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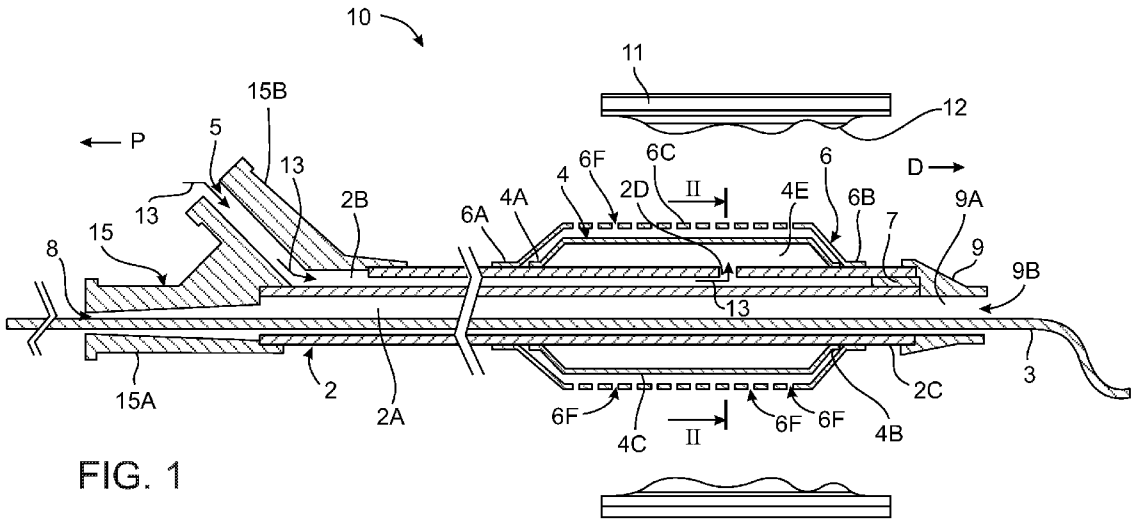

FIG. 1

(57) Abstract: A drug delivery catheter includes a shaft, an inflatable inner balloon attached to the shaft. The inflatable balloon has an outer surface coated with a drug or a composition including a drug. The catheter also includes a perforated outer balloon. The perforated outer balloon surrounds the inflatable inner balloon. The perforated balloon has multiple perforations therein. A method of delivering a drug to a treated site using the catheter includes inserting the catheter into a body cavity to dispose the perforated outer balloon in a site to be treated and inflating the inflatable balloon to treat the site and to deliver the drug to at least some regions of the treated site through the multiple perforations. The body cavity may be a blood vessel or any other body cavity.

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DRUG DELIVERY CATHETER AND METHOD OF USE THEREOF

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to drug delivery catheters and more particularly, but not exclusively, to a drug delivery catheter having an inflatable drug delivering inner balloon and a perforated outer balloon and methods of use thereof.

Drug coated balloons (DCB), emerged as a revascularization strategy that holds the promise of increasing target lesion revascularization (TLR) further and avoiding the need for stenting and reducing associated risks such as in-stent restenosis and fracture.

Ideally, DCBs are intended to maintain the native vessel and leave future treatment options open while maximizing the time to first lesion re-intervention.

Unlike standard percutaneous transluminal angioplasty (PTA) balloons, each DCB is comprised of a balloon, coated by an excipient (carrier matrix/polymer/ transfer agents; Polysorbate, Urea and the like) and a drug (Paclitaxel, Rapamycin, and the like). Different DCBs may differ in the drug dosage, the excipient, coating technology and balloon materials.

Drug delivery catheters are well known in the art. Such catheters may be, for example, angioplasty balloon catheters having an angioplasty balloon which is coated with a drug or a formulation or composition of matter containing a drug or a therapeutically active agent Such drugs may include, *inter alia*, anti-restenosis agents, anti-proliferative agents as well as anti coagulating agents. When such a catheter is used for performing angioplasty treatment such as opening a constricted atheromatous blood vessel such as an artery or a vein, the catheter is inserted into the vasculature and advanced (typically over a guide wire) until the angioplasty balloon is positioned within the constricted region of the blood vessel. After poisoning the catheter, the balloon is inflated and expanded to open or enlarge or dilate the occluded or constricted (stenotic) region of the vessel, as is known in the art. When the balloon is inflated, it comes in contact with the inner surface of the blood vessel and may deliver some of the drug or therapeutic composition to the walls of the blood vessel. The delivery may occur mechanically by adherence of some of the drug or therapeutic composition to the intimal layer upon contact with the drug coated outer surface of the balloon or by dissolution or

elution of the drug in the blood and diffusion of the drug into the intimal layer where the drug may exert a biologically therapeutic effect reducing or preventing proliferation of the blood vessel epithelial cells and the resulting restenosis of the treated vessel site.

A common problem of such prior art drug delivery catheters is that during the insertion of the catheter into the vasculature and the moving of the catheter within the vasculature to reach the treatment site, the drug or therapeutic composition coating the outer surface of the balloon is exposed to the blood contained in the vasculature, which may result in some of the drug or active ingredient in the therapeutic composition to dissolve or become dispersed in the blood before the balloon has reached the desired treatment site. This "washout" effect may be particularly problematic when the drug or active ingredient of the coating formulation is soluble in aqueous media. Some studies of some commercially available DCBs reveal that drug washout may result in some cases in loss of up to 80% of the deliverable drug before the catheter balloon reaches the treatment target, which may significantly reduces the desired therapeutic effect of the treatment.

Moreover, because the pathway through the vasculature needed for reaching the treatment site may be quite often tortuous and may narrow as one approaches the treatment site, the drug coated surface of the balloon may come in contact with the walls of the vasculature which may result in mechanically abrading and/or removing some of the coating of the balloon prior to reaching the treatment site. This dissolving of the active ingredient and/or mechanical degradation of the coating layer of the balloon may result in a reduction in the amount of drug or active ingredient which may be delivered to the treated site with concomitant reduction in treatment efficacy.

Furthermore, as some types of excipients used in DCBs result in flakiness of the composition coating the balloon of the DCB, the passage of the balloon through the vasculature may result not only in loss of drug but may also result in releasing flakes or particles of the coating into the blood stream which may adversely affect the treatment's success rate and may even result in an increase a patient mortality rate as compared to standard angioplasty.

There is therefore a long felt need for a safe and efficient DCB providing an efficient drug delivery to the target region by reducing drug washout and undesirable release of

particulate matter into the blood stream during insertion and passage of the DCB through the vasculature to the target site.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings in which like components are designated by like reference numerals. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the embodiments of the invention may be practiced.

In the drawings:

FIG. 1 is a schematic longitudinal cross sectional view illustrating a drug delivery catheter, in a non-inflated state, in accordance with an embodiment of the drug delivery catheters of the present application;

FIG. 2 is a schematic transversal cross sectional view of the catheter of Fig. 1 taken along the lines II-II when the inner balloon of the catheter is in a non-inflated state;

FIG. 3 is a schematic transversal cross-section of the catheter of Fig. 1 taken along the lines II-II, when the inner balloon of the catheter is in an inflated state;

FIG. 4 is a schematic cross sectional view illustrating part of an OVT drug delivery balloon catheter in an inflated state disposed in a blood vessel, in accordance with an embodiment of the catheters of the present invention;

FIG. 5 is a schematic longitudinal cross sectional view illustrating a rapid- exchange (RE) drug delivery catheter, in a non-inflated state, in accordance with an embodiment of the drug delivery catheters of the present application;

FIG. 6 is a schematic transversal cross sectional view of the catheter of Fig. 5 taken along the lines V-V when the inner balloon of the catheter is in a non-inflated state;

FIG. 7 is a schematic transversal cross-sectional view taken along the lines V-V of Fig. 5, illustrating the catheter of Fig. 5 when the inner balloon of the catheter is in an inflated state;

FIGs. 8 and 9 are schematic transversal cross-sectional views illustrating a drug delivery catheter having a folded inner balloon and a non-folded perforated outer

balloon in an non-inflated state and an inflated state, respectively, in accordance with some embodiments of the catheters of the present application;

FIGs. 10 and 11 are a schematic transversal cross-sectional views illustrating a drug delivery catheter having a folded inner balloon and a folded perforated outer balloon, in an non-inflated state and an inflated state, respectively, in accordance with some embodiments of the catheters of the present application;

FIGs. 12-13 are a schematic transversal cross-sectional views illustrating a drug delivery catheter having a non-folded inner balloon and a folded perforated outer balloon, in an non-inflated state and an inflated state, respectively, in accordance with some embodiments of the catheters of the present application;

FIGs. 14-16 are a schematic longitudinal cross-sectional views illustrating three different drug delivery catheter parts having three different configurations of attachment of the inner and outer balloons to the catheter, in accordance with some embodiments of the catheters of the present application;

FIG.17 is a schematic side view illustrating part of an assembled drug delivery catheter, in accordance with an embodiment of the catheters of the present application;

FIG. 18 is a schematic front view of the catheter of Fig. 17 as viewed in the direction indicated by the arrow F;

FIG. 19 is a schematic side view of the outer perforated balloon of the catheter of Fig. 17;

FIG. 20 is a schematic side view of the shaft and the inner drug coated balloon of the catheter of Fig. 17;

FIG. 21 is a schematic isometric view illustrating the assembled catheter part of Fig. 17;

FIG. 22 is a schematic longitudinal cross sectional view illustrating a rapid exchange (RE) drug delivery catheter having a catheter shaft including an outer conduit and an inner conduit, in accordance with an embodiment of the drug delivery catheters of the present application;

FIG. 23 is a schematic longitudinal cross sectional view illustrating an "over the wire" (OVT) drug delivery catheter having a catheter shaft including an outer conduit and an inner conduit, in accordance with an embodiment of the drug delivery catheters of the present application;

FIG. 24 is a schematic cross sectional view illustrating part of an OVT drug delivery balloon catheter, having a conically shaped inflatable inner balloon and a conically shaped perforated outer balloon, in accordance with an embodiment of the catheters of the present application; and

FIG. 25 is a schematic cross sectional view illustrating part of an OVT drug delivery balloon catheter having stepped inner and outer balloons illustrated in an inflated state, in accordance with an embodiment of the catheters of the present application.

SUMMARY OF THE INVENTION

There is therefore provided, in accordance with an embodiment of the present application, a catheter for delivering a drug. The catheter includes a shaft having an outer surface, an inflatable inner balloon sealingly attached to the shaft, the inflatable inner balloon has an outer surface and at least a portion of the outer surface is coated with a drug or a composition comprising a drug. The catheter also includes a perforated outer balloon sealingly attached to the shaft and/or to the inner balloon. The outer perforated balloon surrounds the inflatable inner balloon. The outer perforated balloon includes a plurality of perforations formed in at least a portion of the perforated outer balloon.

Furthermore, in accordance with some embodiments of the catheter, the shaft is a double lumen hollow shaft having a first lumen for inserting a guide wire there through and a second lumen for passing inflation fluid there through for inflating the inflatable inner balloon.

Furthermore, in accordance with some embodiments of the catheter, the catheter is configured as an "over the wire" (OVT) catheter and the first lumen has a proximal opening at a proximal end of the catheter and a distal opening at the distal end of the catheter for passing the catheter over a guide wire.

Furthermore, in accordance with some embodiments of the catheter, the catheter is configured as a rapid exchange (RE) catheter and the first lumen has an opening disposed on the shaft at a position located between the proximal end of the catheter and the proximal end of the perforated outer balloon. The first lumen has a second opening at the distal end thereof for passing the catheter over a guide wire.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the inflatable inner balloon is sealingly attached to a first region of the outer surface of the shaft, and the distal end of the inflatable inner balloon is sealingly attached to a second region of the outer surface of the shaft.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the perforated outer balloon is sealingly attached to a third region of the outer surface of the shaft and a distal end of the perforated outer balloon is sealingly attached to a fourth region of the outer surface of the shaft. The third region is disposed on the outer surface of the shaft proximal to the first region and the fourth region is disposed on the outer surface of the shaft distal to the second region.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is sealingly attached to the distal end of the inflatable inner balloon.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is sealingly attached to a third region of the outer surface of the shaft. The third region is disposed on the outer surface of the shaft distal to the second region.

Furthermore, in accordance with some embodiments of the catheter, a distal end of the perforated outer balloon is sealingly attached to the distal end of the inflatable inner balloon and a proximal end of the perforated outer balloon is sealingly attached to the outer surface of the shaft at a third region of the outer surface of the shaft. The third region is disposed on the outer surface proximal to the first region.

Furthermore, in accordance with some embodiments of the catheter, the shaft comprises a hollow outer conduit having a first lumen and a hollow inner conduit disposed within the first lumen. The inner conduit has a second lumen suitable for passage over a guide wire. The inner conduit is fixed relative to the outer conduit and is longitudinally unmovable within the second lumen of the inner conduit. A portion of a distal end of the inner conduit protrudes beyond the distal end of the outer conduit.

Furthermore, in accordance with some embodiments of the catheter, the catheter is configured as an "over the wire" (OVT) catheter in which the second lumen of the inner

conduit has a first opening disposed at a proximal end of the shaft and a second opening disposed at the distal end of the catheter, for passing the second lumen over a guide wire.

Furthermore, in accordance with some embodiments of the catheter, the catheter is configured as a rapid exchange (RE) catheter. The proximal end of the inner conduit is bent and is sealingly attached to a region of wall of the outer conduit such that the second lumen has a first opening disposed on an outer surface of the outer conduit at a position located between the proximal end of the catheter and the proximal end of the perforated outer balloon. The second lumen has a second opening disposed at a distal end of the inner conduit for passing the second lumen of the inner conduit over a guide wire.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the inflatable inner balloon is sealingly attached to a first region of an outer surface of the distal end of the outer conduit and a distal end of the inflatable inner balloon is sealingly attached to a second region of an outer surface of the portion of the distal end of the inner conduit that protrudes beyond the distal end of the outer conduit.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the perforated outer balloon is sealingly attached to a third region of the outer surface of the distal end of the outer conduit and a distal end of the perforated outer balloon is sealingly attached to a fourth region of the outer surface of the portion of the inner conduit that protrudes distally beyond the distal end of the outer conduit. The third region is disposed on the outer surface of the outer conduit proximal to the first region and the fourth region is disposed on the outer surface of the inner conduit distal to the second region.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is attached to the distal end of the inflatable inner balloon.

Furthermore, in accordance with some embodiments of the catheter, a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is sealingly attached to a third region of the outer surface of the inner conduit, the third region is disposed on the

outer surface of the portion of the inner conduit that protrudes distally beyond the distal end of the outer conduit distal to the second region.

Furthermore, in accordance with some embodiments of the catheter, a distal end of the perforated outer balloon is sealingly attached to the distal end of the inflatable inner balloon and a proximal end of the perforated outer balloon is sealingly attached to the outer surface of the outer conduit at a third region of the outer surface of the outer conduit, the third region is disposed on the outer surface of the outer conduit proximal to the first region.

Furthermore, in accordance with some embodiments of the catheter, the inner inflatable balloon is selected from, a substantially cylindrically shaped balloon, a substantially conically shaped balloon and a stepped balloon.

Furthermore, in accordance with some embodiments of the catheter, the perforated outer balloon is selected from a substantially cylindrically shaped balloon, a substantially conically shaped balloon and a stepped balloon.

Furthermore, in accordance with some embodiments of the catheter, the drug or composition comprising a drug includes one or more of a therapeutic substance, a diagnostic substance, a drug, a therapeutic composition, a medicament, a diagnostic composition, a physiologically active agent, a biochemically active agent, one or more living cells, DNA, RNA, a nucleic acid, a vector for delivering genetic material to cells in the treated site, an anti-inflammatory agent, an anti-restenosis agent, a cell proliferation inhibitory agent, a smooth muscle proliferation inhibiting agent, paclitaxel, rapamycin, everolimus, a vaso-active agent, a vaso dilating agent, a vaso constricting agent, an antibiotic agent, an anti-coagulative agent, a platelet aggregation inhibiting agent, an anti-fibrosis agent, a pharmaceutically acceptable vehicle, a lipid based vehicle, and any combinations thereof.

Furthermore, in accordance with some embodiments of the catheter, the drug or the composition comprising a drug are encapsulated is a drug carrier system selected from a nanoparticle based carrier system and liposomes.

Furthermore, in accordance with some embodiments of the catheter, the perforated outer balloon comprises a material selected from a compliant material, a semi-compliant material, a non-compliant material, a stretchable material, a non-stretchable material, an annealed stretchable material, a pre-stretched non-stretchable material that has

undergone molecular orienting by biaxial orienting processes, and any combinations thereof.

Furthermore, in accordance with some embodiments of the catheter, the inflatable inner balloon comprises a material selected from a compliant material, a semi-compliant material, a non-compliant material, a stretchable material, a non-stretchable material, an annealed stretchable material, a pre-stretched non-stretchable material that has undergone molecular orienting by biaxial orienting processes, and any combinations thereof.

Furthermore, in accordance with some embodiments of the catheter, the perforated outer balloon comprises a material selected from a polymer based material, Nylon® Nylon 12®, PET, a polyamide PA12, Grilamid® L25, Grilamid® L55, PA11, Polyether block amides PEBAX® 7233, PEBAX®7033, PEBAX® 6333), Grilflex® ELG 6260, Polyester, polyethylene, polyurethane and any combinations thereof.

Furthermore, in accordance with some embodiments of the catheter, the inflatable inner balloon comprises a material selected from a polymer based material, Nylon® Nylon 12®, PET, a polyamide PA12, Grilamid® L25, Grilamid® L55, PA11, Polyether block amides PEBAX® 7233, PEBAX®7033, PEBAX® 6333), Grilflex® ELG 6260, Polyester, polyethylene, polyurethane and any combinations thereof.

Furthermore, in accordance with some embodiments of the catheter, prior to inflation of the inflatable inner balloon, the inflatable inner balloon and the perforated outer balloon are arranged in an arrangement selected from: 1) The inner balloon is not folded and the outer balloon is not folded, 2) The inner balloon is not folded and the outer balloon is folded over the inner balloon, 3) The inner balloon is folded over the shaft and the outer balloon is not folded, and 4) The inner balloon is folded over the shaft and the outer balloon is folded over the inner balloon.

Furthermore, in accordance with some embodiments of the catheter, prior to inflation of the inner balloon, the outer perforated balloon is folded over the inner balloon and at least some perforations of the plurality of perforations of the perforated outer balloon are disposed within one or more folds of the outer perforated balloon.

Furthermore, in accordance with some embodiments of the catheter, inflating the inflatable inner balloon results in stretching of the outer perforated balloon and increasing the area of the plurality of perforations.

Furthermore, in accordance with some embodiments of the catheter, inflating the inflatable inner balloon causes portions of the outer surface of the inner inflatable balloon to curve and protrude from the plurality of perforations.

There is also provided, in accordance with the methods of the present application, a method of delivering a drug to a treatment site in a body cavity using the drug delivery catheters described hereinabove. The method includes the steps of inserting the drug delivery catheter into a body cavity to dispose the perforated outer balloon in a treatment site and inflating the inflatable balloon to treat the site and to deliver at least some of the drug to at least some regions of the treatment site through at least some perforations of the plurality of perforations.

Furthermore, in accordance with some embodiments of the method, the catheter also includes a stent disposed on the perforated outer balloon and the step of inflating also includes expanding and deploying the stent in the treatment site.

Furthermore, in accordance with some embodiments of the method, the body cavity is a blood vessel and the treated region is selected from an atheroma, a plaque and a stenosed region of the blood vessel.

Furthermore, in accordance with some embodiments of the method, the outer perforated balloon of the catheter is a stretchable balloon and the step of inflating also comprises stretching the perforated outer balloon to increase the area of the plurality of perforations.

Furthermore, in accordance with some embodiments of the method, the step of inflating also includes the step of causing at least some portions of the inflated drug coated inner balloon to protrude through the plurality of perforations beyond an outer surface of the outer perforated balloon and to contact at least some portions of the treatment site for facilitating transfer of the drug to the treatment site.

Furthermore, in accordance with some embodiments of the method, prior to the step of inflating, the outer perforated balloon is folded over the inner inflatable balloon and the step of inflating also includes the step of unfolding and expanding the outer perforated balloon.

Furthermore, in accordance with some embodiments of the method, the inflatable inner balloon is folded and the step of inflating also includes the step of unfolding and expanding the inner balloon.

Furthermore, in accordance with some embodiments of the method, the inflatable inner balloon is a folded balloon and the step of inflating also includes the step of unfolding the folded inner balloon.

Furthermore, in accordance with some embodiments of the method, the perforated outer balloon is not folded and is a stretchable balloon and the step of inflating also includes the step of expanding the stretchable perforated outer balloon.

Furthermore, in accordance with some embodiments, the method also includes, prior to the step of inflating, the step of protecting by the perforated outer balloon a drug coated on an outer surface of the inflatable inner balloon.

Furthermore, in accordance with some embodiments of the method, at least the perforated outer balloon is a folded balloon having folds, and wherein the method also includes the step of protecting by the folds of the folded perforated outer balloon at least some perforations of the plurality of perforations from penetration of blood or a body fluid, during the step of inserting.

Furthermore, in accordance with some embodiments of the method, the drug-delivering catheter is selected from an over the wire (OVT) catheter and a rapid exchange (RE) catheter and wherein the step of inserting comprises inserting the catheter into the body cavity over a guide wire.

Furthermore, in accordance with some embodiments of the method, the drug or composition comprising a drug coating the outer surface of the inflatable inner balloon includes one or more of a therapeutic substance, a diagnostic substance, a drug, a therapeutic composition, a medicament, a diagnostic composition, a physiologically active agent, a biochemically active agent, one or more living cells, DNA, RNA, a nucleic acid, a vector for delivering genetic material to cells in the treated site, an anti-inflammatory agent, an anti-restenosis agent, a cell proliferation inhibitory agent, a smooth muscle proliferation inhibiting agent, paclitaxel, rapamycin, everolimus, a vaso-active agent, a vaso dilating agent, a vaso constricting agent, an antibiotic agent, an anti-coagulative agent, a platelet aggregation inhibiting agent, an anti-fibrosis agent, a pharmaceutically acceptable vehicle, a lipid based vehicle, and any combinations thereof.

Finally, in accordance with some embodiments of the method, the method also includes the step of inserting a medical device and/or a diagnostic device through a lumen formed in the catheter shaft.

DETAILED DESCRIPTION OF THE SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to drug delivery catheters and more particularly, but not exclusively, to a drug delivery catheter having a perforated outer balloon and methods of use thereof.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or illustrated in the drawings and/or the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. It is expected that during the life of a patent maturing from this application many relevant catheter constructing methods and catheter and balloon construction materials as well as many new types or drugs and/or therapeutic compositions for preventing or reducing restenosis may be developed and the scope of the terms "balloon" and "angioplasty balloon" "catheter" and "drug" or "therapeutic composition" and "active ingredient" and "active agent" are intended to include all such new technologies, materials and chemical compounds or therapeutic agents *a priori*.

As used herein the term "about" refers to ± 10 %. The word "exemplary" is used herein to mean "serving as an example, instance or illustration." Any embodiment described as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments and/or to exclude the incorporation of features from other embodiments.

The word "optionally" is used herein to mean "is provided in some embodiments and not provided in other embodiments." Any particular embodiment of the invention may include a plurality of "optional" features unless such features conflict.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

The term "preferably" means "preferably but not obligatorily".

