>paragraphs [0013], [0014], [0056], [0061], [0065], [0084], [0089]; figures 1a,1b,4,16 | 1-4, 7-33,35, 38,39 |
| X | WO 2009/005933 A1 (XTENT INC [US]; SNOW DAVID W [US]; RUANE PATRICK H [US])<br>8 January 2009 (2009-01-08)<br>paragraphs [0057], [0058], [0060] - [0066]; figures 1,2a,2b | 1-18, 23-33, 35-39 |
| X | US 2009/254063 A1 (OEPEN RANDOLF VON [US] ET AL) 8 October 2009 (2009-10-08)<br><br>paragraphs [0054], [0073] - [0079]; figures 1,1b,1c,2-4 | 1-4, 7-27,34, 35,38,39 |

-/--

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

[X] See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 March 2015 | 12/03/2015 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Bielsa, David |

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/066788

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| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2011/077731 A1 (LEE HENRY H [US] ET AL) 31 March 2011 (2011-03-31)<br><br>paragraphs [0056] - [0058]; figures 14-17<br>----- | 1-4, 7-17, 19-33, 35,38,39 |
| A | US 2002/133118 A1 (GERDTS MICHAEL [US] ET AL) 19 September 2002 (2002-09-19)<br>paragraphs [0020] - [0028]; figures 1,2<br>----- | 1-39 |
| A | US 2013/268051 A1 (ATLANI DAVID [FR] ET AL) 10 October 2013 (2013-10-10)<br>paragraphs [0029], [0086], [0091], [0093], [0094]; figure 7<br>----- | 1-39 |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/066788

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 2013237950 A1 | 12-09-2013 | NONE | |
| WO 2009005933 A1 | 08-01-2009 | US 2009105686 A1 | 23-04-2009 |
| | | WO 2009005933 A1 | 08-01-2009 |
| US 2009254063 A1 | 08-10-2009 | EP 2396068 A1 | 21-12-2011 |
| | | US 2009254063 A1 | 08-10-2009 |
| | | WO 2010093665 A1 | 19-08-2010 |
| US 2011077731 A1 | 31-03-2011 | NONE | |
| US 2002133118 A1 | 19-09-2002 | AT 466612 T | 15-05-2010 |
| | | AU 2006203615 A1 | 07-09-2006 |
| | | CA 2408866 A1 | 26-09-2002 |
| | | EP 1368085 A2 | 10-12-2003 |
| | | ES 2341219 T3 | 17-06-2010 |
| | | JP 2004519296 A | 02-07-2004 |
| | | US 2002133118 A1 | 19-09-2002 |
| | | US 2003199821 A1 | 23-10-2003 |
| | | US 2004167601 A1 | 26-08-2004 |
| | | US 2005171473 A1 | 04-08-2005 |
| | | US 2007016282 A1 | 18-01-2007 |
| | | US 2009105808 A1 | 23-04-2009 |
| | | US 2013226308 A1 | 29-08-2013 |
| | | WO 02074378 A2 | 26-09-2002 |
| US 2013268051 A1 | 10-10-2013 | CA 2825366 A1 | 09-08-2012 |
| | | EP 2670362 A1 | 11-12-2013 |
| | | FR 2970864 A1 | 03-08-2012 |
| | | JP 2014509219 A | 17-04-2014 |
| | | US 2013268051 A1 | 10-10-2013 |
| | | WO 2012104763 A1 | 09-08-2012 |