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicated number "to" a second indicated number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals there between.

It is also noted that the term "drug coated balloon" and its conjugates means a balloon having an outer surface to which an amount of drug or drug containing formulation or a drug containing mixture of substances has been applied or added. The drug may be coated onto the outer surface of the balloon or may be applied to the outer surface of the balloon by any other suitable method known in the art. Thus, the word "coated" is not used in a limited sense and should be construed to broadly mean also that the drug has been added or applied or adhered to the balloon using any method of application known in the art. Furthermore, it is noted that the term "drug coated surface", "drug coated

balloon" and their conjugates are generally used throughout the present application and claims, to mean any surface or balloon which may be either coated with or covered with or otherwise includes or comprises either a single drug or a mixture of multiple drugs or a material composition including one or more drugs or biologically active agents, with or without a suitable carrier and/or excipient. Such compositions may also include any drug-releasing matrix or substance formulated to carry one or more drugs or biologically active agents therein, as is well known in the art of drug delivery catheters. Thus, the use of the word "drug" is not intended to restrict the scope of the above terms to a single drug only but means one or more drugs or one or more active agents with or without other substances and/or matrices and/or drug carriers and/or drug containing liposomes and/or any combinations thereof. The above terms are also intended to include drugs and/or compositions of matter that may be in a solid form, in a liquid form, in a gel form or in any other suitable form for carrying and delivering one or more biologically active agents to a treated region of the vasculature, as is well known in the art of drug delivering catheters.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials below. In case of conflict, the patent specification, including definitions, as described will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof.

Typically, common engineering terms as known in the art of balloon catheters are defined as follows:

"Load" – is defined as the force or pressure acting on a component (such as an inner balloon, an outer perforated balloon, and a lumen of a catheter shaft).

"Stretchable" – is used to define a component or structure or material that changes its shape or dimensions permanently after application of load (such as increase of

diameter) by at least 10% of its original size and is deformed plastically under a working load.

"Non-stretchable" – is used to define a component or structure or material that does not permanently change its shape or dimensions after application of load by more than 10 % of its original size or dimension.

"Compliant" - is used to define a component or structure or material that reversibly changes shape or dimension after application of load (such as an increase of diameter, and/or length, and the like) by at least 15% of its original size or dimension and is deformed super–elastically (in a rubber-like manner under a working load).

"Semi-Compliant" – is used to define a component or structure or material that reversibly changes its shape or dimension after application of load (such as increase of diameter) in the range of 2%- 15% of its original size or dimension and is deformed elastically under a working load).

"Non-Compliant" – is used to defined a component or structure or material that reversibly changes its shape or dimension after application of load (such as increase of diameter or length, and the like) by 0% - 2% of its original size or dimension and is either not deformed or is deformed elastically under a working load, within the above indicated range.

It is noted that in the above definitions, it is assumed that no brakeage or tearing of the material, component or structure occurs during the application of the load.

TABLE 1 below lists some of the materials suitable for use in making the inner (drug coated) inflatable balloons and/or the outer perforated balloons of the catheters of the present application and classifies such materials with regard to their mechanical properties as related to the above term definitions.

TABLE 1

Material FAMILY	*Material grade*	*S*	*NS*	*C*	*SC*	*NC*
Polyamide (PA) (Any Grade) non- Oriented		Yes	No	No	No	No
PA 12 oriented	Grilamid® L25	no	Yes	No	Yes	No
	Grilamid® L55	No	Yes	No	Yes	No
PA 11 oriented	Rilsan BESNO	No	Yes	No	Yes	No
Polyether block amides (PEBA)	PEBAX 7233 non oriented	Yes	No	No	No	No
	PEBAX 7233 oriented	No	Yes	No	Yes	No
	PEBAX 7033 non oriented	Yes	No	No	No	No
	PEBAX 7033 oriented	No	Yes	No	Yes	No
	PEBAX 6333	SW About 12-16%	No	No	Yes	No
	PEBAX 5533 **	SW about 20-30%	No	SW About 20-30%	No	No
	Grilflex ® ELG 6260	SW about 12-16%	No	No	Yes	No
PET PET/Polystyrene) oriented	Mylar ®	No	No	No	No	Yes
Polyethylene (PE) non-oriented	HD/LD/LLD	Yes	No	No	Yes *	No

* there will be noticeable elastic shrinkage after plastic deformation.

** PEBAX 5533 is a material with mechanical properties similar (but not identical) to a hard but non-vulcanized rubber.

In **TABLE 1**, the following shorthand denotations are used to represent the following mechanical properties:

S – represents "Stretchable".
NS – represents " Non-Stretchable".
C – represents "Compliant".
SC – represents "Semi-Compliant".
NC – represents "Non-Compliant".
SW – represents "Somewhat".

It is noted that throughout the drawing figures of the present application, the distal side of a catheter is denoted by the letter **D** and the proximal side of a catheter is denoted by the letter **P**. An arrow associated with the letter **D** points towards the distal direction and an arrow associated with the letter P points at the proximal direction**.** This directional notation is also used to indicate the distal and proximal sides or ends of other components of the catheters disclosed in the present application.

Reference is now made to Fig. 1 which is a schematic longitudinal cross sectional view illustrating a drug delivery catheter, in a non-inflated state, in accordance with an embodiment of the drug delivery catheters of the present application.

It is noted that the distance between the outer surface 2C of the shaft 2 and the inner surface 4D of the inner balloon 4 as well as the distance between the outer surface 4C of the inner balloon 4 and the inner surface 6D of the balloon 6 are somewhat exaggerated in Fig. 1 for the sake of clarity of illustration (in order to clearly discern the different parts and portions of the inner balloon 4 and the outer balloon 6). In some embodiments of the catheters of the present application, some parts or portions of the inner surface 4D of the inner balloon 4 may be in contact with the outer surface 2C of the shaft 2 and some parts or portions of the inner surface 6D of the outer balloon 6 may be in contact with the outer surface 4C of the inner balloon 4.

The catheter 10 is configured as an "over the wire" (OVT) catheter. The catheter 10 includes a hollow shaft 2, an inner balloon 4 and a perforated outer balloon 6. The shaft 2 may be a double lumen hollow shaft having a first lumen 2A for passing the catheter 10 over a guide wire 3, and a second lumen 2B for passing inflation fluid there through for inflating the inner balloon 4. In accordance with some embodiments of the catheters of the present application, the shaft 2 (or any of the other shafts disclosed in the present application may be made of or may include materials such as, but not limited to, a

biocompatible thermoplastic polymer, Nylon®, Pebax®, polyurethane, Polyethyleneterephtalate (PET), stainless steel or any other suitable material.

In accordance with some embodiments of the catheters of the present application, the outer perforated balloon 6 of the catheter 10 (or any of the other outer perforated balloons of any of the other catheters disclosed in the present application) may be made of or may include a material selected from a polymer based material, Nylon® Nylon 12®, PET, a polyamide PA12, Grilamid® L25, Grilamid® L55, PA11, Polyether block amides PEBAX® 7233, PEBAX®7033, PEBAX® 6333), Grilflex® ELG 6260, Polyester, polyethylene, polyurethane, and any combinations thereof.

The proximal end 4A of the inner balloon 4 is sealingly attached to a first region of the outer surface 2C of the shaft 2 and the distal end 4B of the inner balloon 4 is sealingly attached to a second region of the outer surface 2C of the shaft 2. The proximal and distal end 4A and 4B, respectively, of the inner balloon 4 may be sealingly attached to the outer surface 2C by gluing or welding or thermal bonding or ultrasonic welding or by any other suitable attachment method as is known in the art. The outer surface 4C of the inner balloon 4 is coated or covered with a layer of a drug or a layer of a material composition or therapeutic formulation or therapeutic composition comprising one or more drugs and/or active agents, and/or active ingredient(s) as is well known in the art (it is noted that, in all of the drawing figures the catheter embodiments disclosed in the present application, the layer of drug or composition coating the outer surface of the inner balloons is not shown, for the sake of clarity of illustration).

For example, the coating the inner balloons of the drug delivery balloon catheters of the present application (such as but not limited to the coating on the outer surface 4C of the inner balloon 4) may include, but are not limited to, one or more of a therapeutic substance, a diagnostic substance, a drug, a therapeutic composition, a medicament, a diagnostic composition, a physiologically active agent, a biochemically active agent, one or more living cells, DNA, RNA, a nucleic acid, a vector for delivering genetic material to cells in the treated site, an anti-inflammatory agent, an anti-restenosis agent, a cell proliferation inhibitory agent, a smooth muscle proliferation inhibiting agent, paclitaxel, rapamycin, everolimus, a vaso-active agent, a vaso dilating agent, a vaso constricting agent, an antibiotic agent, an anti-coagulative agent, a platelet aggregation inhibiting agent, an anti-fibrosis agent, a pharmaceutically acceptable vehicle, a lipid

based vehicle, and any combinations thereof. It is noted that any drug or biologically active substance that are included in the drug delivery catheters of the present invention, including but not limited to any of the substances and compositions disclosed hereinabove may be encapsulated in nanoparticle carrier systems and/or in liposomes, as is well known in the art.

The lumen 2B of the shaft has an opening 2D that opens into the lumen 4E of the inner balloon 4. A proximal connecting member 15 is suitably sealingly attached to the proximal end of the shaft 2. The proximal connector member 15 includes a hollow guide wire port 15A and a hollow inflation port 15B. The Lumen 2B may be used for inflating the inner balloon 4 by injecting a suitable inflation fluid through a suitable opening 5 at the end of the inflation port 15B. The hollow inflation port is in fluidic communication with the lumen 2B of the shaft 2 and through the lumen 2B and the opening 2D and with the lumen 4E of the inner balloon 4. The inflation of the inner balloon 4 may be performed by connecting the inflation port 15 to a suitable indeflator (not shown in Fig. 1) as is well known in the art of angioplastic balloon catheters. To enable inflation and deflation of the inner balloon 4, the distal end of the second lumen 2B is sealed by a sealing plug member 7 that is sealingly attached within the distal end of the second lumen 2B. The direction of flow of such an inflation fluid through the catheter during inflation of the inner balloon 4 is shown by the arrows 13.

Optionally, the catheter 10 also includes a soft tip 9 attached to the distal end of the shaft 2. The soft tip 9 may be a tapered member made of a soft resilient material. The soft tip 9 may be shaped as a hollow conical or frusto-conical tip but other shapes such as, but not limited to a hollow rounded open cap (not shown) may also be used if desired. The soft tip 9 may be made from a soft pliable material, such as but not limited to PEBAX 5533, PEBAX 6333, a soft thermoplastic polyurethane (TPU), a thermoplastic silicone-urethane copolymer (TSUC), or other suitable soft and/or pliable materials. Preferably, but not obligatorily, the material of the soft tip 9 may include a radio-opaque filler, such as but not limited to, barium sulphate ($BaSO_4$) or the like. Such radio-opaque filler-including soft tip may be used as a radio-opaque marker indicating the approximate position of the distal balloon end when viewed using angiographic methods to position the catheter.

The soft tip 9 is a hollow tip having a passage 9A passing there through. The passage has an orifice 9B which opens at the distal end of the soft tip 9. The soft tip 9 may be glued or bonded or otherwise fixedly or detachably attached to the distal end of the shaft 2 (such as, but not limited to, by gluing, bonding, thermal bonding, or by mounting without bonding and the like). A guide wire 3 may be inserted into a proximal opening 8 disposed in a hollow guide wire insertion port 15A included in the connector member 15 at the proximal end of the catheter 10. The guide wire 3 may pass through the hollow passage 2A of the shaft 2 and through the passage 9A of the soft tip 9 and may exit from the orifice 9B at the distal end of the soft tip 9 as illustrated in Fig. 1. The soft tip 9 facilitates passage of the catheter 10 through bending or tortuous bodily passages or blood vessels, without excessively damaging or injuring the walls of the bodily passage or of the blood vessel. However, the soft tip 9 is optional and the catheters disclosed in the present application may be constructed and used without such a soft tip.

The outer balloon 6 surrounds the inner balloon 4 for protecting the drug coated outer surface 4C of the inner balloon 4. The outer balloon 6 has multiple perforations 6F therein. The perforations 6F may be multiple openings formed in the wall of the outer balloon6. The perforations 6F in the specific exemplary embodiment illustrated in Figs 1-2, are circular perforations arranged in six substantially parallel rows of perforations along the length of the outer balloon 6. However, in accordance with some embodiments of the catheters of the present application, the perforations may have other non-circular opening shapes, such as, for example, elliptical openings, square openings, elongated openings, slot-like openings, or any other suitable shapes of openings. Such openings may or may not be arranged in longitudinal rows and the number of rows (if used) may be any suitable number in the range of 2- 30 rows (but a number of rows higher than 30 may also be used in some embodiments), depending, *inter alia*, on the size of the openings, the physical properties of the material(s) from which the outer balloon 6 is made, the type and chemical/physical characteristics of the drug or therapeutic composition attached to the outer surface 4C of the inner balloon 4 and the particular application of the catheter.

If rows of perforations are used, the number of perforations in a row may depend, *inter alia*, on the length of the outer balloon 6, the size of the openings, the physical

properties of the material(s) from which the outer balloon 6 is made, the type and chemico-physical characteristics of the drug or therapeutic composition attached to the outer surface 4C of the inner balloon 4 and the particular application of the catheter.

It is noted that the perforation diameter (for circular perforations 6F) or the perforation's area (for non-circular perforations 6F) may (optionally) become larger when the inner balloon 4 is inflated, depending, *inter alia*, on the degree of compliance of the material from which the outer balloon 6 is made as is disclosed in detail hereinafter.

The outer balloon 6 has a proximal end 6A and a distal end 6B. The length of the outer balloon 6 may (optionally) be larger than the length of the inner balloon 4. The proximal end 6A of the outer balloon 6 is sealingly attached to a third region of the outer surface 2C of the shaft 2 and the distal end 6B of the outer balloon 6 is sealingly attached to a fourth region of the outer surface 2C of the shaft 2. The proximal and distal end 6A and 6B, respectively, of the outer balloon 6 may be sealingly attached to the outer surface 2C by gluing or welding or thermal bonding or ultrasonic welding or by any other suitable attachment method as is known in the art.

In the specific embodiment of the OVT catheter illustrated in Fig. 1, the third region of the surface 2C to which the proximal end 6A of the outer balloon 6 is sealingly attached may be located on the surface 2C proximal to the location of the third region of the surface 2C to which the proximal end 4A of the inner balloon 4 is sealingly attached. The fourth region of the surface 2C to which the distal end 6B of the outer balloon 6 is sealingly attached may be located on the surface 2C distal to the location of the second region of the surface 2C to which the distal end 4B of the inner balloon 4 is sealingly attached.

However, in some embodiments of the catheters of the present application (not shown in Fig. 1), the length of the outer balloon 6 may be either equal to or shorter than the length of the inner balloon 4. In such embodiments, the proximal end of the outer balloon may be sealingly attached directly to the outer surface of the proximal end of the inner balloon and the distal end of the outer balloon may be sealingly attached directly to the outer surface of the distal end of the inner balloon.

Reference is now made to Figs. 2-3. Fig. 2 is a schematic transversal cross section of the catheter of Fig. 1 taken along the lines II-II when the inner balloon of the catheter is

in a non-inflated state. Fig. 3 is a schematic transversal cross-section of the catheter of Fig. 1 taken along the lines II-II, when the inner balloon of the catheter is in an inflated state.

Turning to Fig. 2, the inner balloon 4 is illustrated in a non-inflated state. It is noted that the distance between the outer surface 2C of the shaft 2 and the inner surface 4D of the inner balloon 4 as well as the distance between the outer surface 4C of the inner balloon 4 and the inner surface 6D of the balloon 6 are somewhat exaggerated for the sake of clarity of illustration. In some embodiments of the catheters of the present application, some parts or portions of the inner surface 4D of the inner balloon 4 may be in contact with the outer surface 2C of the shaft 2 and some parts or portions of the inner surface 6D of the outer balloon 6 may be in contact with the outer surface 4C of the inner balloon 4.

Turning to Fig. 3, when the inner balloon 4 is inflated with inflation fluid at the nominal inflation pressure, the inner balloon 4 may expand to an inflated state. If the inner balloon 4 is made from a compliant material or a semi-compliant material (see detailed definitions and TABLE 1, hereinafter), the cross-sectional area (or the mean diameter) of the inner balloon 4 in the inflated state may be substantially larger than the cross-sectional area (or the mean diameter) of the inner balloon 4 in the non- inflated state as illustrated in Fig. 3. If the outer balloon 6 is also made from a compliant, or a semi-compliant material, the outer balloon 6 may also expand radially such that the cross-sectional area (or the mean diameter) of the outer balloon 6 after inflation of the inner balloon 4 is larger than the cross-sectional area (or the mean diameter) of the outer balloon 6 before inflation of the inner balloon 4. Typically, after inflation of the inner balloon 4 with the nominal inflation pressure, the parts or portions of the inner balloon 4 which face the perforations 6F may expand to form convex regions 4K, 4L, 4M, 4N, 4P and 4Q which bulge radially and may extend beyond of the perforations 6F as illustrated in Fig. 3. In operation, when the catheter 10 is positioned such that the outer balloon 6 is within the site to be treated and the inner balloon 4 is inflated to the nominal inflation pressure, part of the drug coated surface of the convex regions 4K, 4L, 4M, 4N, 4P and 4Q may come in contact with the blood vessel wall (not shown in Fig. 3) or with the wall of any other bodily passage within which the catheter 10 is disposed. The contact between the bulging convex regions 4K, 4L, 4M, 4N, 4P and 4Q may assist in the

delivery of drug or active ingredient(s) from the composition coating or attached to the convex regions 4K, 4L, 4M, 4N, 4P and 4Q to portions of the wall of the treated blood vessel or other body passage being treated.

It is noted that in the specific catheter embodiment illustrated in Figs. 1-3, the inner balloon 4 may be made from a compliant or semi-compliant material and the outer balloon 6 may made from a semi-compliant material or from a non-compliant material. Therefore, after the inner balloon 4 is inflated at the nominal inflation pressure, the area of the perforations 6F may remain the same (or may increase very slightly) relative to the area of the perforations before the inflation of the inner balloon because the outer balloon 6 may either slightly expand radially due to the pressure exerted thereon by the expanding inner balloon 4 in the case in which the outer balloon is semi-compliant, or may not expand radially or only negligibly expand radially in the case in which the outer balloon 6 is non-compliant.

However, in embodiments of the catheters in which the outer balloon 6 is made of a compliant material (see, for example, the catheter 20 of Figs. 4-6 hereinafter), the elasticity of the outer balloon 6 may result in a substantial radial expansion (elastic radial stretching) of the outer balloon 6 in response to the inflation of the inner balloon 4 at the nominal inflation pressure. This elastic stretching and increase in the cross-sectional area of the compliant outer balloon 6 may result in a substantial increase of the area of the perforations 6F of the outer balloon 6 relative to the area of the perforations 6F before the inflation of the inner balloon 4. This substantial increase in the area of the perforations 6F in such a compliant outer balloon enables a larger area of the drug coated outer surface 4C of the inner balloon to protrude (and convexly bulge) beyond the outer surface 6C of the outer balloon through the enlarged perforations 6F. In such embodiments of the catheter having a compliant outer perforated balloon 6, the perforations 6F may have a relatively small area in the non-expanded state of the outer balloon 6 that may advantageously provide improved covering and protection of the drug coated surface 4C of the inner balloon 4. After inflating the inner balloon 4 at nominal pressure, the area of the perforations 6F advantageously increases, which may substantially increase the total area of the drug coated surface of the inner balloon 4 that contacts the treated region for delivering the drug.

Reference is now made to Fig. 4 which is a schematic cross sectional view illustrating part of an OVT drug delivery balloon catheter in an inflated state disposed in a blood vessel, in accordance with an embodiment of the catheters of the present invention.

The shaft 2, the soft tip 9 of the catheter 20 and the guide wire 3 are similar to those of the catheter 10 of Fig. 1. The catheter 20 includes an inner balloon 14 and an outer balloon 16. The proximal end 14A of the inner balloon 14 is sealingly attached to a first region of the outer surface 2C of the shaft 2 and the distal end 14B of the inner balloon 14 is sealingly attached to a second region of the outer surface 2C of the shaft 2. The proximal and distal end 14A and 14B, respectively, of the inner balloon 14 may be sealingly attached to the outer surface 2C by gluing or welding or thermal bonding or ultrasonic welding or by any other suitable attachment method as is known in the art. The outer surface 14C of the inner balloon 4 may be coated or covered with a layer of a drug or a layer of a material composition or therapeutic formulation or therapeutic composition comprising one or more drugs and/or active agents, and/or active ingredients as is disclosed in detail for the inner balloon 4 of Fig. 1. The inner balloon 14 is enclosed within the perforated outer balloon 16 that surrounds the inner balloon 14. When the inner balloon 14 of the catheter 20 is inflated (by introducing an inflation fluid at a nominal inflation pressure into the lumen 2B of the shaft 2), the inner balloon 14 is inflated by the inflation fluid entering (in the direction illustrated by the arrow 13) through the opening 2D into the lumen of the balloon 14. The inner balloon 14 may be made from a compliant material or a semi-compliant material and the perforated outer balloon semi compliant 16 may be made from a non-compliant, semi compliant or compliant material. In the specific example illustrated in Fig. 4, the perforations 16F of the perforated outer balloon 16 are arranged in multiple rows along the length of the outer balloon 16 with each row having four perforations 16F. After inflation of the inner balloon 14, portions 14K, 14L, 14M and 14N of the balloon 14 convexly protrude through the four perforations 16F of the row of perforations illustrated in the cross-sectional view of Fig. 4 such that the drug coated convex surface of the portions 14K, 14L, 14M and 14N may come in contact with portions of the surface 12 of the plaque (or atheroma) 11 being treated by the catheter 20. The contact between the drug coated surface of the portions 14K, 14L, 14M and 14N with portions of the surface 12 of the plaque 11 may deliver part of the drug to the treated blood vessel.

It is noted that while in the exemplary catheter 20 of Fig. 4, the rows of perforations 16F of the perforated balloon 16 each include four perforations, this is by no means obligatory, and in some embodiments of the catheter the number of perforations in a longitudinal row may be larger or smaller than four. Furthermore, the perforations in the perforated outer balloons of the catheters of the present applications need not obligatorily be arranged in rows. In accordance with some embodiments of the catheters of the present application, the perforations of the perforated outer balloon of the catheter may be randomly arranged on the surface of the perforated outer balloon, preferably (but not obligatorily) such that the mean number of perforations per unit area of the surface of the balloon is constant along the surface of the outer perforated balloon. However, any type of arrangement of the perforations on the surface of the outer perforated balloon may be implemented, including but not limited to, linear rows of perforations, a single helical arrangement or multiple helical arrangements of perforations or any other uniform or non-uniform arrangement of perforations on the surface of the outer perforated balloon.

The total number of perforations in the perforated outer balloons of the drug delivery catheters of the present application may depend, *inter alia*, on the total surface area of the outer balloon, the perforations' diameter (for circular perforations) or the perforations' area (for non-circular perforations), the compliance of the outer balloon and the wall thickness of the outer balloon, and the mechanical properties of the material(s) from which the outer balloon is made.

Reference is now made to Fig. 5 which is a schematic longitudinal cross sectional view illustrating a rapid exchange drug delivery catheter, in a non-inflated state, in accordance with an embodiment of the drug delivery catheters of the present application.

The catheter 30 is configured as a rapid exchange (RE) catheter. The catheter 30 includes a hollow shaft 22, an inner balloon 24 and a perforated outer balloon 26. The shaft 22 may be a double lumen hollow shaft having a first lumen 22A for passing the catheter 30 over a guide wire 3, and a second lumen 22B for passing inflation fluid there through for inflating the inner balloon 243. The guide wire 3 may be inserted into the first lumen 22A through an opening 22G of the first lumen 22A. The opening 22G is disposed on the shaft 22 at a position located between the proximal end of the catheter and the proximal end 26A of the outer perforated balloon 26. The shaft 22 may be made

from, or may include flexible materials, as disclosed in detail hereinabove for the shaft 2 of Fig. 1. The proximal end 24A of the inner balloon 24 may be sealingly attached to a first region of the outer surface 22C of the shaft 22 and the distal end 24B of the inner balloon 24 may be sealingly attached to a second region of the outer surface 22C of the shaft 22. The proximal and distal ends 24A and 24B, respectively, of the inner balloon 24 may be sealingly attached to the outer surface 22C by gluing or welding or thermal bonding or ultrasonic welding or by any other suitable attachment method as is known in the art and as disclosed hereinabove. The outer surface 24C of the inner balloon 24 is coated with or covered with a layer of a drug or a layer of a material composition or therapeutic formulation or therapeutic composition comprising one or more drugs and/or active agents, and/or an active ingredients as is well known in the art and as disclosed in detail hereinabove for the inner balloon 4 of Figs. 1-3.

The lumen 22B of the shaft has an opening 22D that opens into the lumen 24E of the inner balloon 24. The Lumen 22B may be used for inflating the inner balloon 24 by injecting a suitable inflation fluid through a suitable inflation port 25 attached at the proximal part of the shaft 22 and fluidically connected to the second lumen 22B and through the second lumen 22B to the lumen 24E of the inner balloon 24. The inflation of the inner balloon 24 may be performed by connecting the inflation port 25 to a suitable indeflator (not shown in Fig. 5) as is well known in the art of angioplastic balloon catheters. To enable inflation and deflation of the inner balloon 24, the distal end of the second lumen 22B is sealed by a sealing plug member 27 that is sealingly attached within the distal end of the second lumen 22B.

The catheter 30 may also (optionally) include a soft tip 9 attached to the distal end of the shaft 22 which may be similar in construction and implementation to the soft tip 9 of the catheter 10 of Fig. 1 hereinabove.

The outer balloon 26 surrounds the inner balloon 24 for protecting the drug-coated surface of the inner balloon 24. The outer balloon 26 has multiple small perforations 26F therein. The perforations 26F may be multiple openings formed in the wall of the outer balloon 26. The perforations 26F may be circular perforations arranged in multiple rows of perforations along the length of the outer balloon 26. However, in accordance with some embodiments of the catheters of the present application, the perforations may have other non-circular opening shapes, such as, for example, elliptical openings, square

openings, elongated openings, slot-like openings, or any other suitable shapes of openings. As disclosed hereinabove for the perforations 6F (of Fig. 1) and 16F (of Fig. 4), the perforations 26F may or may not be arranged in longitudinal linear rows and the number of rows (if used) may be any suitable number in the range of 2- 50 rows, depending, *inter alia*, on the size of the openings, the physical properties of the material(s) from which the outer balloon 26 is made, the type and chemical/physical characteristics of the drug or therapeutic composition attached to the outer surface 24C of the inner balloon 24 and the particular application of the catheter. In some embodiments of the RE catheters of the present application, the arrangement of the perforations may be irregular or random, or in accordance with any of the types of perforation arrangements disclosed hereinabove for the catheters 10 and 20.

If rows of perforations are used, the number of perforations in a row may depend, *inter alia*, on the length of the outer balloon 26, the size of the perforations, the physical properties of the material(s) from which the outer balloon 26 is made, the type and chemical-physical characteristics of the drug or therapeutic composition attached to the outer surface 24C of the inner balloon 24 and the particular application of the catheter.

It is noted that the perforation diameter for circular perforations 26F or the perforation area (for non-circular perforations) may (optionally) become larger when the inner balloon 24 is inflated, depending, *inter alia*, on the degree of compliance of the material from which the outer balloon 26 is made as is disclosed in detail hereinafter.

The outer balloon 24 has a proximal end 24A and a distal end 24B. The length of the outer balloon 26 may be larger than the length of the inner balloon 24. The proximal end 26A of the outer balloon 24 is sealingly attached to a third region of the outer surface 22C of the shaft 22 and the distal end 26B of the outer balloon 26 is sealingly attached to a fourth region of the outer surface 22C of the shaft 22. The proximal and distal ends 26A and 26B, respectively, of the outer balloon 26 may be sealingly attached to the outer surface 22C by gluing or welding or thermal bonding or ultrasonic welding or by any other suitable attachment method as is known in the art.

In the specific embodiment of the RE catheter illustrated in Fig. 5, the third region of the surface 22C to which the proximal end 26A of the outer balloon 26 is sealingly attached may be located on the surface 22C proximal to the location of the third region of the surface 22C to which the proximal end 24A of the inner balloon 24 is sealingly

attached. The fourth region of the surface 22C to which the distal end 26B of the outer balloon 26 may be sealingly attached may be located on the surface 22C distal to the location of the second region of the surface 22C to which the distal end 24B of the inner balloon 24 is sealingly attached.

However, in some embodiments of the catheters of the present application (not shown in Fig. 5), the length of the outer balloon 26 may be either equal to or shorter than the length of the inner balloon 24. In such embodiments, the proximal end of the outer balloon 26 may be sealingly attached directly to the outer surface of the proximal end of the inner balloon 24 and the distal end of the outer balloon 26 may be sealingly attached directly to the outer surface of the distal end of the inner balloon 24. Examples of such balloon attachments are disclosed in detail in Figs. 14-16 hereinafter.

In some other embodiments of the RE and OVT catheters of the present application, the distal ends of the inner balloon and/or the outer balloon of the catheter may be sealingly attached to the soft tip 9 while the proximal end of the inner balloon and/or the outer balloon may be sealingly attached to the surface of the shaft of the catheter. Alternatively, the proximal end of the inner balloon may be sealingly attached to the outer surface of the shaft while the proximal end of the outer balloon is sealingly attached to the outer surface of the proximal end of the inner balloon while the distal end of the inner balloon may be attached to the tip 9 and the distal end of the outer balloon may be sealingly attached to the distal end of the inner balloon.

It is noted that any possible permutations of the attachment of the distal and/or proximal ends of the inner and outer balloons to the surfaces of either the catheter shaft, or the tip 9, or the outer surface of the inner balloon, are possible in implementing some embodiments of the catheters (of both RE and OVT types of catheters) of the present application and are included in the scope of the present invention.

Reference is now made to Figs. 6 and 7. Fig. 6 is a schematic transversal cross section illustrating the catheter of Fig. 5 taken along the lines V-V when the inner balloon of the catheter is in a non-inflated state. Fig. 7 is a schematic transversal cross-section taken along the lines V-V of Fig. 5, illustrating the catheter of Fig. 5 when the inner balloon of the catheter is in an inflated state.

Turning to Fig. 6, the inner balloon 24 is illustrated in a non-inflated state. It is noted that the distance between the outer surface 22C of the shaft 22 and the inner surface 24D

of the inner balloon 24 as well as the distance between the outer surface 24C of the inner balloon 24 and the inner surface 26D of the balloon 26 are somewhat exaggerated for the sake of clarity of illustration. In some embodiments of the catheters of the present application, when the inner balloon is in the non-inflated state, some parts or portions of the inner surface 24D of the inner balloon 24 may be in contact with the outer surface 22C of the shaft 22 and some parts or portions of the inner surface 26D of the outer balloon 26 may be in contact with the outer surface 24C of the inner balloon 24.

Turning to Fig. 7, when the inner balloon 24 is inflated with inflation fluid at the nominal inflation pressure, the inner balloon 24 may expand radially to an inflated state. If the inner balloon 24 is made from a compliant material or a semi-compliant material (see detailed definitions and TABLE 1, hereinafter), the cross-sectional area (or the mean diameter) of the inner balloon 24 in the inflated state may be substantially larger than the cross-sectional area (or the mean diameter) of the inner balloon 24 in the non-inflated state as illustrated in Fig. 5. If the outer balloon 26 is also made from a compliant material or from a semi-compliant material, the outer balloon 26 may also expand radially such that the cross-sectional area (or the mean diameter) of the outer balloon 26 after inflation of the inner balloon 24 is larger than the cross-sectional area (or the mean diameter) of the outer balloon 26 before inflation of the inner balloon 24. Typically, after inflation of the inner balloon 24 with the nominal inflation pressure, the parts or portions of the inner balloon 24 which face the perforations 26F may expand and bulge externally out of the perforations 26F to form convex regions which bulge radially and may extend beyond of the perforations 26F as shown in the enlarged detail of Fig. 7 illustrating some regions 24K, 24L and 24M of the inner drug coated balloon 24 which bulge convexly through the opposing open perforations 26F of the outer balloon 26.

In operation, when the catheter 30 is positioned such that the outer balloon 26 is within the site to be treated (not shown in Figs. 5-7 for the sake of clarity of illustration) and the inner balloon 24 is inflated to the nominal inflation pressure, part of the drug coated external surface of the convex bulging regions (such as, the exemplary bulging regions 24K, 24L and 24M shown in the enlarged detail of Fig. 7) may come in contact with the blood vessel wall (not shown in Fig. 7) or with the wall of any other bodily passage within which the catheter 30 is disposed. The contact between the bulging

convex regions of the inner balloon 24 may assist the delivery of the drug or active ingredient(s) from the composition coating or attached to the convex bulging regions of the inner balloon 24 to portions of the wall of the treated blood vessel or other body passage being treated.

It is noted that in the specific catheter embodiment illustrated in Figs. 5-7, the inner balloon 24 may be made from a compliant material or from a semi-compliant material and the outer balloon 26 may made from a compliant or semi-compliant material. Therefore, after the inner balloon 24 is inflated at the nominal inflation pressure, the area of the perforations 26F may substantially increase relative to the area of the perforations 26F before the inflation of the inner balloon 24 because the outer balloon 26 may substantially radially expand (and elastically stretch) due to the pressure exerted thereon by the expanding inner balloon 24. The elasticity and compliance of the outer balloon 26 may result in a substantial radial expansion (elastic stretching) of the outer balloon 26 in response to the inflation of the inner balloon 24 at the nominal inflation pressure. This elastic stretching and increase in the cross-sectional area of the compliant outer balloon 26 may result in a substantial increase of the area of the perforations 26F of the outer balloon 26 relative to the area of the perforations 26F before the inflation of the inner balloon 4. This substantial increase in the area of the perforations 26F in such a compliant outer balloon enables a larger area of the drug coated outer surface 24C of the inner balloon to protrude and convexly bulge beyond the outer surface 26C of the outer balloon 26 through the enlarged perforations 26F.

In such embodiments of the catheter having a compliant or semi-compliant outer perforated balloon 26, the perforations 26F may be made to have a relatively small area in the non-inflated (non-expanded) state of the outer balloon 26 in order to advantageously provide improved covering and protection of the drug coated surface 24C of the inner balloon 24 during the insertion and advancing of the catheter 20 through the vasculature (or other bodily passage) to the selected treatment site. After inflating the inner balloon 24 at the nominal inflation pressure, the area of the perforations 26F increases, which may substantially increase the total area of the drug coated surface of the inner balloon 24 that contacts the treated region for delivering the drug.

Therefore, catheters having compliant or semi-compliant outer perforated balloons, advantageously provide efficient protection of the drug coated outer surface of the inner balloon due to the small area of the perforations in the perforated outer balloon in the non-inflated state of the outer balloon which is the state used for inserting the catheter into the vasculature and moving the distal part of the catheter to the selected region of treatment (such as, for example, an atheroma or plaque or a stenosed part of a blood vessel), resulting in a reduced exposure of the drug coated surface of the inner balloon to the blood, while during treatment by inflation of the inner balloon, such compliant or semi-compliant outer balloons advantageously allow the perforations to substantially increase in area which increases the area of the drug coated external surface of the inner balloon which may protrude through enlarged perforations and contacts the treated region and releasing the drug or active agents released into the treated region or in the vicinity thereof. While this increase in the area of the perforations of the perforated outer balloon during and after inflation of the inner balloon may happen to some degree in all types of the catheters disclosed in the present application (because even a non-compliant outer balloon, as defined hereinafter, may exhibit a slight but measurable stretching and radial expansion), it may be quite substantial in embodiments of the catheters having a compliant outer perforated balloon and a non-compliant or semi compliant inner drug coated balloon. In such embodiments, during and after the inflation of the inner balloon at the nominal inflation pressure, while the inner balloon may expand radially, there is only a relatively small elastic stretching of the inner balloon while there is a substantial stretching of the outer perforated balloon and a concomitant substantial increase in the area the of perforations in the outer balloon, resulting in a relatively large increase in the drug coated surface exposed through the enlarged perforations and available to be released onto the treated site. This may advantageously increase the total amount of drug released into the treated region.

In embodiments having a compliant or a semi-compliant outer perforated balloon and a non-compliant or semi-compliant inner (drug coated) balloon, the above described effect (of the increase in the area of drug coated surface exposed through the expanded perforations) may be smaller in magnitude than the effect in catheters having a compliant outer balloon and a non-compliant inner balloon but is still significant.

Typically, for a given fixed compliance of the inner drug coated balloon (irrespective of whether the inner balloon is compliant, semi-compliant or non compliant) the area of drug coated surface exposed through the expanded perforations after inflation of the inner balloon at the nominal pressure increases as the compliance of the outer perforated balloon increases.

It is noted that, for increasing the protecting effect of the outer perforated balloon on the drug coated outer surface of the inner balloon, it may be advantageous to minimize or reduce the area (or the diameter, for circularly shaped perforations) of the perforations at the non-inflated state of the inner balloon because it is at this non-inflated state of the inner balloon in which the catheter is inserted into the vasculature and moved through the vasculature towards the treatment site that the undesired effect of drug washout and or dilution and loss of the drug into the bloodstream may happen. Therefore, at this stage it may be preferred to minimize or at least reduce the exposure of the drug coated outer surface of the inner balloon to the blood (or any other bodily fluids in the bodily passage into which the catheter is inserted). This may be achieved in several different ways.

The first way is to minimize or reduce the size and the cross sectional area of the perforations in the outer perforated balloon during insertion and passage of the catheter through the vasculature. This may be achieved by using compliant or semi-compliant outer perforated balloons having very small perforation diameter or cross sectional area before inflation of the inner balloon, and by producing the perforation in the outer balloon using methods allowing the forming of perforations having a very small cross sectional area (in the non expanded state of the outer balloon). Such methods may include ablative balloon perforation using a laser beam, balloon perforation using hot micro-needles, Photo-etching, die cutting, selective photo-curing or any other method known in the art for producing small perforations in an elastic material. For example, in accordance with some embodiments of the catheters, the outer perforated balloon may be made from a very elastic stretchable material (such as, for example, very thin Latex®, Polyurethane, silicone elastomers, PEBAX® 3335, PEBAX® 3325 and ePTFE (expanded polytetrafluoroethylene).

When the outer perforated balloon comprises such very small perforations, the exposure of the drug coated outer surface of the inner balloon to the blood during

insertion and moving of the catheter within the vasculature is significantly reduced due to the small size and area of the perforations, advantageously reducing drug release into the vasculature prior to reaching the treatment site. Once the treatment site is reached and the inner balloon is inflated, the stretching and radial expansion of the outer perforated balloon results in a substantial increase in the perforations' area and concomitant release of the drug into the treated vascular region.

The exemplary catheter embodiment illustrated in Figs 1-3 may operate in this way since the area of the perforations 6F in the non-expanded state of the outer balloon 6 illustrated in Fig. 2 is relatively small as compared to the area of the perforations 6F in the expanded state of the outer balloon 6 after inflation of the inner balloon 4 at the nominal inflation pressure, as illustrated in Fig. 3. Such an embodiment may advantageously reduce drug loss during passage of the catheter 10 within the vasculature while allowing significant drug delivery at the treatment site due to substantial increase in the area of the perforations 6F after inflation of the inner balloon 4. Additionally, if the inner drug coated balloon 4 is made sufficiently compliant (and elastic), the convex bulging of the regions of the drug coated outer surface of the inner balloon 4 (such as the exemplary the bulging regions 4K, 4L, 4M, 4N, 4P and 4Q of Fig. 3) through the enlarged perforations 6F beyond the outer surface 6C of the outer balloon 6 may allow contact of the bulging regions with the treated surface of the blood vessel to further improve drug delivery into the target region.

A second way to reduce drug washout from the drug coated balloon during passage of the catheter through the vasculature, is to fold the drug coated inner balloon such that at least some portions of the outer surface of inner balloon are tightly covered (and thus protected) by other portions of the outer surface of the folded inner balloon.

Reference is now made to Figs. 8-9 which are a schematic transversal cross-sectional views illustrating a drug delivery catheter having a folded inner balloon and a non-folded perforated outer balloon in an non-inflated state and an inflated state, respectively, in accordance with some embodiments of the catheters of the present application.

The shaft 2 of the catheter 40 may be configured as an OVT catheter shaft (see Figs. 1-3). The catheter 40 includes the shaft 2, an inner drug coated balloon 44 and an outer perforated balloon 46. The first lumen 2C, the guide wire 3 and the second lumen 2B

may be as disclosed in detail with respect to the catheter 10 of Fig. 1. The inner balloon 44 and the perforated outer balloon 46 may be sealingly attached to the shaft 2 as disclosed in detail for the inner balloon 4 and the outer perforated balloon 6 of Fig. 1. However, any of the methods of sealingly attaching the inner balloons and the outer perforated balloons of the catheters disclosed and/or illustrated in the drawing figures of the present application may be used in implementing the catheter 40. The catheter 40 may or may not include a soft tip (such as, for example, the soft tip 9 of Fig. 1). In embodiments of the catheter 40 that include a soft tip (not shown in the cross sectional view of Figs. 8-9), the distal end of the inner balloon 44 may be sealingly attached to the soft tip, the distal end of the outer perforated balloon 46 may be sealingly attached to the soft tip or, alternatively may be sealingly attached to the distal end of the inner balloon 44.

The inner balloon 44 may be a non-compliant, or semi-compliant or compliant balloon. The outer perforated balloon 46 may be a compliant balloon or a semi-compliant balloon. In the non-inflated state, the inner balloon 44 may have a diameter larger than the non-radially expanded diameter of the outer perforated balloon 44. The outer surface 44C of the inner balloon 44 is covered with or coated with a drug or composition (not shown in Figs. 8-9 for the sake of clarity of illustration) as disclosed in detail hereinabove with respect to the inner balloon 4 of Fig. 1.

It is noted that when the inner balloon 44 is in the non-inflated state, the distance between the outer surface 2C of the shaft 2 and the inner surface 44D of the inner balloon 44 as well as the distance between the outer surface 44C of the inner balloon 44 and the inner surface 46D of the outer perforated balloon 46 are somewhat exaggerated in Fig. 8 for the sake of clarity of illustration (in order to clearly discern the different parts and portions of the inner balloon 44 and the outer perforated balloon 46). In some embodiments of the catheters of the present application, some parts or portions of the inner surface 44D of the inner balloon 44 may be in contact with the outer surface 2C of the shaft 2 and some parts or portions of the inner surface 46D of the outer perforated balloon 46 may be in contact with the outer surface 44C of the inner balloon 44. Therefore, when the inner balloon 44 is in the non-inflated state, the inner balloon 44 may be actually folded around the shaft 2 as well as around itself in a much tighter manner than that illustrated in the schematic cross-sectional view of Fig. 8. Such tight

folding may advantageously reduce the crossing-profile of the distal part of the catheter 40.

Additionally, the tight folding of the inner balloon 4 around itself also advantageously results in improved protection of at least some portions the drug coated outer surface 44C of the inner balloon 44. For example, the surface region 44K of the outer surface 44C of the inner balloon 44 may be tightly folded over the surface region 44L for protecting the drug coating both surface regions 44K and 44L. Similarly, the surface region 44M of the outer surface 44C of the inner balloon 44 may be tightly folded over the surface region 44N for protecting the drug coating both surface regions 44M and 44N, and the surface region 44P of the outer surface 44C of the inner balloon 44 may be tightly folded over the surface region 44Q for protecting the drug coating both surface regions 44P and 44Q. Such tight folding of the inner balloon 44 may prevent any blood entering the outer perforated balloon 46 through the perforations 46F from penetrating between the tightly contacting surface regions 44K and 44L, 44M and 44N, and 44P and 44Q, respectively, or at least substantially reduce the penetration of blood between the contacting surface regions.

Furthermore, even if some blood does penetrate the perforations 46F and seeps in between the contacting surface regions 44K and 44L, 44M and 44N, and 44P and 44Q, respectively, upon insertion of the catheter 40 into the vasculature and moving the catheter towards the target region, the amount of blood penetrating between these contacting surface regions is relatively small due to the relatively small area of the perforations 46F of the outer perforated balloon 46 which is in the non-expanded state prior to inflation of the inner balloon 44.

As the outer perforated balloon 46 is not folded and has a diameter which is relatively small prior to the inflation of the inner balloon 44, the inner surface 46D of the outer perforated balloon 46 may be tightly wrapped around the folded inner balloon 46, such that at least several surface regions of the inner surface 46D may be in tight contact with opposing drug coated outer surface regions of the outer surface 44C of the inner balloon 44. For example, the surface region 46R of the outer perforated balloon 46 may be in tight contact with the opposing surface region 44S of the drug covered outer surface 44C of the inner balloon 44, the surface region 46V of the outer perforated balloon 46 may be in tight contact with the opposing surface region 44W of the drug covered outer surface

44C of the inner balloon 44 and so on. This tight contact between such surface regions of the inner surface 46D of the outer perforated balloon 46 and the opposing surface regions of the outer (drug coated) surface 44C of the inner balloon 44, may also protect such opposing regions from premature drug washout by blood in the vasculature and may further improve drug retaining, resulting in higher amounts of the drug being deliverable to the target site after the inner balloon 44 is inflated at the treatment target site.

Moreover, even if some small amount of blood does penetrate between the contacting surface regions 44K and 44L, 44M and 44N, and 44P and 44Q and have dissolved some of the drug coating the contacting surface regions 44K and 44L, 44M and 44N, and 44P and 44Q, the ability of that drug-carrying small amount of blood to escape into the blood stream through the perforations 46F may be severely limited due to the relatively long path between the perforations 46F and the blood held between the contacting surface regions 44K and 44L, 44M and 44N, and 44P and 44Q. As any space available inside the outer perforated balloon 46 (in its non-expanded state) may be somewhat fluidically isolated from the main blood flow in the vasculature (mainly due to the relatively small area of the perforations 46F prior to inflation of the inner balloon 44), the mixing of any drug carrying blood held within the outer perforated balloon 46 with the blood flowing within the vasculature may be quite restricted and may possibly even be diffusion limited or close to diffusion limited which advantageously reduces untimely drug elution prior to reaching of the target region and treatment thereof. In embodiments of the catheter 40 in which the perforations 46F are circular in shape, the double headed arrow **D1** schematically represents the diameter of the perforations 46F in the non-expanded state of the outer perforated balloon 46 prior to inflation of the inner balloon 44.

Turning to Fig. 9, once the outer balloon 46 is placed at the target region to be treated and the inner balloon 44 is inflated at the nominal inflation pressure, the inner balloon 44 expands and unfolds to fill the space within the outer perforated balloon 46 and to push against the inner surface 46D of the outer perforated balloon 46 and expand the diameter of the compliant (or semi-compliant) outer perforated balloon 46. The expansion and elastic stretching of the perforated outer balloon 46 by the inflating inner balloon 44, results in increasing the cross sectional area of the perforations 46F and may

allows portions of the drug coated outer surface of the inner balloon 44 to convexly bulge through the enlarged perforations 46F and to eventually come in contact with the treated plaque or atheroma or inner surface of the blood vessel being angioplastically treated by the expanding outer perforated balloon 46 and inner balloon 44. For example, the drug coated convexly bulging regions 44E, 44F, 44G, 44H, 44I, and 44J of the outer surface of the inner balloon 46 may come in contact with the surface of the treated region and may deliver the drug thereto. Furthermore, if a small amount of blood penetrated through the perforations 46F into the perforated outer balloon 46 and dissolved some of the drug of the outer surface 44C of the inner balloon 44, the inflation of the inner balloon 44 performed at the treated region may eject some of the drug containing blood through the enlarged perforations 46F of the expanded perforated outer balloon 46 directly in the vicinity of the treated region, effectively increasing the amount of drug available at the treated region. In embodiments of the catheter 40 in which the perforations have a circular shape, the double headed arrow **D2** schematically represents the diameter of the enlarged perforations 46F after the inner balloon 44 has been inflated at the nominal inflation pressure. For embodiments having compliant and semi-compliant outer perforated balloons 46, **D2>D1**.

For embodiments of the catheter 40 in which the shape of the perforations 46F is non-circular, the area of the perforations 46F in the non-expanded state of the outer perforated balloon 46 prior to inflation of the inner balloon 44 is **S1** and the area of the enlarged perforations 46F after the inner balloon 44 has been inflated at the nominal inflation pressure is **S2**. In embodiments of the catheter 40 having compliant and semi-compliant outer perforated balloons 46, **S2>S1**.

For semi compliant and compliant outer balloons, the change in the perforation diameter and area is related to the change in inner balloon diameter. Typically, **D2/D1≅d2/d1**, and **S2/S1≅(d2/d1)**^{2} where **d1** is the diameter of the inner balloon in the non-inflated state and **d2** is the diameter of the inner balloon in the inflated state (which may be the nominal inflated diameter of the inner balloon). If the inner and outer balloons are semi compliant, the change in the perforations' diameter may be in the order of **D2/D1** = 1.05-1.15 depending on the inflation pressure used.

Generally, the change (increase) in the diameter and/or area of the perforations is related to the inflation pressure within the inner balloon. The change in the area of the

perforations (whether circular or non-circular perforations) is proportional to the of the inflation pressure $\mathbf{P_i}$ squared $\mathbf{S2/S1} \propto (\mathbf{P_i})^2$ because for non-compliant and semi compliant balloons the balloon diameter is approximately linearly dependent on P_i.

However, it is noted that the above relation does not necessarily hold true for compliant, highly elastic balloons (such as for example, balloons made of Latex®) in which there is no linear dependence of the balloon diameter $\mathbf{P_i}$.

Additionally when the inner balloon is inflated, in a catheter that includes both the inner balloon and a perforated outer balloon as disclosed hereinabove, it is expected that the value of the ratio **S2/S1** may be somewhat smaller than $(\mathbf{d2/d1})^2$ as the outer perforated balloon may restrain the radial expansion of the inner balloon. The actual diameter of the inner balloon inflated to the nominal inflation pressure as measured in a catheter including an inner balloon and a perforated outer balloon may be significantly smaller than the diameter of the inner balloon as measured in the inner balloon when the inner balloon is not restricted by an outer perforated balloon (i.e. as measured in a similar catheter having only an inner balloon and lacking the outer perforated balloon).

If $\mathbf{D2_{I+O}}$ is the diameter of the inner balloon inflated to the nominal inflation pressure in a catheter having both an inner balloon and a perforated outer balloon, $\mathbf{D2_I}$ is the diameter of the inner balloon inflated to the nominal inflation pressure in a catheter having only an inner balloon and lacking the outer perforated balloon, $\mathbf{d1_I}$ is the diameter of the non inflated inner balloon in a catheter including only an inner balloon and $\mathbf{d1_I}$ is the diameter of the inner balloon in a non-inflated state in a catheter including only an inflatable inner balloon, typically $\mathbf{D2_{I+O}} < \mathbf{D2_I}$ resulting in $\mathbf{S2/S1} < (\mathbf{d2_I/d1_I})^2$.

Therefore, the higher the restriction to expansion exerted on the inner balloon by the outer perforated balloon, the smaller is the increase in perforation diameter and/or perforation area after inflation of the inner balloon. This effect may be more prominent in catheters having a compliant inner balloon and a non-compliant or semi compliant outer perforated balloon (due to the higher resistance to expansion of such perforated outer balloons) and may be less prominent in catheters having a compliant inner balloon and a compliant perforated outer balloon. Intermediate effects may occur in catheters having a semi compliant inner balloon and a semi compliant outer perforated balloon.

It is therefore noted, that the increase in the diameter and/or the perforation area may depend, *inter alia*, on the degree of compliance of the inner balloon, the degree of

compliance of the outer perforated balloon, the wall thickness of the inner balloon and the outer perforated balloon, and the inflation pressure of the inner balloon.

It is further noted that in catheters having folded inner and/or folded outer balloons, the term **D1** refers to the diameter of the outer perforated balloon in an unfolded state and prior to inflation of the inner balloon, the term **d1** refers to the diameter of the inner balloon in an unfolded state and prior to inflation of the inner balloon and the term $\mathbf{d1_I}$ refers to the diameter of the inner balloon in an unfolded state and prior to the inflation of the inner balloon.

It is noted that in accordance with some embodiments the catheters of the present application, the catheter 40 may be also implemented as a RE catheter by using the shaft 22 as disclosed hereinabove with respect to the catheter 30 of Figs. 5-7 instead of the shaft 2 (as disclosed with respect to Figs 1-3). Such a RE catheter, may be inserted into the vasculature and moved towards a target region over the guide wire 3 as is well known in the art of rapid exchange catheters. The protection of the drug coated inner balloon 44 by the surrounding perforated outer balloon 46, and the inflation of the inner balloon 44 to for treating the target region and for delivering a drug to the treated target region may operate as disclosed in detail hereinabove with respect to Figs. 8-9, irrespective of whether the catheter it is implemented as an OVT catheter or a RE catheter.

An additional way to reduce drug washout from the drug coated balloon during passage of the catheter through the vasculature, is the folding of both the drug coated inner balloon and the outer perforated balloon of the catheter, such that at least some portions of the outer surface of inner balloon are tightly covered (and thus protected) by other portions of the outer surface of the folded inner balloon and/or to fold the outer perforated balloon over itself, in such a way that at least some of the perforations in the outer perforated balloon are covered or partially covered by folded parts folded of the outer perforated balloon.

Reference is now made to Figs. 10-11 which are a schematic transversal cross-sectional views illustrating a drug delivery catheter having a folded inner balloon and a folded perforated outer balloon, in an non-inflated state and an inflated state, respectively, in accordance with some embodiments of the catheters of the present application.

Turning to Fig. 10, the catheter 50 includes a shaft 2, an inner drug coated balloon 54 attached to the shaft 2 and an outer perforated balloon 56 attached to the shaft 2 and surrounding the inner balloon 54. The shaft 2 of the catheter 50 may be configured as an OVT catheter shaft (see Figs. 1-3). The first lumen 2C of the shaft 2, the guide wire 3 and the second lumen 2B of the shaft 2 may be configured as disclosed in detail with respect to the catheter 10 of Fig. 1. The inner balloon 54 and the perforated outer balloon 56 may be sealingly attached to the shaft 2 as disclosed in detail for the inner balloon 4 and the outer perforated balloon 6 of Fig. 1. However, any of the methods of sealingly attaching the inner balloons and the outer perforated balloons of the catheters disclosed and/or illustrated in the drawing figures of the present application may be used in implementing the catheter 50. The catheter 50 may or may not include a soft tip (such as, for example, the soft tip 9 of Fig. 1). In embodiments of the catheter 50 that include a soft tip (not shown in the cross sectional view of Figs. 10-11), the distal end of the inner balloon 54 may be sealingly attached to the soft tip, the distal end of the outer perforated balloon 56 may be sealingly attached to the soft tip or, alternatively may be sealingly attached to the distal end of the inner balloon 54.

The inner balloon 54 may be a non-compliant, or a semi-compliant or a compliant balloon. The outer perforated balloon 56 may be a compliant balloon or a semi-compliant balloon (but may also be a non-compliant balloon in some embodiments of the catheter 50). The outer surface 54C of the inner balloon 54 is covered with or coated with a layer of drug or composition (not shown in Figs. 10-11 for the sake of clarity of illustration) as disclosed in detail hereinabove with respect to the inner balloon 4 of Fig. 1. The perforated outer balloon 56 may have multiple perforations 56F therein. When the inner balloon 54 and the outer perforated balloon 56 are in the folded state prior to the inflation of the inner balloon 54, the diameter of the perforations 56F is **D3**. In embodiments of the catheter 50 in which the perforations 56F have a non-circular shape, the cross sectional area of the perforations 56F is **S3** (not shown in Fig. 10)

It is noted that when the inner balloon 54 is in the non-inflated state, the distance between the outer surface 2C of the shaft 2 and the inner surface 54D of the inner balloon 54 as well as the distance between the outer surface 54C of the inner balloon 54 and the inner surface 56D of the outer perforated balloon 56 are somewhat exaggerated in Fig. 10 for the sake of clarity of illustration (in order to clearly discern the different

parts and portions of the inner balloon 54 and the outer perforated balloon 56). In some embodiments of the catheters of the present application, some parts or portions of the inner surface 54D of the inner balloon 54 may be in contact with the outer surface 2C of the shaft 2 and some parts or portions of the inner surface 56D of the outer perforated balloon 56 may be in close contact with the outer surface 54C of the inner balloon 54. Therefore, when the inner balloon 54 is in the non-inflated state, the inner balloon 54 may actually be tightly folded around the shaft 2 as well as around certain parts thereof in a much tighter manner than that illustrated in the schematic cross-sectional view of Fig. 10. Similarly, the outer perforated balloon 56 may be tightly folded around parts of the inner balloon 54 as well as well as around certain parts of itself. Such tight folding arrangement may advantageously reduce the crossing-profile of the distal part of the catheter 50. In such a tightly folded configuration, some or all of the perforations 56F may actually be tightly covered by the corresponding opposing folded regions of the Outer perforated balloon 56. For example, the three perforations 56F illustrated in the transversal cross-sectional view of Fig. 10 may be tightly covered by the folded regions 56H, 56 I and 56J opposing the perforations 56F. Such an arrangement in which at least some perforations of the plurality of perforations 56F of the perforated outer balloon 56 are disposed within one or more folds of the outer perforated balloon 56 and the folds are tightly folded, may significantly reduce loss of drug during insertion and passage of the catheter into the vasculature or other body cavities. Such a tightly folded arrangement may seal or at least partially seal the perforations 56F and may advantageously reduce or even prevent the penetration of blood (or other bodily fluids) into the perforations 56F which in turn reduces or prevents washout of the drug from the drug coated or drug covered outer surface 54C of the inner balloon 54, resulting in improved drug retention during the insertion of the catheter 50 into the vasculature and the moving of the distal end of the catheter 50 within the vasculature towards the treatment target site.

Turning now to Fig. 11, when the inner balloon 54 of the catheter 50 is inflated at the nominal inflation pressure, the inner balloon 54 expands and unfolds and causes the outer perforated balloon 56 to also expand and unfold as illustrated in Fig. 11. The perforations 56F may or may not increase in diameter (for perforations having a circular shape) or increase in their area after unfolding and expansion of the outer perforated

balloon 56, depending on the properties of the material from which the perforated outer balloon 56 is made. If the perforated outer balloon 56 is non-compliant, there may be a negligible enlargement or no enlargement of the diameter and/or area of the perforations 56F.

If the perforated outer balloon 56 is semi-compliant or compliant and the perforations 56F are circular, there may be a substantial enlargement of the diameter **D4** of the perforations 56F (as illustrated in Fig. 11) such that **D4>D3**. If the perforated outer balloon 56 is semi-compliant or compliant and the perforations 56F are non-circular, there may be a substantial enlargement of the area **S4** of the perforations 56F (as illustrated in Fig. 11) as compared to the area of the perforations **S3** when the inner balloon 56, such that **S4>S3**.

If the inner balloon 54 of the catheter 50 is a compliant balloon or a semi-compliant balloon, the inflation of the inner balloon 54 at the nominal inflation pressure may result in parts of the inflated balloon 54 convexly bulging through the perforations 56F such that portions of drug coated outer surface 54C of the inner balloon 54 may protrude outside of the perforations 56F and may contact the treated region (such as, for example, an atheroma in a blood vessel, a stenosed region of the blood vessel, or a plaque in a blood vessel) and may effectively deliver the drug thereto, as disclosed in detail. For example, in the cross-sectional view of Fig. 11, the regions 54K, 54L and 54M, protrude beyond the outer surface 56C of the expanded outer perforated balloon 56 through the perforations 56F.

It is noted that in accordance with some embodiments of the catheters of the present application, the catheter 50 may be also implemented as a RE catheter by using the shaft 22 as disclosed hereinabove with respect to the catheter 30 of Figs. 5-7 instead of the shaft 2 (as disclosed with respect to Figs 1-3). Such a RE catheter may be inserted into the vasculature and moved towards a target region over the guide wire 3 as is well known in the art of rapid exchange catheters. The protection of the drug coated inner balloon 54 by the surrounding perforated outer balloon 56 and the inflation of the inner balloon 54 for treating the target region and for delivering a drug to the treated target region may operate as disclosed in detail hereinabove with respect to Figs. 1 and 6-7, irrespective of whether the catheter it is implemented as an OVT catheter or a RE catheter.

Reference is now made to Figs. 12-13 which are a schematic transversal cross-sectional views illustrating a drug delivery catheter having a non-folded inner balloon and a folded perforated outer balloon, in an non-inflated state and an inflated state, respectively, in accordance with some embodiments of the catheters of the present application.

Turning to Fig. 12, the catheter 60 includes a shaft 2, an inner drug coated balloon 64 attached to the shaft 2 and an outer perforated balloon 66 attached to the shaft 2 and surrounding the inner balloon 64. The shaft 2 of the catheter 60 may be configured as an OVT catheter shaft (see Figs. 1-3). The first lumen 2C of the shaft 2, the guide wire 3 and the second lumen 2B of the shaft 2 may be configured as disclosed in detail with respect to the catheter 10 of Fig. 1. The inner balloon 64 and the perforated outer balloon 66 may be sealingly attached to the shaft 2 as disclosed in detail for the inner balloon 4 and the outer perforated balloon 6 of Fig. 1. However, any of the methods of sealingly attaching the inner balloons and the outer perforated balloons of the catheters disclosed and/or illustrated in the drawing figures of the present application may be used in implementing the catheter 60. The catheter 60 may or may not include a soft tip (such as, for example, the soft tip 9 of Fig. 1). In embodiments of the catheter 60 that include a soft tip (not shown in the cross sectional view of Figs. 12-13), the distal end of the inner balloon 64 may be sealingly attached to the soft tip, the distal end of the outer perforated balloon 66 may be sealingly attached to the soft tip or, alternatively may be sealingly attached to the distal end of the inner balloon 64.

The inner balloon 64 may be a semi-compliant balloon, or a compliant balloon. The outer perforated balloon 66 may be a non-compliant balloon or a semi-compliant balloon (but may also be a compliant balloon in some embodiments of the catheter 50). The outer surface 64C of the inner balloon 64 is covered with or coated with a layer of drug or composition (not shown in Figs. 12-13 for the sake of clarity of illustration) as disclosed in detail hereinabove with respect to the inner balloon 4 of Fig. 1. The Inner balloon 64 may be a non-folded balloon having a cross sectional area (in the non-inflated state) smaller than the cross section area of the outer perforated balloon 66 (in the non-expanded state). The total surface area of the outer perforated balloon 66 in its non-expanded state is larger than the total surface area of the inner balloon 64 in a non-

inflated state. The perforated outer balloon 66 may have multiple perforations 66F therein.

When the inner balloon 64 is in a non-inflated state and the outer perforated balloon 66 is in the folded state prior to the inflation of the inner balloon 64, the diameter of the perforations 66F is **D5**. In embodiments of the catheter 60 in which the perforations 56F have a non-circular shape, the area of the perforations 56F is **S5** (not shown in Fig. 12).

It is noted that when the inner balloon 64 is in the non-inflated state, the distance between the outer surface 2C of the shaft 2 and the inner surface 64D of the inner balloon 64 and the distance between the outer surface 64C of the inner balloon 64 and the inner surface 66D of the outer perforated balloon 66 are somewhat exaggerated in Fig. 12 for the sake of clarity of illustration (in order to clearly discern the different parts and portions of the inner balloon 64 and the outer perforated balloon 66). In some embodiments of the catheters of the present application, the inner surface 64D of the inner balloon 64 may be in contact with the outer surface 2C of the shaft 2 and some parts or portions of the inner surface 66D of the outer perforated balloon 66 may be in close contact with the outer surface 64C of the inner balloon 64. Similarly, some portions of the outer perforated balloon 66 may be tightly folded around parts of the inner balloon 64 as well as well as around some other portions of itself. Such tight folding arrangement may advantageously reduce the crossing-profile of the distal part of the catheter 60. In such a tightly folded configuration, the perforations 66F may actually be tightly covered by the corresponding opposing folded regions of the outer perforated balloon 66. For example, the three perforations 66F illustrated in the transversal cross-sectional view of Fig. 12 may be tightly covered by the folded regions 66H, 66I and 66J opposing the perforations 66F. Such an arrangement in which at least some perforations of the plurality of perforations 66F of the perforated outer balloon 66 are disposed within one or more folds of the outer perforated balloon 66 and the folds are tightly folded, may significantly reduce loss of drug during insertion and passage of the catheter into the vasculature or other body cavities. Such a tightly folded arrangement may seal or at least partially seal the perforations 66F and may advantageously reduce or even prevent the penetration of blood or other bodily fluids into the perforations 66F which in turn reduces or prevents washout of the drug from the drug coated or drug covered outer surface 64C of the inner balloon 64, resulting in improved drug retention during the

insertion of the catheter 60 into the vasculature and the moving of the distal end of the catheter 60 within the vasculature towards the treatment target site.

Turning now to Fig. 13, when the inner balloon 64 of the catheter 60 is inflated at the nominal inflation pressure, the inner balloon 64 expands and its cross sectional area increases and causes the outer perforated balloon 56 to unfold and expand as it is being radially pushed outwardly (away from the shaft 2) by the expanding inflated inner balloon 64, as illustrated in Fig. 13. The perforations 66F may or may not increase in diameter (for perforations having a circular shape) or may or may not increase in their area (for perforations having a non-circular shape) after unfolding and expansion of the outer perforated balloon 66, depending on the properties of the material from which the perforated outer balloon 66 is made. If the perforated outer balloon 66 is non-compliant, there may be a negligible enlargement or no enlargement of the diameter and/or area of the perforations 66F.

If the perforated outer balloon 66 is a semi-compliant balloon or a compliant balloon and the perforations 66F are circular, there may be a substantial enlargement of the diameter **D5** of the perforations 66F (as illustrated in Fig. 13) such that **D6>D5**. If the perforated outer perforated balloon 66 is a semi-compliant balloon or a compliant balloon and the perforations 66F are non-circular, there may be a substantial enlargement of the area **S5** of the perforations 66F, such that **S6>S5**.

If the inner balloon 64 of the catheter 60 is a compliant balloon or a semi-compliant balloon, the inflation of the inner balloon 64 at the nominal inflation pressure may result in parts of the inflated balloon 64 convexly bulging through the perforations 66F such that portions of drug coated outer surface 64C of the inner balloon 64 may protrude outside of the perforations 66F and may contact the treated region (such as, for example, an atheroma in a blood vessel, a stenosed region of the blood vessel, or a plaque in a blood vessel) and may effectively deliver the drug thereto, as disclosed in detail hereinabove. For example, in the cross-sectional view of Fig. 13, the regions 64K, 64L and 64M, protrude beyond the outer surface 66C of the expanded outer perforated balloon 66 through the perforations 66F.

It is noted that in accordance with some embodiments of the catheters of the present application, the catheter 60 may be also implemented as a RE catheter by using the shaft 22 (disclosed hereinabove with respect to the catheter 30 of Figs. 5-7) instead of the

shaft 2. Such an RE catheter embodiment may be inserted into the vasculature and moved towards a target region over the guide wire 3 as is well known in the art of rapid exchange catheters. The protection of the drug coated inner balloon 64 by the surrounding folded perforated outer balloon 66 and the inflation of the inner balloon 64 for treating the target region and for delivering a drug to the treated target region may be performed as disclosed in detail hereinabove with respect to Figs. 1 and 6-7, irrespective of whether the catheter it is implemented as an OVT catheter or a RE catheter.

It will be appreciated by those skilled in the art that the type of attachment of the inner balloon and the outer perforated balloon to the shaft of the catheter need not be limited to the particular implementation illustrated in Figs. 1, 4, and 5-7.

Reference is now made to Figs. 14-16 which are a schematic longitudinal cross-sectional views illustrating three different drug delivery catheter parts having three different configurations of attachment of the inner and outer perforated balloons to the catheter, in accordance with some embodiments of the catheters of the present application.

Turning to Fig. 14, the OVT catheter 70 includes the shaft 2 (as disclosed in detail in Fig. 1), an inner drug coated balloon 74 and an outer perforated balloon 76. The inner drug coated balloon 74 may be any type of inner balloon disclosed in the present application and may be made from a non-compliant material or from a semi-compliant material or from a compliant material. The inner balloon 76 may be a folded balloon or a non-folded balloon (prior to inflation thereof) as disclosed hereinabove. The perforated outer balloon 76 has multiple perforations 76F therein. The perforated outer balloon 76 may be any type of outer balloon disclosed in the present application and may be made from a non-compliant material or a semi-compliant material or a compliant material. The outer perforated balloon 76 may be a folded outer balloon or a non-folded outer balloon (prior to the inflation of the inner balloon 74) as disclosed hereinabove. The proximal end 74A of the inner balloon 74 is sealingly attached (by any attachment method disclosed hereinabove) to a first region of the outer surface 2C of the shaft 2 and the distal end 74B of the inner balloon 74 may be sealingly attached to a second region of the outer surface 2C of the shaft 2. The second region of the surface 2C is located distal to the first region of the surface 2C. The proximal end 76A of the outer perforated balloon 76 may be sealingly attached (by any attachment method disclosed hereinabove)

to the proximal end 74A of the inner balloon 74. The distal end 76B of the outer perforated balloon 76 may be sealingly attached (by any attachment method disclosed hereinabove) to the distal end 74B of the inner balloon 74. The catheter 70 may be passed over the guide wire 3 that may be disposed in a first lumen 2A of the shaft 2 as disclosed in detail with respect to the catheter 10 of Fig. 1. The inner balloon 74 may be inflated by a suitable inflation fluid (not shown) passing through the opening 2D in the second lumen 2B of the shaft 2 as disclosed in detail with respect to the catheter 10 of Fig. 1. The methods of inserting the catheter 70 into the vasculature, moving the catheter 70 towards the target region, inflating the inner balloon 74 for treating the target region and delivering a drug to the target region may be similar to the methods disclosed hereinabove in detail for any of the OVT catheter embodiments disclosed in the present application.

Turning to Fig. 15, the OVT catheter 80 includes the shaft 2 (as disclosed in detail hereinabove and illustrated in Fig. 1), an inner drug coated balloon 84 and an outer perforated balloon 86. The inner drug coated balloon 84 may be any type of inner balloon disclosed in the present application and may be made from a non-compliant material or a semi-compliant material or a compliant material. The inner balloon 86 may be a folded balloon or a non-folded balloon (prior to inflation thereof) as disclosed in detail hereinabove. The perforated outer balloon 86 has multiple perforations 86F therein. The perforated outer balloon 86 may be any type of outer balloon disclosed in the present application and may be made from a non-compliant material or a semi-compliant material or a compliant material. The outer perforated balloon 86 may be a folded outer balloon or a non-folded outer balloon (prior to the inflation of the inner balloon 84) as disclosed hereinabove. The proximal end 84A of the inner balloon 84 is sealingly attached (by any attachment method disclosed hereinabove) to a first region of the outer surface 2C of the shaft 2 and the distal end 84B of the inner balloon 84 may be sealingly attached to a second region of the outer surface 2C of the shaft 2. The second region of the surface 2C is located distal to the first region of the surface 2C. The proximal end 86A of the outer perforated balloon 86 may be sealingly attached (by any attachment method disclosed hereinabove) to a third region of the outer surface 2C of the shaft 2. The third region is located proximal to the first region on the shaft 2. The distal end 86B of the outer perforated balloon 86 may be sealingly attached (by any

attachment method disclosed hereinabove) to the distal end 84B of the inner balloon 84. The catheter 80 may be passed over the guide wire 3 that may be disposed in a first lumen 2A of the shaft 2 as disclosed in detail with respect to the catheter 10 of Fig. 1. The inner balloon 84 may be inflated by a suitable inflation fluid (not shown) passing through the opening 2D in the second lumen 2B of the shaft 2, as disclosed in detail with respect to the catheter 10 of Fig. 1. The methods of inserting the catheter 80 into the vasculature, moving the catheter 80 towards the target region, inflating the inner balloon 84 for treating the target region and delivering a drug to the target region may be similar to the methods disclosed hereinabove in detail for any of the OVT catheter embodiments disclosed in the present application.

Turning to Fig. 16, the OVT catheter 90 includes the shaft 2 (as disclosed in detail hereinabove and illustrated in Fig. 1), an inner drug coated balloon 94 and an outer perforated balloon 96. The inner drug coated balloon 94 may be any type of inner balloon disclosed in the present application and may be made from a non-compliant material or from a semi-compliant material or from a compliant material. The inner balloon 96 may be a folded balloon or a non-folded balloon (prior to inflation thereof) as disclosed hereinabove. The perforated outer balloon 96 has multiple perforations 96F therein. The perforated outer balloon 96 may be any type of outer balloon disclosed in the present application and may be made from a non-compliant material, or from a semi-compliant material or from a compliant material.

The outer perforated balloon 96 may be a folded outer balloon or a non-folded outer balloon (prior to the inflation of the inner balloon 94) as disclosed hereinabove. The proximal end 94A of the inner balloon 94 may be sealingly attached (by any attachment method disclosed hereinabove) to a first region of the outer surface 2C of the shaft 2 and the distal end 94B of the inner balloon 94 may be sealingly attached to a second region of the outer surface 2C of the shaft 2. The second region of the outer surface 2C is located distal to the first region of the surface 2C. The proximal end 96A of the outer perforated balloon 96 may be sealingly attached (by any attachment method disclosed hereinabove) to the proximal end 94A of the inner balloon 94. The distal end 96B of the outer perforated balloon 96 may be sealingly attached (by any attachment method disclosed hereinabove) to a third region of the outer surface 2C of the shaft 2 such that

the third region of the outer surface 2C is located distal to the second region along the shaft 2 (as illustrated in Fig. 16).

The catheter 90 may be passed over the guide wire 3 that may be disposed in a first lumen 2A of the shaft 2 as disclosed in detail with respect to the catheter 10 of Fig. 1. The inner balloon 94 may be inflated by a suitable inflation fluid (not shown) passing through the opening 2D in the second lumen 2B of the shaft 2 as disclosed in detail with respect to the catheter 10 of Fig. 1. The methods of inserting the catheter 90 into the vasculature, moving the catheter 90 towards the target region, inflating the inner balloon 94 for treating the target region and delivering a drug to the target region may be similar to the methods disclosed hereinabove in detail for any of the OVT catheter embodiments disclosed in the present application.

It is noted that the types of attachment of the inner balloon to the shaft 2 and the methods of attachment of the outer perforated balloon to the shaft 2 or to the proximal end and/or the distal end of the inner balloon are not limited to OVT type of the catheters of the present application and that similar types of attachments may be used in RE catheters in which the shaft construction is similar to that of the shaft 22 of the RE catheter 30 illustrated in Fig. 5.

Reference is now made to Figs. 17-21. Fig.17 is a schematic side view of part of an assembled drug delivery catheter, in accordance with an embodiment of the catheters of the present application. Fig. 18 is a schematic front view of the catheter of Fig. 17 as viewed in the direction indicated by the arrow F. Fig. 19 is a side view of the outer perforated balloon of the catheter of Fig. 17. Fig. 20 is a schematic side view of the shaft and the inner drug coated balloon of the catheter of Fig. 17. Fig. 21 is a schematic isometric view of the assembled catheter of Fig. 17.

Turning to Figs. 17-21, the drug delivering catheter 100 includes an RE type double lumen shaft 102 similar in construction and operation of the shaft 22 of the catheter 30 (of Fig. 5). The catheter 100 also includes an inflatable inner drug coated balloon 104 (shown in detail in Fig. 19 hereinafter) and an outer perforated balloon 106. It is noted that the catheter 100 of Figs 17, 18 and 21 is illustrated in a state in which the inner balloon 104 is inflated at the nominal inflated diameter.

The inner drug coated balloon 104 may be sealingly attached to the outer surface 102C shaft 102 using any of the attachment methods disclosed in detail hereinabove

with respect to the inner balloon 6 of Fig. 1. The inner balloon 104 may be inflated by an inflation fluid introduced into a suitable inflation lumen (not shown) which is formed within the shaft 102. The inflation fluid may enter the inner balloon 106 through a suitable opening in the inflation lumen (not shown in Figs. 17-21). The inflation lumen of the inner balloon 104 may be implemented similar to the lumen 22B of the shaft 22 of Fig. 5 and the opening into the lumen of the inner balloon 104 may be implemented similar to the opening 22D of the shaft 22 of Fig. 5. The inner balloon 104 may be implemented as a non-folded balloon and the outer surface 104C of the inner balloon 104 is coated by or covered with a drug or a drug containing composition as disclosed hereinabove in detail with respect to the inner balloon 4 of Fig. 1. The inner balloon 104 may be made from a compliant material or from a semi-compliant material or from a non-compliant material as disclosed hereinabove.

The outer perforated balloon 106 surrounds the inner balloon 104 and may be sealingly attached to the outer surface 102C of the shaft 102. In the exemplary embodiment of the catheter 100 illustrated in Fig. 17, the proximal end 106A and the distal end 106B of outer perforated balloon 106 may be sealingly attached to the shaft 102. However, any of the attachment configurations of the inner balloons and/or the outer perforated balloons to the shaft 102 and/or to each other disclosed in the present application and illustrated in the drawing figures may be used in various different embodiments of the catheter 100, such as, for example, the attachment configurations illustrated in Figs 1, 14, 15 and 16.

Furthermore, while the specific embodiment of the catheter 100 of Fig. 21 does not include a soft tip, at least some embodiments of the catheter 100 may also include a soft tip similar to the soft tip 9 of Fig. 1. In such embodiments including the soft tip 9, the distal end of the inner balloon 104 and/or the distal end of outer perforated balloon 106 or both distal ends of the inner balloon 104 and the outer perforated balloon 106 may be attached to the soft tip 9. Alternatively, in some embodiments of the catheter 100 that include the soft tip 9, the distal end of the inner balloon 104 may be sealingly attached to the soft tip 9 and the distal end 106B of the outer perforated balloon 106 may be sealingly attached to the distal end of the inner balloon 104.

The outer perforated balloon 106 has multiple circular perforations 106F therein. In the particular exemplary embodiment of the catheter 100, the perforations 106F are

arranged on the outer perforated balloon 106 in four linear rows, each row includes twelve perforations 106F. However, this is not obligatory to practicing the invention and any practical number of rows may be used, with each row including any practical number of perforations depending, inter alia, on the perforation size and shape, the diameter of the outer perforated balloon, the length of the balloon and other considerations. The perforations may also be arranged, if desired, in any practically desired arrangement, including but not limited to, non-linear rows, helical rows, multiple helical rows or even in a random or other non-random but non-uniform arrangement as is disclosed hereinabove in detail for other catheter embodiments.

It is noted that while in the specific embodiment of the catheter 100 the diameter of the circular perforations 106F is relatively large after the inner balloon has been inflated, The diameter of the perforations 106F may be either quite small (as compared to the diameter of the same perforations 106F in the state before the inner balloon 104 has been inflated). In such a case, the outer perforated balloon 106 may be made from a compliant material or from a semi-compliant material and may be able to elastically expand when pushed out by the inner balloon 104 during and after inflation of the inner balloon 104, resulting in a substantial increase in the diameter of the perforations 106F due to the elastic expansion of the outer perforated balloon 106 due to inflation of the inner balloon 104.

In other embodiments of the catheter 100, the outer perforated balloon 106 may be made from a non-compliant material, in which case the diameter of the perforations 106F may not significantly change or may increase very little during and after the inflation of the inner balloon 104.

It is noted that while the inner balloon 104 of Fig. 20 is illustrated in an inflated state for the sake of clarity of illustration and the outer perforated balloon 106 of Fig. 19 is illustrated in a fully expanded state (as it would be after the inner balloon has been inflated to the nominal inflated diameter), in at least some embodiments of the catheter 100 in the state preceding the inflation of the inner balloon 104, either the inner balloon 104 or the outer perforated balloon 106 or both the inner balloon 104 and the outer perforated balloon 106 may be folded around the shaft 102 and/or around the inner balloon 104 as disclosed in detail with respect to the catheters 40, 50 and 60 (of Figs. 8, 10 and 12, respectively).

In accordance with other embodiments of the catheter 100, at the state prior to the inflation of the inner balloon 104, the inner balloon 104 and/or the outer perforated balloon 106 may be in a non-folded configuration as disclosed in detail hereinabove with respect to the catheter 10 of Fig. 2.

Any such combination and permutation of configurations the outer perforated balloon 106 and the inner balloon 104 in the state before inflation of the inner balloon 104 is possible in different embodiments of the catheter 100. Such combinations may include for example, the inner balloon 104 being non-folded and the perforated outer balloo106 being non-folded, the inner balloon 104 being non-folded and the perforated outer balloon 106 being folded, the inner balloon 104 being folded and the perforated outer balloon 106 being non-folded, and both the inner balloon 104 and the perforated outer balloon 106 being folded.

Returning to Figs.17 and 21, when the inner balloon 104 has been inflated at the nominal inflation pressure, the pressure inside the inflated inner balloon 104 causes the multiple regions 104P of the inner balloon 104 facing the perforations 106F to further expand and convexly bulge through the perforations 106 and protrude radially beyond the outer surface 106C. As the outer surface of the regions 106P is coated or covered by a drug or a composition as disclosed in detail hereinabove, after the inflation of the inner balloon 104 at the treatment site, the drug may be delivered to the treatment site at the regions of contact between the drug coated surfaces of the regions 104P and the treated region. Furthermore, the protective effects of the outer perforated balloon 106 of the catheter 100 resulting in reducing drug loss during passage within the vasculature, may operate, in accordance with the particular configurations of the embodiments of the catheter 100, as disclosed in detail hereinabove with respect to any of the catheters 10, 20, 30, 40, 50, 60, 70, 80 and 90.

It is noted that the type of catheter shaft usable in the drug delivery catheters of the present application is not limited to the shaft types disclosed hereinabove. For example, while the shaft 2 of Figs. 1-4 and 8-21, the shaft 22 of Figs. 5-7 are dual lumen shafts having a first lumen for inflation of the inflatable inner balloon and a second lumen for passing a guide wire there through, the catheter shafts of the drug delivery catheters of the present application may have three lumens where a first lumen (not shown) is used for inflation of the inflatable inner balloon, a second lumen for passing a

guide wire there through and a third lumen (not shown) that may be used f or injecting a contrast enhancing fluid there through or for inserting a medical instrument there through (either a diagnostic medical instrument such as, for example an IVUS diagnostic catheter or probe, or any other type of medical diagnostic device) or a medical device for treating the treatment site (such as, for example, a surgical microblade, a rotablator device, a laser fiber for tissue ablation, a radio frequency (RF) delivering probe, or any other type of surgical or medical treatment device). Such triple lumen shafts may therefore be used in some embodiments of the drug delivery catheters of the present application. Additionally, some embodiments of the catheters of the present application may include a number of lumens which may be greater than three lumens (i.e. catheter shafts including 4 or 5 lumens may be implemented in the drug delivery catheters disclosed herein, if needed, depending, inter alia, on the specific application, the allowable diameter of the catheter shaft, the type of required treatment and other considerations.

Furthermore, in some catheter embodiments, the catheter shaft may include two conduits as disclosed hereinafter.

Reference is now made to FIG. 22 which is a schematic longitudinal cross sectional view illustrating a rapid exchange (RE) drug delivery catheter having a catheter shaft including an outer conduit and an inner conduit, in accordance with an embodiment of the drug delivery catheters of the present application.

The rapid exchange drug delivery catheter 20 includes a catheter shaft 202 that includes an outer conduit 207 and an angled inner conduit 205 disposed within the outer conduit 207. The catheter 200 also includes an inflatable drug coated inner balloon 204 attached to the distal portion of the shaft 202, an outer perforated balloon 206 attached to the distal portion of the shaft 202 and a hollow connector member 212 sealingly attached to the proximal portion of the shaft 202. The proximal part of the connector member 212 includes a fluid port 212A having a hollow passage 216 passing there through. The inner conduit 207 has an outer diameter that is smaller than the diameter of the lumen 220 of the outer conduit 207. The proximal end 207P of the outer conduit 207 is firmly and sealingly attached to a recess 212R formed in the distal portion of the connector member 212, by suitably bonding or gluing or welding or ultrasonically welding of the proximal part 207P within the recess 212R.

The drug coated inner inflatable balloon 204 has a proximal end 204A sealingly attached to the outer surface of the distal end 207D of the outer conduit 207 by bonding or gluing or thermal bonding or ultrasonic welding, using any of the attaching or bonding or gluing or welding methods described in detail hereinabove. The balloon 204 has a distal end 204B sealingly attached to the outer surface 205C of the distal end 205D of the inner conduit 205 by bonding or gluing or welding or ultrasonic welding, using any of the attaching or bonding or gluing or welding methods described in detail hereinabove. The balloon 204 is fluidically in communication with the fluid port 212A through the lumen 220 of the outer conduit 207.

Inflation fluid (not shown) may be introduced into the lumen 220 and therefrom into the lumen of the inner balloon 204 through the passage 216 formed in a fluid port 212A, as disclosed in detail hereinabove by using an indeflator (not Shown) or a syringe (not shown) filled with inflation fluid connected to the fluid port 212A.

The inner conduit 205 has a straight portion 205B and an angled portion 205A which is bent or inclined at an angle to the straight portion 205B. The angled portion 205A pierces the wall of the outer conduit 207 and is sealingly and firmly attached to the wall of the outer conduit 207 to prevent leakage of any inflation fluid introduced into the lumen 220 through the opening 216 of the fluid port 212A. As the angled portion 205A is firmly sealingly attached to the wall of the outer conduit 207, the inner conduit 205 is longitudinally fixed relative to the outer conduit 207 and is longitudinally unmovable relative to the outer conduit 207 (i.e., the inner conduit 205 cannot be moved in the proximal or distal direction relative to the outer conduit 207). The distal end 205D of the inner conduit 205 extends distally beyond the distal end 207D of the outer conduit 207 such that a portion of the inner conduit 205 protrudes distally and extends distally beyond the distal end 207D of the outer conduit 207.

A hollow soft tip 209 may (optionally, but not obligatorily) be attached to the distal end 205D of the inner conduit 205 (as disclosed in detail with respect to the soft tip 9 of Fig. 1).

An opening 215 is disposed in the wall of the outer conduit 207 at the proximal end of the angled portion 205A of the inner conduit 205. The opening 215 allows the insertion of a guide wire 3 into the lumen 213 of the inner conduit 205. The guide wire

3 may be pushed through the lumen 213 until it exits from an opening 209A at the distal end of the soft tip 209.

The perforated outer balloon 206 has a distal end 206B and a proximal end 206A. The proximal end 206A of the balloon 206 is sealingly attached to the distal end 207D of the outer conduit 207 by gluing, bonding, thermal bonding, ultrasonic welding or by any other suitable attachment method. The distal end 206B of the outer perforated balloon 206 is sealingly attached to the distal end 205D of the inner conduit 205 by gluing, bonding, thermal bonding, ultrasonic welding or by any other suitable attachment method.

In some embodiments, the inflatable inner balloon 204 and the perforated outer balloon 206 may be arranged around the catheter shaft 202 in a non-wrapped (non-folded) arrangement similar to the arrangement of the balloons 4 and 6 around the shaft 2 as illustrated in Figs. 2-3 hereinabove. In such embodiments, the inner balloon 205 surrounds is not folded and surrounds the distal portion of the inner conduit 205 that protrudes distally beyond the distal end 207D of the outer conduit 207, and the outer perforated balloon 207 is also not folded and surrounds the inner balloon 204.

In some other embodiments, the inflatable inner balloon 204 and the perforated outer balloon 206 may be arranged around the catheter shaft 202 in a wrapped (folded) arrangement similar to the arrangement of the balloons 44 and 46 around the shaft 2 as illustrated in Figs 8-9 hereinabove. In such embodiments, the inner balloon 204 is wrapped or folded around the distal portion of the inner conduit 205 that protrudes distally beyond the distal end 207D of the outer conduit 207 and the outer perforated balloon 206 is not folded and surrounds the folded inner balloon 204.

In some additional embodiments, the inflatable inner balloon 204 and the perforated outer balloon 206 may be arranged around the catheter shaft 202 in a wrapped (folded) arrangement similar to the arrangement of the balloons 54 and 56 around the catheter shaft 2 as illustrated in Figs 10-11 hereinabove. In such embodiments, the inner balloon 204 is wrapped or folded around the distal portion of the inner conduit 205 that protrudes distally beyond the distal end 207D of the outer conduit 207 and the outer perforated balloon 206 is wrapped or folded around the inner balloon 204

In some additional embodiments, the inflatable inner balloon 204 and the perforated outer balloon 206 may be arranged around the catheter shaft 202 such that the inner

balloon 204 surrounds the inner conduit 205 in a non-folded arrangement and the outer perforated balloon 206 is arranged in wrapped (folded) arrangement around the distal part 207D of the outer conduit 207 and around the non-folded inner balloon 205 that surrounds the distal part 205D of the inner conduit 205. This arrangement is similar to the arrangement of the balloons 64 and 66 around the catheter shaft 2 as illustrated in Figs 12-13 hereinabove.

The various steps of operating the rapid exchange catheter 200 are similar to the steps of operating the over the wire (OVT) catheters and the rapid exchange (RE) as described hereinabove and illustrated in Figs. 1-21, with the exception that the guide wire 3 is inserted into the lumen 213 of the inner conduit 205 through the opening 215 disposed on the wall of the outer conduit 207 However, other steps of the operation of the catheter 200, including inserting the catheter into the body or bodily vasculature, moving the catheter within the vasculature to reach a region to be treated, inflating the inner balloon 204 to expand the inner balloon 204 and the outer balloon 206 for treating a constriction or atheromatous plaque within the vessel (as illustrated in Figs. 1 -13) and for delivering at least some of the drug coating the inner balloon 204 through some or all of the perforations 206 F of the expanded perforated balloon 206 with or without the optional step of deployment of an stent disposed on the outer perforated balloon 206.

In embodiments of the catheter 200, in which one or more of the inner balloon 204 and the outer balloon 206 are folded as disclosed hereinabove, the lower crossing profile achieved by the folded configuration improves the passability and pushability of the distal end of the catheter 200, into and/or through the blood vessel and/or a constricted region such as an atheroma or plaque in an atheromatous blood vessel.

Reference is now made to FIG. 23, which is a schematic longitudinal cross sectional view illustrating an "over the wire" (OVT) drug delivery catheter having a catheter shaft including an outer conduit and an inner conduit, in accordance with an embodiment of the drug delivery catheters of the present application.

The OVT catheter 300 includes a catheter shaft 302, an inner drug coated inflatable balloon 304, an outer perforated balloon 306 and a connector member 312. The shaft 302 includes an outer conduit 307 and an inner conduit 305 disposed within the outer conduit 307. The inner inflatable balloon 304 is similar in structure and composition to

the inner inflatable balloon. The outer conduit 307 is preferably (but not obligatorily) a tubular conduit. The outer conduit 307 has a distal end 307D and a proximal end 307P. The inner conduit 305 is disposed within the lumen 320 of the outer conduit 307. The inner conduit 305 is also preferably (but not obligatorily) a tubular conduit having an outer diameter smaller than the diameter of the lumen 320 of the outer conduit 307. The inner conduit 305 has a distal end 305D and a proximal end 305P. The distal end 305D of the inner conduit 305 extends (protrudes) beyond the distal end 307D of the outer conduit 307 such that a distal portion of the inner conduit 305 protrudes distally from and extends distally beyond the distal end 307D of the outer conduit 307. The inner conduit 305 and the outer conduit 307 (as well as the inner conduit 205 and the outer conduit 207 of the catheter 200) may be made from flexible materials, such as but not limited to, Nylon®, Pebax®, polyurethane, Polyethyleneterephtalate (PET), stainless steel or from any other suitable flexible material as disclosed in detail hereinabove with respect to the shaft 2 (of Fig. 1).

The proximal end 305P of the inner conduit 305 and the proximal end 307P of the outer conduit 307 are sealingly and firmly attached to the connector member 312 as illustrated in Fig. 23. The attachment of the proximal ends 305P and 307P to the connector member 312 may be done by bonding, thermal bonding, gluing or by any other suitable attaching method. The connector member 312 may be made from any suitable material, including but not limited to, a polymer, a metal or an alloy (such as, but not limited to, PEBAX, Stainless steel or any other suitable engineering plastic or polymer based structural material). Due to the firm attachment of the proximal ends 305P and 307P to the connector member 312, the inner conduit 305 is not movable longitudinally with respect to the outer conduit 307.

The connector member 312 has two hollow passages therein. A first hollow passage 316 opens into the lumen of the inner conduit 6 and allows the insertion of a guide wire 14 into and through the lumen of the inner conduit 313 through a guide wire insertion port 312A of the connector member 312. The lumen 313 may be passed over a guide wire 3, and the guide wire 3 may be used to guide the insertion of the catheter 300 into a treatment region within a body passage (such as, but not limited to, a blood vessel). A second hollow passage 318 is formed within a fluid port 312B of the connector member 312 that allows the introduction of an inflation fluid into the space 320 formed

between the inner surface 307C of the outer conduit 307 and the outer surface 305C of the inner conduit 305. If the inner conduit 305 and the outer conduit 307 have a circular cross-section, the lumen 320 is an annular lumen.

Because of the fixed attachment of both the inner conduit 305 and the outer conduit 307 to the connector member 312, the inner conduit 305 is axially unmovable and cannot be longitudinally moved with respect to the outer conduit 307 in the proximal-distal direction. However, due to the flexibility of the inner conduit 305 and the outer conduit 307, the shaft 302 of the catheter 300 may be flexed and bent sideways such that it is capable of being pushed along the guide wire 3 within tortuous or bending bodily passages (such as, but not limited to, blood vessels).

The inflatable inner balloon 304 and the perforated outer balloon 306 may be similar in construction and composition to the inflatable inner balloon 4 and the perforated outer balloon 6, respectively (of Figs. 1-3), as disclosed in detail hereinabove.

The inner balloon 304 is typically capable of withstanding inflation pressures within the range of 4-25 atmospheres. However, the inner balloon 304 may be implemented to withstand inflation pressures lower than 4 atmospheres or higher than 25 atmospheres, depending, inter alia on the balloon dimensions, balloon wall thickness, the material from which the balloon is made and the specific application for which the catheter is designed.

Typical dimensions of the inner balloon 304 may be a balloon diameter in the range of 2-8 millimeters, a balloon length in the range of 8-300 millimeters and a balloon wall thickness in the range of 0.01- 0.1 millimeters. However, these ranges are by no means obligatory or limiting and other higher or lower values of the balloon length, balloon diameter and balloon wall thickness which are outside the typical ranges indicated above may also be used, depending, inter alia, on the specific application for which the catheter is designed.

In some embodiments, the inflatable inner balloon 304 and the perforated outer balloon 306 may be arranged around the catheter shaft 302 in a non-wrapped (non-folded) arrangement similar to the arrangement of the balloons 4 and 6 around the shaft 2 as illustrated in Figs. 2-3 hereinabove. In such embodiments, the inner balloon 305 surrounds is not folded and surrounds the distal portion of the inner conduit 305 that

protrudes distally beyond the distal end 307D of the outer conduit 307, and the outer perforated balloon 307 is also not folded and surrounds the inner balloon 304.

In some other embodiments, the inflatable inner balloon 304 and the perforated outer balloon 306 may be arranged around the catheter shaft 302 in a wrapped (folded) arrangement similar to the arrangement of the balloons 44 and 46 around the shaft 2 as illustrated in Figs 8-9 hereinabove. In such embodiments, the inner balloon 304 is wrapped or folded around the distal portion of the inner conduit 305 that protrudes distally beyond the distal end 307D of the outer conduit 307, and the outer perforated balloon 306 is not folded and surrounds the folded inner balloon 304.

In some additional embodiments, the inflatable inner balloon 304 and the perforated outer balloon 306 may be arranged around the catheter shaft 302 in a wrapped (folded) arrangement similar to the arrangement of the balloons 54 and 56 around the catheter shaft 2 as illustrated in Figs 10-11 hereinabove. In such embodiments, the inner balloon 304 is wrapped or folded around the distal portion of the inner conduit 305 that protrudes distally beyond the distal end 307D of the outer conduit 307 and the outer perforated balloon 306 is wrapped or folded around the inner balloon 304.

In some additional embodiments, the inflatable inner balloon 304 and the perforated outer balloon 306 may be arranged around the catheter shaft 302 such that the inner balloon 304 surrounds the inner conduit 305 in a non-folded arrangement and the outer perforated balloon 306 is arranged in wrapped (folded) arrangement around the distal part 307D of the outer conduit 307 and around the non-folded inner balloon 305 that surrounds the distal part 305D of the inner conduit 305. This arrangement is similar to the arrangement of the balloons 64 and 66 around the catheter shaft 2 as illustrated in Figs 12-13 hereinabove.

The various steps of operating the OVT catheter 300 are similar to the steps of operating the over the wire (OVT) catheters and the rapid exchange (RE) as described hereinabove and illustrated in Figs. 1-22, with the exception that the guide wire 3 is inserted into the lumen 313 of the inner conduit 305 through the opening of the hollow passage 516 of the guide wire insertion port 312A However, other steps of the operation of the catheter 300 may be similar to the steps disclosed hereinabove with respect to the operation of any of the catheters disclosed herein, including inserting the catheter 300 into the body or bodily vasculature, moving the catheter 300 within the

vasculature to reach a region to be treated, inflating the inner balloon 304 to expand (and/or unfold, where relevant, depending on the specific arrangement of the inner balloon 304 and the outer perforated balloon of the catheter embodiment being used) the inner balloon 304 and the outer balloon 306 for treating a constriction or atheromatous plaque within the vessel (as illustrated in Figs. 1-13) and for delivering at least some of the drug coating the inner balloon 304 through some or all of the perforations 306 F of the expanded perforated balloon 306 with or without the optional step of deployment of an stent disposed on the outer perforated balloon 306.

In embodiments of the catheter 300, in which one or more of the inner balloon 304 and the outer balloon 306 are folded as disclosed hereinabove, the lower crossing profile achieved by the folded configuration improves the passability and pushability of the distal end of the catheter 300, into and/or through the blood vessel and/or a constricted vessel region such as an atheroma or plaque in an atheromatous blood vessel.

It is noted that the shapes of the inflatable drug coated inner balloons and of the perforated outer balloons of the drug delivery catheters of the present application are not limited to the balloon shapes disclosed hereinabove and illustrated in Figs. 1-23. Rather the inflatable inner balloons and the perforated outer balloons of the drug delivery catheters of the present application may have any suitable shape depending, inter alia on the application.

Reference is now made to Fig. 24, which is a schematic cross sectional view illustrating part of an OVT drug delivery balloon catheter, having a conically shaped inflatable inner balloon and a conically shaped perforated outer balloon, in accordance with an embodiment of the catheters of the present application.

The catheter 400 (only part of which is illustrated in Fig. 24) may configured as an "over the wire" (OVT) catheter. The catheter 400 may include a hollow shaft 2, a conically shaped inflatable inner balloon 404 attached to the shaft 2 and a perforated conically shaped outer balloon 406 attached to the shaft 2. The balloons 404 and 406 may be made from any of the materials disclosed hereinabove. The outer surface 404C of the inflatable inner balloon 404 is coated with a drug or with a composition comprising a drug (or a combination of drugs) as disclosed in detail hereinabove with respect to the balloon 4 of Fig. 1.

All of the different various combinations of attachment of the proximal end 404A and distal end 404B of the balloon 404 and of the proximal end 406A and the distal end 406B of the balloon 406 to various regions of the surface 2C of the shaft 2 (as illustrated in Figs. 1, 14, 15 and 16) may be used in different embodiments of the catheter 400.

In some embodiments, the inner balloon 404 may be non-folded. In some other embodiments, the balloon 404 may be folded around the shaft 2. In some embodiments, the perforated outer balloon 406 may be non-folded. In some other embodiments, the perforated outer balloon 406 may be folded around the inner balloon 404 and/or portion(s) of the shaft 2. The arrangement of such different combinations and permutations of folding arrangements may be similar to the arrangements illustrated in Figs. 2,3,5,6, and 8-11).

When the conical inner balloon 404 is inflated, it may unfold (if it was folded initially) and expand to reach a nominal inflated diameter. The inflation and expansion of the balloon 404 may result in unfolding the perforated outer balloon 406 (if it was folded initially) and expands the outer perforated balloon 406. If the inner balloon 404 and/or the perforated balloon 406 are made from a stretchable material, the balloons 404 and/or 406 may also stretch following the inflation of the inflatable balloon 404.

If the perforated outer balloon 406 is made from a stretchable material(s), the diameter and/or the area of the perforations 406F may increase compared to their diameter and area prior to inflation of the inner inflatable balloon 404. This perforation enlarging action may increase the area of the portions of drug coated outer surface 404C of the inner balloon 404 which may protrude through the perforations 406F to contact the treated region (of the body cavity or blood vessel), which may result in more efficient drug transfer to the treated region, as disclosed in detail hereinabove for other embodiments of the catheters.

The shaft 2 may be similar to the shaft 2 of Fig. 1 as disclosed in detail hereinabove and is a double lumen hollow shaft having a first lumen 2A for passing the catheter 400 over a guide wire 3, and a second lumen 2B for passing inflation fluid there through for inflating the inflatable inner balloon 404 through an opening 2D. A proximal connector member (not shown in Fig. 24) of the catheter 400 may be similar to the connector member 15 of Fig. 1 hereinabove. The proximal connector member 15 may

be used for inflating and/or deflating the inflatable inner balloon 404 through the inflation port 15B as disclosed in detail hereinabove for the catheter 10 of Fig. 1. The passing of the catheter 400 over a guide wire 3 may be performed using the opening 9B of the soft tip 9 and the guide wire insertion port 15A of the proximal connector member 15, as disclosed in detail hereinabove with respect to the catheter 10 of Fig. 1.

The proximal end 404A of the inner balloon 404 is sealingly attached to a first region of the outer surface 2C of the shaft 2 and the distal end 404B of the inner balloon 404 is sealingly attached to a second region of the outer surface 2C of the shaft 2. The proximal and distal end 404A and 404B, respectively, of the inner balloon 404 may be sealingly attached to the outer surface 2C by gluing or welding or thermal bonding or ultrasonic welding or by any other suitable attachment method. The outer surface 4C of the inner balloon 4 is coated or covered with a layer of a drug or a layer of a material composition or therapeutic formulation or therapeutic composition comprising one or more drugs and/or active agents, and/or active ingredient(s) as is disclosed in detail for the balloon 4 hereinabove (it is noted that, in all of the drawing figures the catheter embodiments disclosed in the present application, the layer of drug or composition coating the outer surface of the inner balloons is not shown, for the sake of clarity of illustration).

In contrast to the inflatable inner balloon 4 and the perforated outer balloon 6 of Fig. 1 which may be generally cylindrical balloons with tapering ends, the inflatable inner balloon 404 and the perforated outer balloon 406 are generally conically shaped balloons which may have tapering ends.

Such conical balloons may be effectively used in cases in which the part of the vasculature that needs to be treated is also conically shaped. For example, such conical balloons may be used for treating lesions and/or opening constricted regions of peripheral blood vessels such as, for example, peripheral veins of the legs or the arms or in any other type of blood vessel or bodily cavity that has a conical shape.

It is noted that the distance between the outer surface 2C of the shaft 2 and the inner surface 404D of the inner balloon 404 as well as the distance between the outer surface 404C of the inner balloon 404 and the inner surface 406D of the balloon 406 are somewhat exaggerated in Fig. 24 for the sake of clarity of illustration (in order to clearly discern the different parts and portions of the inner balloon 404, the outer balloon 506

and the shaft 2). In some embodiments of the catheters of the present application, some parts or portions of the inner surface 404D of the inner balloon 404 may be in contact with the outer surface 2C of the shaft 2 and some parts or portions of the inner surface 406D of the outer balloon 406 may be in contact with the outer surface 404C of the inner balloon 404.

Reference is now made to FIG. 25 which is a schematic cross sectional view illustrating part of an OVT drug delivery balloon catheter having stepped inner and outer balloons illustrated in an inflated state, in accordance with an embodiment of the catheters of the present application.

The catheter 500 (only a part of which is illustrated in Fig. 25) may include the catheter shaft 2 as disclosed in detail hereinabove a stepped inflatable drug coated inner balloon 504 sealingly attached to the shaft 2, a stepped perforated outer balloon 506 that may be sealingly attached to the shaft 2 and the hollow soft tip 9 attached to the distal end of the shaft 2 as disclosed in detail hereinabove.

The proximal end 504A of the inner balloon 504 is sealingly attached to the outer surface 2C of the shaft 2. The distal end 504B of the inner balloon 504 is sealingly attached to the outer surface 2C of the shaft 2.The proximal end 506A of the inner balloon 504 is sealingly attached to the outer surface 2C of the shaft 2. The distal end 506B of the inner balloon 506 is sealingly attached to the outer surface 2C of the shaft 2. When the inner balloon 504 is inflated with inflation fluid at the nominal inflation pressure, the inflation fluid enters the lumen 504E of the balloon 504 from the opening 2D of the shaft 2 and exerts pressure on the inner surface 504D of the balloon 504 to inflate the balloon 504. The inflation and expansion of the inner balloon 504 of may result in the opening (and/or unfolding, if the outer balloon 506 is in a folded state prior to inflation of the inner balloon 504) and expanding of the outer perforated balloon 506. The expansion of the outer perforated balloon 506 may result in an in the open area of the multiple perforations 506F of the outer balloon 506, as disclosed hereinabove in detail with respect to other catheter embodiments. When the inner drug coated balloon 504 is inflated at the nominal inflation pressure, the parts or portions of the balloon 504 underlying the perforations 506F may bulge or become convexly curved and/or may protrude beyond the outer surface of the perforated balloon 506. For example, the exemplary convexly curved protruding portions 504K, 504L and 504M of the inner

balloon 504 protrude out of the corresponding perforations 506F and their drug or composition coated outer surfaces may come in contact with the region to be treated(not shown in Fig. 25), as disclosed in detail hereinabove with respect to the catheters 10, 20, 30, 40 and 50.

When the inner balloon 504 is inflated to the nominal inflation pressure (as illustrated in Fig. 25), the stepped perforated outer balloon 506 has a substantially cylindrical proximal portion (schematically underlying the double headed arrow **U**), a substantially cylindrical middle portion (schematically underlying the double headed arrow **V**), and a distal portion (schematically underlying the double headed arrow **W**).

When the inner balloon 504 is inflated to the nominal inflation pressure, the inner balloon 504 has a substantially cylindrical proximal portion (schematically underlying the double headed arrow **U**), a substantially cylindrical middle portion (schematically underlying the double headed arrow **V**), and a distal portion (schematically underlying the double headed arrow **W**).

When the inner balloon 504 is inflated to the nominal inflation pressure, the diameter of the cylindrical middle portion of the balloon 504 is larger than the diameter of the proximal and distal cylindrical portions of the inner balloon 504.

When the inner balloon 504 is inflated to the nominal inflation pressure, the diameter of the cylindrical middle portion of the outer balloon 506 is larger than the diameter of the proximal and distal cylindrical portions of the outer balloon 506.

As may be seen in Fig. 25, only the middle portion (with the larger diameter) of the outer balloon 506 is perforated, while the proximal portion and the distal portion of the outer balloon 506 which have smaller diameters are not perforated.

In some embodiments, the entire outer surface 504C of the inner balloon 504 may be coated or covered by the drug(s) or the composition comprising a drug (or drugs). In some other embodiments, only a portion or part of the outer surface 504C of the inner balloon 504 may be coated with such drug(s) or composition including a drug (or drugs). For example, in the embodiment illustrated in Fig. 25, only the portion of the outer surface 504C of the middle portion of the inner balloon 504 may coated with the drug(s) or composition.

In some embodiments, prior to inflation of the inflatable inner balloon 504, each of the inner stepped inflatable balloon 504 and/or the outer perforated balloon 506 may be

either folded or non-folded, and all possible combinations of folded and non-folded balloons disclosed in the present application for other catheter embodiments may be applied to the arrangement of the balloons 504 and 506 of the catheter 500 in different embodiments thereof. For example, in the non-inflated or pre-inflated state of the catheter 500, in some embodiments, the inner balloon 504 may be non-folded and the outer balloon 506 may be non-folded. In other embodiments, the inner balloon 504 may be non-folded and the outer balloon 506 may be folded. In yet other embodiments, the inner balloon 504 may be folded and the outer balloon 506 may be non-folded. In other embodiments, the inner balloon 504 may be folded and the outer balloon 506 may be folded.

Furthermore, the attachment of the proximal ends (504A and 506A) and the distal ends (504B and 506B) of the inner balloon 504 and the outer balloon 506, respectively, to various different regions of the outer surface 2C of the shaft 2 and/or to each other, may be arranged, in different embodiments of the catheter with stepped balloons, in any of the types of attachment arrangements disclosed in detail hereinabove with respect to the catheters 10, 20, 30, 40, 50, 70, 80 and 90.

In accordance with some exemplary embodiments, the inner inflatable balloons disclosed in the present application may be a non-compliant or semi-compliant balloon which may be made from a suitable polymer based material, such as, but not limited to, Nylon® (such as, for example, Nylon 12®), PET, polyamide (PA) such as PA12 (for example Grilamid® L25, L55 and the like), PA11, Polyether block amides (PEBA, such as for example PEBAX® 7233, PEBAX®7033 and PEBAX®6333), various types of Grilflex® (such as, for example, ELG 6260), and the like. Nevertheless, is accordance with certain embodiments of the catheters disclosed herein, the inflatable inner balloons used may be made of a highly compliant material such as, for example, rubber, Latex® and any other highly compliant biocompatible elastic materials known in the art. However, any other suitable biocompatible material known in the art and suitable for fabrication of catheter balloons may be used in implementing the balloons of the present application.

The outer perforated balloons disclosed in the present application may be a non-compliant balloon or a semi-compliant balloon which may be made from a suitable polymer based material, such as, but not limited to, Nylon® (such as, for example Nylon

12®), PET, polyamide (PA) such as PA12 (for example Grilamid® L25, L55 and the like), PA11, Polyether block amides (PEBA, such as for example PEBAX® 7233, PEBAX®7033 and PEBAX®6333), various types of Grilflex® (such as, for example, ELG 6260), or any other suitably biocompatible compliant or semi-compliant material known in the art. Nevertheless, is accordance with certain embodiments of the catheters disclosed herein, the outer perforated balloons used in some of the catheters of the present application may be made of a highly compliant material such as, for example, rubber, Latex® and any other highly compliant biocompatible elastic materials known in the art. However, any other suitable biocompatible material known in the art and suitable for fabrication of catheter balloons may be used in implementing the balloons of the present application.

Typical dimensions of the perforated outer balloons (such as, but not limited to the outer perforated balloons 6, 16, 26, 46, 56, 66, 76, 86, 96 and 106) may be a balloon diameter in the range of 2-8 millimeters, a balloon length in the range of 8-300 millimeters and a balloon wall thickness in the range of 0.01-0.1 millimeters. However, these ranges are by no means obligatory or limiting and other higher or lower values of the balloon length, balloon diameter and balloon wall thickness outside the typical ranges indicated above may be used, depending, *inter alia*, on the specific application for which the catheter is designed.

Typically, the outer perforated balloons of the catheters of the present application are capable of withstanding the forces exerted by the corresponding inner (drug coated) balloon used in the catheter when the inner balloon of the catheter is inflated to its nominal inflated diameter. The outer perforated balloons may also increase the internal pressure the inner balloon can withstand by supporting (or reinforcing) the inner balloon when the inner balloon 4 is inflated. This desirable reinforcing effect may be achieved by suitably selecting, *inter alia*, the wall thickness of the outer perforated balloon 6, and the mechanical properties of the material(s) from which the outer perforated balloon is made.

Typical dimensions of the outer perforated balloons of the catheters of the present application may be a balloon diameter in the range of 2-15 millimeters, a balloon length in the range of 8-300 millimeters and a balloon wall thickness in the range of 0.01-0.1 millimeter. However, these ranges are by no means obligatory or limiting and other

higher or lower values of the outer perforated balloon length, outer perforated balloon diameter and outer perforated balloon wall thickness outside the typical ranges indicated above may be used, depending, inter alia, on the specific application for which the catheter is designed. For example, if the catheter is used for treating peripheral veins, the diameter of the outer perforated balloon in the fully expanded state and the diameter of the inner balloon at the nominal inflation pressure may be even larger than 15 millimeters (if treating large peripheral veins or the vena cava).

Thus, in any of the catheters of the present application any of the following combinations may be usable:

a) A stretchable (semi-compliant or compliant) outer perforated balloon with a non-compliant, non-stretchable inner balloon.

b) A stretchable (semi-compliant or compliant) outer perforated balloon with a semi-compliant, stretchable inner balloon.

c) A non-stretchable (non-compliant) outer perforated balloon with a semi-compliant, stretchable inner balloon.

d) A non-stretchable (non-compliant) outer perforated balloon with a highly compliant inner balloon.

e) A stretchable (semi-compliant) outer perforated balloon with a highly compliant inner balloon (such as, for example a Latex® balloon).

In the above combinations **a-e**, the inner inflatable drug coated balloon and/or the outer perforated balloon may be folded or not folded, as required by the application and by the circumference of the inner balloon and/or the outer perforated balloon when they are in the non-inflated state or in the non opened and/or non-unfolded state.

It is noted that in some embodiments of the drug delivering catheters of the present application, the length of the inner balloon may be equal to the length of the outer perforated balloon (see for an example the catheter 70 of Fig. 14), while in some other embodiments of the catheter, the length of the inner balloon may be smaller than the length of the outer perforated balloon (see the exemplary catheters 80 and 90 of Figs. 15 and 16, respectively and the exemplary catheters 200 300, 400 and 500 of Figs. 22, 23, 24 and 25, respectively).

In other embodiments (not shown in the drawing figures) in which the proximal and distal ends of the outer perforated balloon are attached to the proximal and distal ends,

respectively of the inner balloon, the length of the inner balloon (as measured from the most distal end of the inner balloon to the most proximal end of the inner balloon) may be actually larger than the length of the outer perforated balloon (as measured from the most distal end of the outer perforated balloon to the most proximal end of the outer perforated balloon).

In use, any of the drug delivery catheters disclosed in the present application may be inserted into the vasculature using any clinically acceptable entry point as is known in the art. After insertion of the catheter (preferably over a guide wire), the catheter is navigated through the vasculature in a non-inflated or pre-inflated state to advantageously achieve protection against drug washout and to prevent or at least reduce any flakes or particles of the drug carrying formulation from entering the blood stream. Once the distal part of the catheter is placed in the region to be treated (such as, for example, a stenosed blood vessel region, an atheroma or a plaque), the inner balloon of the catheter may be inflated at the nominal inflation pressure to expand (and/or unfold, if relevant) the inner balloon. The inner balloon may also radially expand and/or unfold, (if relevant) the outer perforated balloon by radially pushing the outer perforated balloon. The pushing by the radially expanding inner balloon may either increase the area of the perforations and/or may uncover any perforations that were covered by regions of the outer perforated balloon (if the outer perforated balloon is folded). The pushing by the radially expanding inner balloon may also result in both increasing the area of the perforations and uncovering previously covered perforations (such as, for example, in catheter embodiments with semi-compliant inner and outer perforated balloons having a folded outer perforated balloon, or in catheter embodiments with a compliant inner balloon and a compliant outer perforated balloon and a folded outer perforated balloon).

After inflation of the inner balloon, the expanded outer perforated balloon pushes the walls of the treated region and may open or enlarge the constricted lumen of the blood vessel and may also compress and/or compact the atheroma.

At the inflated state, due to the enlargement of the area of the perforations and/or the uncovering of perforations previously covered by parts of the folded perforated outer balloon, the drug or drugs may be applied to the treated region by exiting through the enlarged area of the perforations, facilitating drug transfer from the drug coated surface

of the inner balloon to at least some regions of the treatment site. In some embodiments of the catheters, this drug transfer to the treated region may be assisted by the protrusion of drug coated surface regions of the inner balloon which may bulge out of the perforations and may contact the walls of the treated region of the blood vessel when the inner balloon is inflated at the nominal inflation pressure. Optionally, if the catheter carries a stent (which may be optionally disposed on the outer surface of the outer perforated balloon), the inflation of the inner balloon may also open and deploy the stent, as is well known in the art of angioplasty using stent carrying catheters. After treatment of the target region is performed (with or without stent deployment), the inner balloon may be deflated. After deflating of the inner balloon, the inner balloon and the outer perforated balloon may radially contract, and the catheter may be withdrawn through the vasculature and removed from the body.

It is noted that the above disclosed methods for using the drug delivery catheters of the present application, may also include further steps in which the guide wire 3 may be removed (if a guide wire was being used in the method) from the lumen of the catheter into which it was inserted and a surgical tool and/or a diagnostic tool or any other assisting tools for angioplasty may be inserted into the same lumen and advanced towards the treated region to further treat or manipulate the target region if necessary.

Such tools may include, but are not limited to, a surgical blade, a snare, a rotablator, a surgical laser device, a laser-coupled optical fiber, an occluding inflatable balloon or any other surgical tools or assisting tools known in the art. Diagnostic tools may include, but are not limited to, a camera, an infra-red camera or any other optical imaging tool, an ultrasonic imaging tool (IVUS), a miniature MRI tool for imaging blood vessel walls, a chemical sensor, and any other suitable diagnostic tool. Such surgical tools and/or diagnostic tools and/or assisting tools may be inserted into the lumen of the catheter that is used for passage of a guide wire (after removing the guide wire) at any stage of use of the catheter, including, but not limited to, the stage in which the outer balloon is disposed in the target region but before inflation of the inner balloon of the catheter, the stage after the inner balloon is inflated at the nominal inflation pressure, or any other suitable stage of the operation of the catheter.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single

embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference 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. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A catheter for delivering a drug, the catheter comprising:

a shaft having an outer surface;

an inflatable inner balloon sealingly attached to the shaft, the inflatable inner balloon has an outer surface, at least a portion of the outer surface is coated with a drug or a composition comprising a drug; and

a perforated outer balloon sealingly attached to the shaft and/or to the inner balloon, the outer perforated balloon surrounds the inflatable inner balloon, the outer perforated balloon comprises therein a plurality of perforations formed in at least a portion of the perforated outer balloon.

2. The catheter according to claim 1, wherein the shaft is a double lumen hollow shaft having a first lumen for inserting a guide wire therethrough and a second lumen for passing inflation fluid therethrough for inflating the inflatable inner balloon.

3. The catheter according to claim 2, wherein the drug delivery catheter is configured as an "over the wire" (OVT) catheter and the first lumen has a proximal opening at a proximal end of the catheter and a distal opening at the distal end of the catheter for passing the catheter over a guide wire.

4. The catheter according to claim 2, wherein the catheter is configured as a rapid exchange (RE) catheter and the first lumen has an opening disposed on the shaft at a position located between the proximal end of the catheter and the proximal end of the perforated outer balloon, the first lumen has a second opening at the distal end thereof for passing the catheter over a guide wire.

5. The catheter according to any of claims 1-4, wherein a proximal end of the inflatable inner balloon is sealingly attached to a first region of the outer surface of the shaft and a distal end of the inflatable inner balloon is sealingly attached to a second region of the outer surface of the shaft.

6. The catheter according to claim 5, wherein a proximal end of the perforated outer balloon is sealingly attached to a third region of the outer surface and a distal end of the perforated outer balloon is sealingly attached to a fourth region of the outer surface, the third region is disposed on the outer surface proximal to the first region and the fourth region is disposed on the outer surface distal to the second region.

7. The catheter according to claim 5, wherein a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is sealingly attached to the distal end of the inflatable inner balloon.

8. The catheter according to claim 5, wherein a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is sealingly attached to a third region of the outer surface of the shaft, the third region is disposed on the outer surface of the shaft distal to the second region.

9. The catheter according to claim 5, wherein a distal end of the perforated outer balloon is sealingly attached to the distal end of the inflatable inner balloon and a proximal end of the perforated outer balloon is sealingly attached to the outer surface of the shaft at a third region of the outer surface of the shaft, the third region is disposed on the outer surface proximal to the first region.

10. The catheter according to claim 1, wherein the shaft comprises a hollow outer conduit having a first lumen and a hollow inner conduit disposed within the first lumen, the inner conduit has a second lumen suitable for passage over a guide wire, the inner conduit is fixed relative to the outer conduit and is longitudinally unmovable within the second lumen of the inner conduit, wherein a portion of a distal end of the inner conduit protrudes beyond the distal end of the outer conduit.

11. The catheter according to claim 10, wherein the catheter is configured as an "over the wire" (OVT) catheter wherein the second lumen of the inner conduit has a

first opening disposed at a proximal end of the shaft and a second opening disposed at the distal end of the catheter, for passing the second lumen over a guide wire.

12. The catheter according to claim 10, wherein the catheter is configured as a rapid exchange (RE) catheter, wherein the proximal end of the inner conduit is bent and is sealingly attached to a region of wall of the outer conduit such that the second lumen has an first opening disposed on an outer surface of the outer conduit at a position located between the proximal end of the catheter and the proximal end of the perforated outer balloon, the second lumen has a second opening disposed at a distal end of the inner conduit for passing the second lumen of the inner conduit over a guide wire.

13. The catheter according to any of claims 11-12, wherein a proximal end of the inflatable inner balloon is sealingly attached to a first region of an outer surface of the distal end of the outer conduit and a distal end of the inflatable inner balloon is sealingly attached to a second region of an outer surface of the portion of the distal end of the inner conduit that protrudes beyond the distal end of the outer conduit.

14. The catheter according to claim 13, wherein a proximal end of the perforated outer balloon is sealingly attached to a third region of the outer surface of the distal end of the outer conduit and a distal end of the perforated outer balloon is sealingly attached to a fourth region of the outer surface of the portion of the inner conduit that protrudes distally beyond the distal end of the outer conduit, the third region is disposed on the outer surface of the outer conduit proximal to the first region and the fourth region is disposed on the outer surface of the inner conduit distal to the second region.

15. The catheter according to claim 13, wherein a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is attached to the distal end of the inflatable inner balloon.

16. The catheter according to claim 13, wherein a proximal end of the perforated outer balloon is sealingly attached to the proximal end of the inflatable inner balloon and a distal end of the perforated outer balloon is sealingly attached to a third region of the outer surface of the inner conduit, the third region is disposed on the outer surface of the portion of the inner conduit that protrudes distally beyond the distal end of the outer conduit distal to the second region.

17. The catheter according to claim 13, wherein a distal end of the perforated outer balloon is sealingly attached to the distal end of the inflatable inner balloon and a proximal end of the perforated outer balloon is sealingly attached to the outer surface of the outer conduit at a third region of the outer surface of the outer conduit, the third region is disposed on the outer surface of the outer conduit proximal to the first region.

18. The catheter according to any of claims 1-17, wherein the inner inflatable balloon is selected from, a substantially cylindrically shaped balloon, a substantially conically shaped balloon and a stepped balloon.

19. The catheter according to any of claims 1-17, wherein the perforated outer balloon is selected from a substantially cylindrically shaped balloon, a substantially conically shaped balloon and a stepped balloon.

20. The catheter according to any of the previous claims, wherein the drug or composition comprising a drug includes one or more of a therapeutic substance, a diagnostic substance, a drug, a therapeutic composition, a medicament, a diagnostic composition, a physiologically active agent, a biochemically active agent, one or more living cells, DNA, RNA, a nucleic acid, a vector for delivering genetic material to cells in the treated site, an anti-inflammatory agent, an anti-restenosis agent, a cell proliferation inhibitory agent, a smooth muscle proliferation inhibiting agent, paclitaxel, rapamycin, everolimus, a vaso-active agent, a vaso dilating agent, a vaso constricting agent, an antibiotic agent, an anti-coagulative agent, a platelet aggregation inhibiting agent, an anti-fibrosis agent, a pharmaceutically acceptable vehicle, a lipid based vehicle, and any combinations thereof.

21. The catheter according to any of the preceding claims, wherein the drug or the composition comprising a drug are encapsulated is a drug carrier system selected from a nanoparticle based carrier system and liposomes.

22. The catheter according to any of the preceding claims, wherein the perforated outer balloon comprises a material selected from a compliant material, a semi-compliant material, a non-compliant material, a stretchable material, a non-stretchable material, an annealed stretchable material, a pre-stretched non-stretchable material that has undergone molecular orienting by biaxial orienting processes, and any combinations thereof.

23. The catheter according to any of the preceding claims, wherein the inflatable inner balloon comprises a material selected from a compliant material, a semi-compliant material, a non-compliant material, a stretchable material, a non-stretchable material, an annealed stretchable material, a pre-stretched non-stretchable material that has undergone molecular orienting by biaxial orienting processes, and any combinations thereof.

24. The catheter according to any of claims 1-21 and 23, wherein the perforated outer balloon comprises a material selected from a polymer based material, Nylon® Nylon 12®, PET, a polyamide PA12, Grilamid® L25, Grilamid® L55, PA11, Polyether block amides PEBAX® 7233, PEBAX®7033, PEBAX® 6333), Grilflex® ELG 6260, Polyester, polyethylene, polyurethane and any combinations thereof.

25. The catheter according to any of claims 1-22 and 24, wherein the inflatable inner balloon comprises a material selected from a polymer based material, Nylon® Nylon 12®, PET, a polyamide PA12, Grilamid® L25, Grilamid® L55, PA11, Polyether block amides PEBAX® 7233, PEBAX®7033, PEBAX® 6333), Grilflex® ELG 6260, Polyester, polyethylene, polyurethane and any combinations thereof.

26. The catheter according to any of the preceding claims, wherein prior to inflation of the inflatable inner balloon, the inflatable inner balloon and the perforated outer balloon are arranged in an arrangement selected from,

the inner balloon is not folded and the outer balloon is not folded,

the inner balloon is not folded and the outer balloon is folded over the inner balloon,

the inner balloon is folded over the shaft and the outer balloon is not folded, and

the inner balloon is folded over the shaft and the outer balloon is folded over the inner balloon.

27. The catheter according to any of claims 1-25, wherein prior to inflation of the inner balloon, the outer perforated balloon is folded over the inner balloon and wherein at least some perforations of the plurality of perforations of the perforated outer balloon are disposed within one or more folds of the outer perforated balloon.

28. The catheter according to any of claims 1-21 and 24-27, wherein inflating the inflatable inner balloon results in stretching of the outer perforated balloon and increasing the area of the plurality of perforations.

29. The catheter according to any of claims 1-21 and 24-27, wherein inflating the inflatable inner balloon causes portions of the outer surface of the inner inflatable balloon to curve and protrude from the plurality of perforations.

30. A method of delivering a drug to a treatment site in a body cavity, the method comprising the steps of:

inserting the drug delivery catheter according to any of claims 1-29 into a body cavity to dispose the perforated outer balloon in a treatment site;

inflating the inflatable balloon to treat the site and to deliver at least some of the drug to at least some regions of the treatment site through at least some of the plurality of perforations.

31. The method according to claim 30, wherein the catheter also includes a stent disposed on the perforated outer balloon and wherein the step of inflating also includes expanding and deploying the stent in the treatment site.

32. The method according to any of claims 30-31, wherein the body cavity is a blood vessel and the treated region is selected from an atheroma, a plaque and a stenosed region of the blood vessel.

33. The method according to any of claims 30-32, wherein the outer perforated balloon of the catheter is a stretchable balloon and wherein the step of inflating also comprises stretching the perforated outer balloon to increase the area of the plurality of perforations.

34. The method according to any of claims 30-33, wherein the step of inflating also includes the step of causing at least some portions of the inflated drug coated inner balloon to protrude through the plurality of perforations beyond an outer surface of the outer perforated balloon and to contact at least some portions of the treatment site for facilitating transfer of the drug to the treatment site.

35. The method according to any of claims 30-34, wherein prior to the step of inflating, the outer perforated balloon is folded over the inner inflatable balloon and wherein the step of inflating also includes the step of unfolding and expanding the outer perforated balloon.

36. The method according to claim 35, wherein the inflatable inner balloon is folded and wherein the step of inflating also includes the step of unfolding and expanding the inner balloon.

37. The method according to any of claims 30-34, wherein the inflatable inner balloon is a folded balloon and wherein the step of inflating also includes the step of unfolding the folded inner balloon.

38. The method according to claim 37, wherein the perforated outer balloon is not folded and is a stretchable balloon and wherein the step of inflating also includes the step of expanding the stretchable perforated outer balloon.

39. The method according to any of claims 30-38, wherein the method also includes, prior to the step of inflating, the step of protecting by the perforated outer balloon a drug coated on an outer surface of the inflatable inner balloon.

40. The method according to any of claims 30-34, wherein at least the perforated outer balloon is a folded balloon having folds, and wherein the method also includes the step of protecting by the folds of the folded perforated outer balloon at least some perforations of the plurality of perforations from penetration of blood or a body fluid, during the step of inserting.

41. The method according to any of claims 30-40, wherein the drug delivering catheter is selected from an over the wire (OVT) catheter and a rapid exchange (RE) catheter and wherein the step of inserting comprises inserting the catheter into the body cavity over a guide wire.

42. The method according to any of claims 30-41, wherein the drug or composition comprising a drug coating the outer surface of the inflatable inner balloon includes one or more of a therapeutic substance, a diagnostic substance, a drug, a therapeutic composition, a medicament, a diagnostic composition, a physiologically active agent, a biochemically active agent, one or more living cells, DNA, RNA, a nucleic acid, a vector for delivering genetic material to cells in the treated site, an anti-inflammatory agent, an anti-restenosis agent, a cell proliferation inhibitory agent, a smooth muscle proliferation inhibiting agent, paclitaxel, rapamycin, everolimus, a vaso-active agent, a vaso dilating agent, a vaso constricting agent, an antibiotic agent, an anti-coagulative agent, a platelet aggregation inhibiting agent, an anti-fibrosis agent, a pharmaceutically acceptable vehicle, a lipid based vehicle, and any combinations thereof.

43. The method according to any of claims 30-42, wherein the method also includes the step of inserting a medical device and/or a diagnostic device through a lumen formed in the catheter shaft.

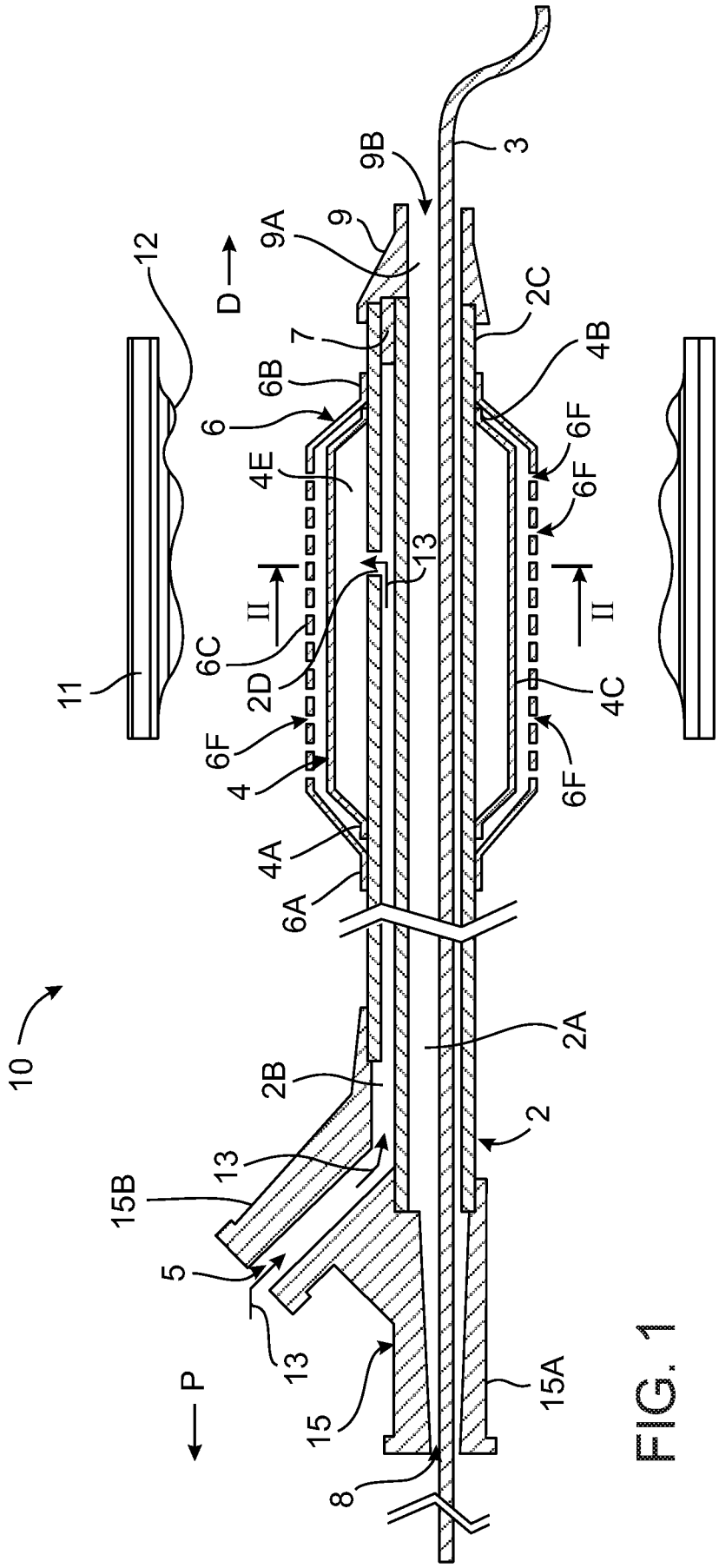
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FIG. 1

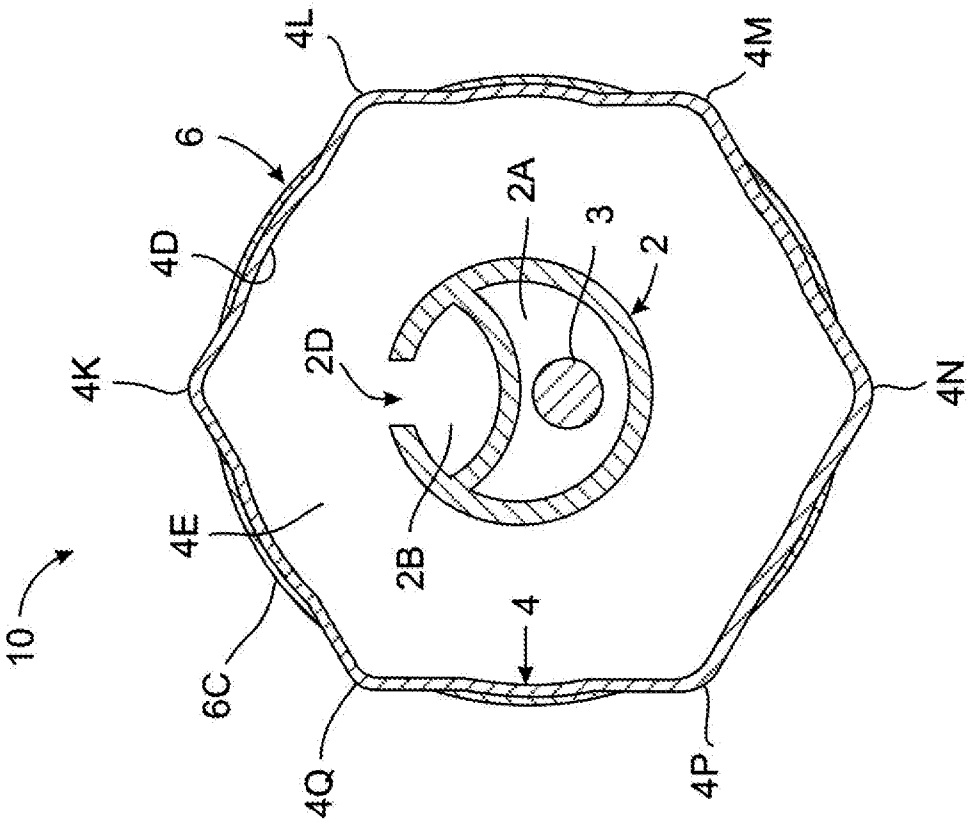
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FIG. 3

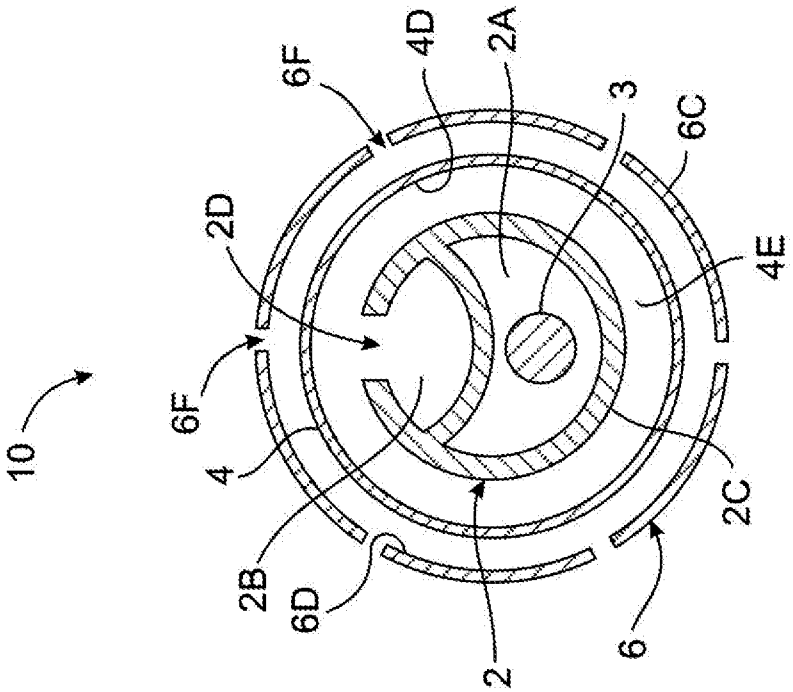
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FIG. 2

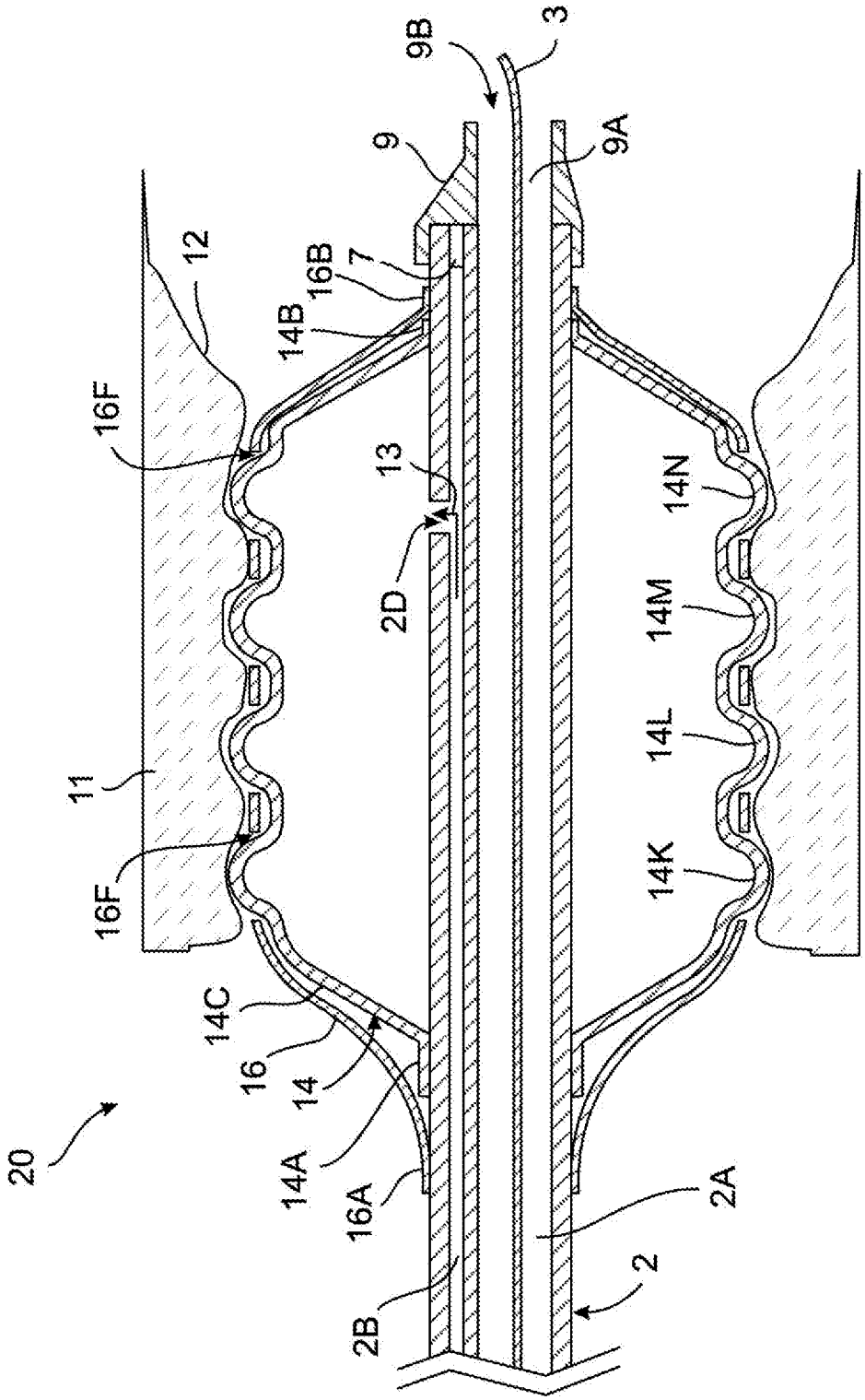
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FIG. 4

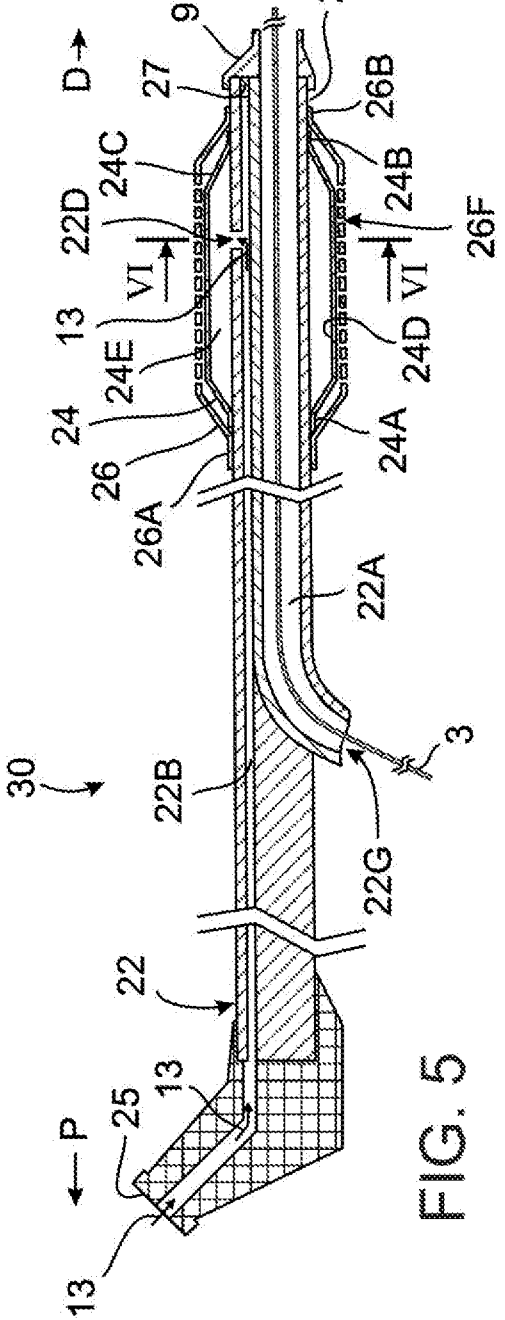

FIG. 5

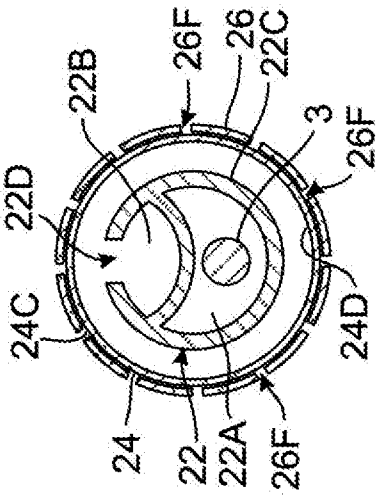

FIG. 6

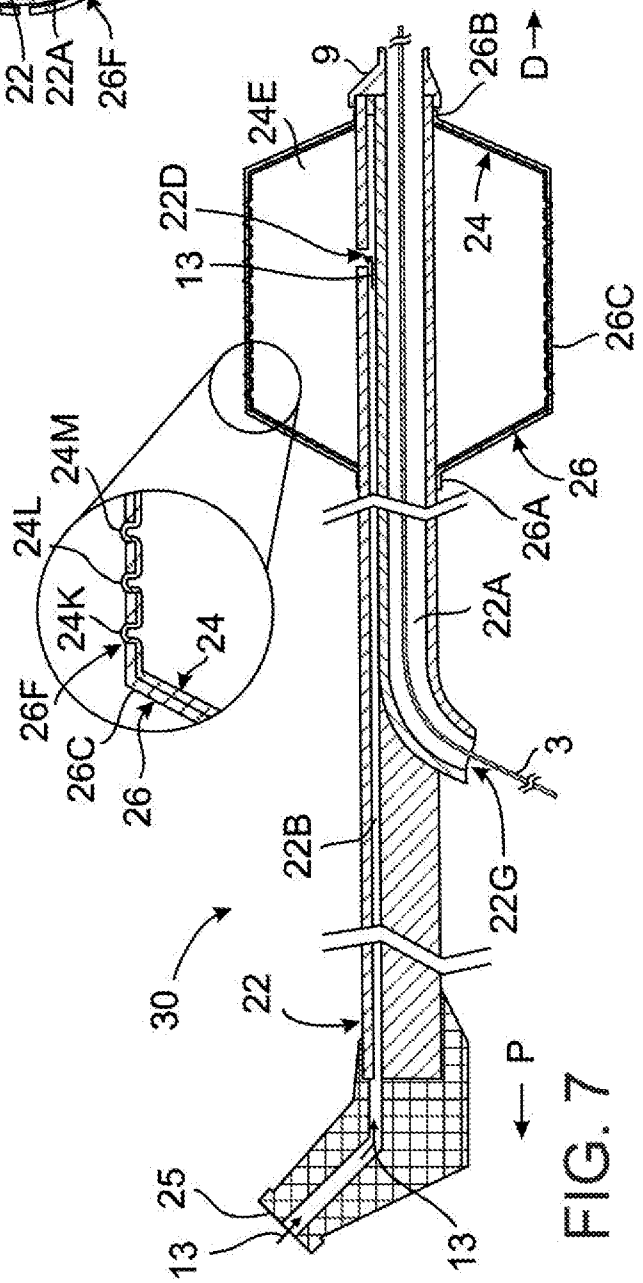

FIG. 7

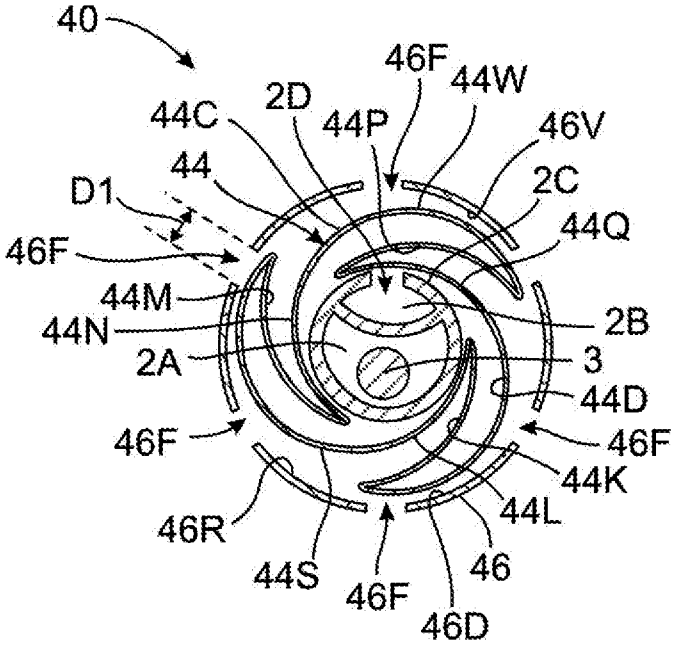
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FIG. 8

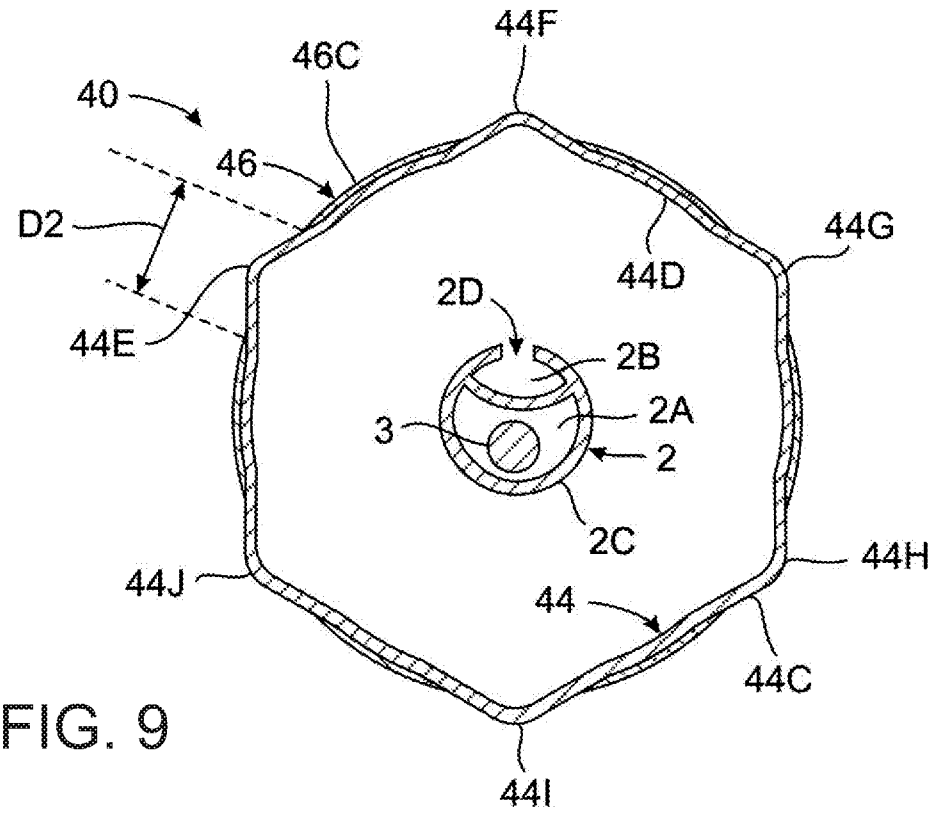
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FIG. 9

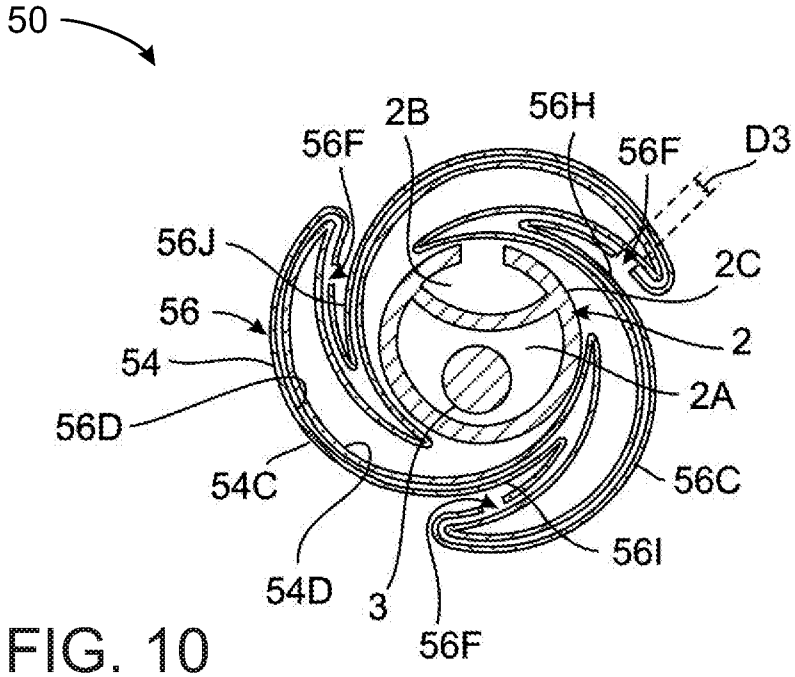
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FIG. 10

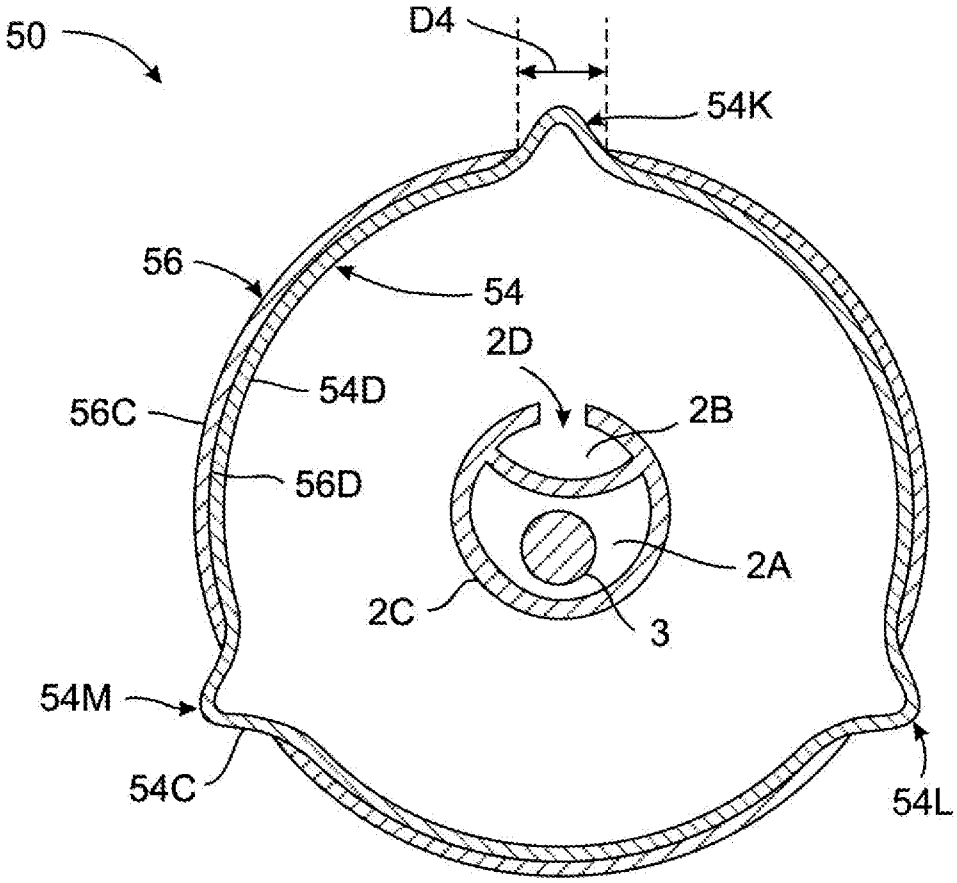
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FIG. 11

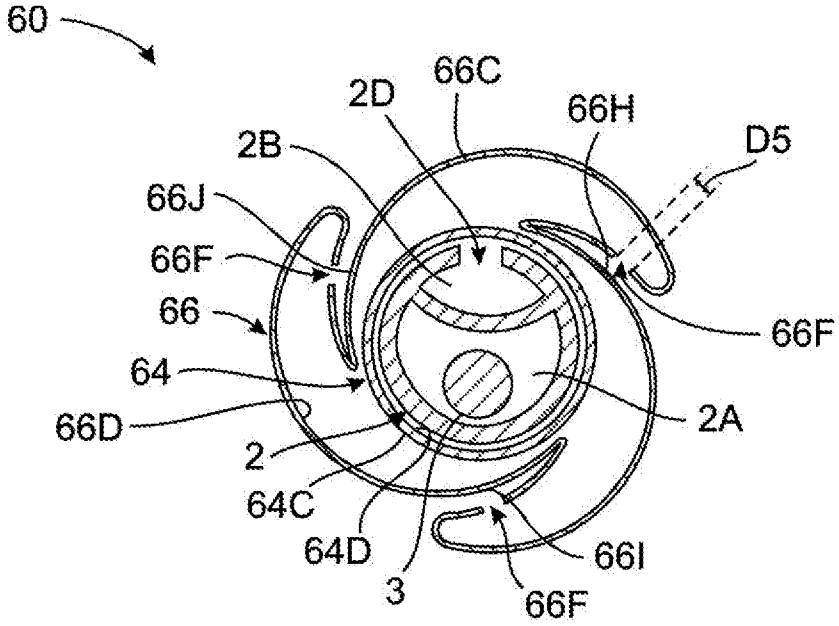
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FIG. 12

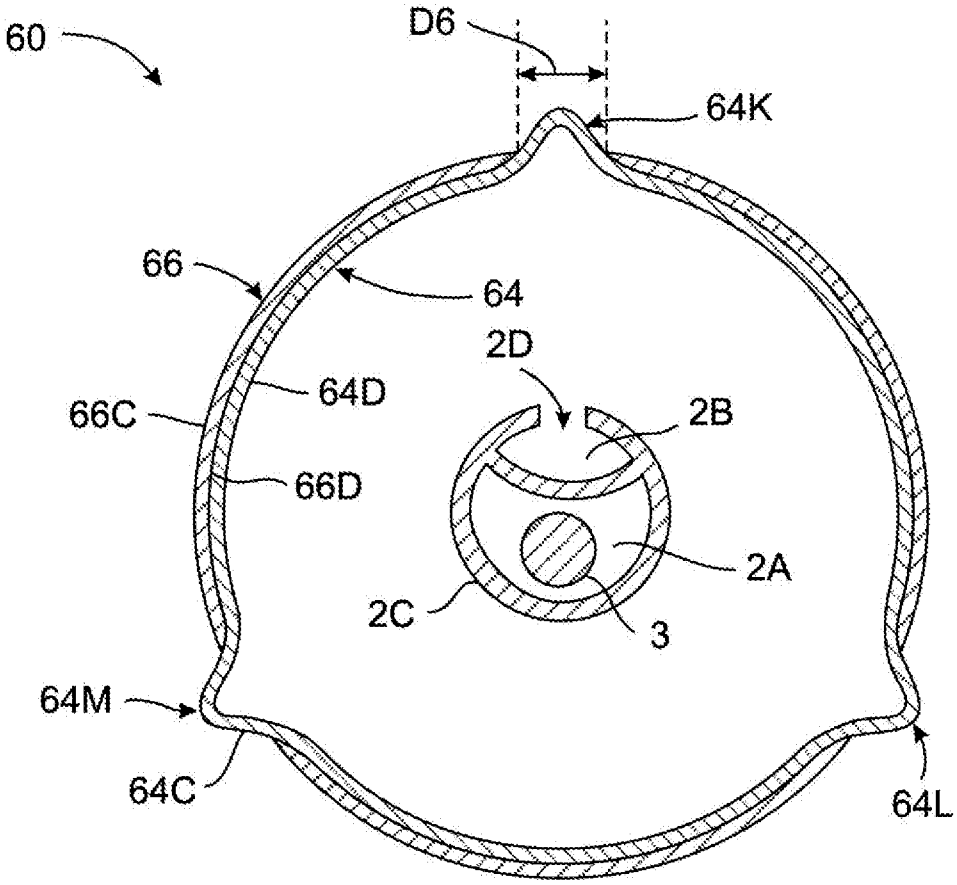
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FIG. 13

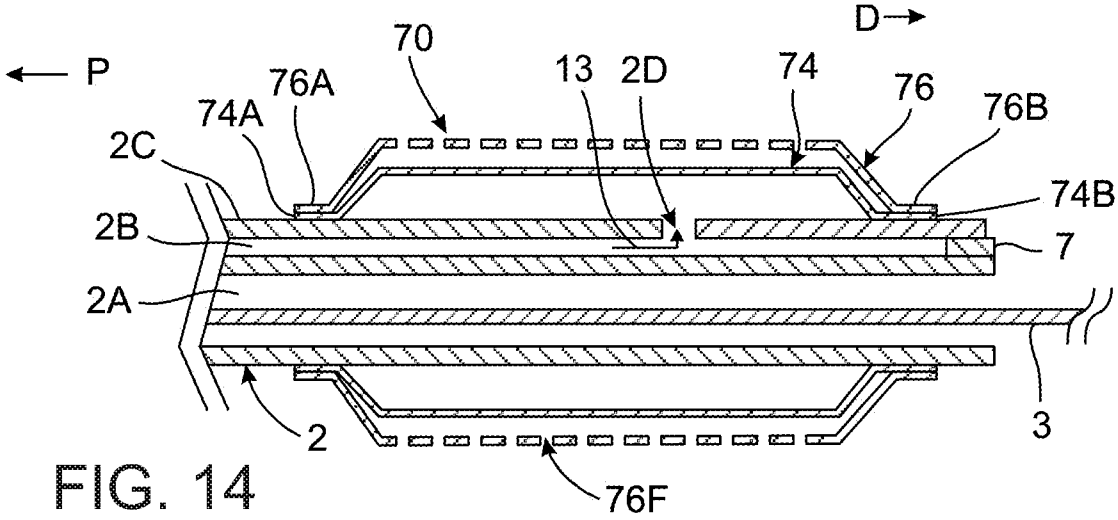

FIG. 14

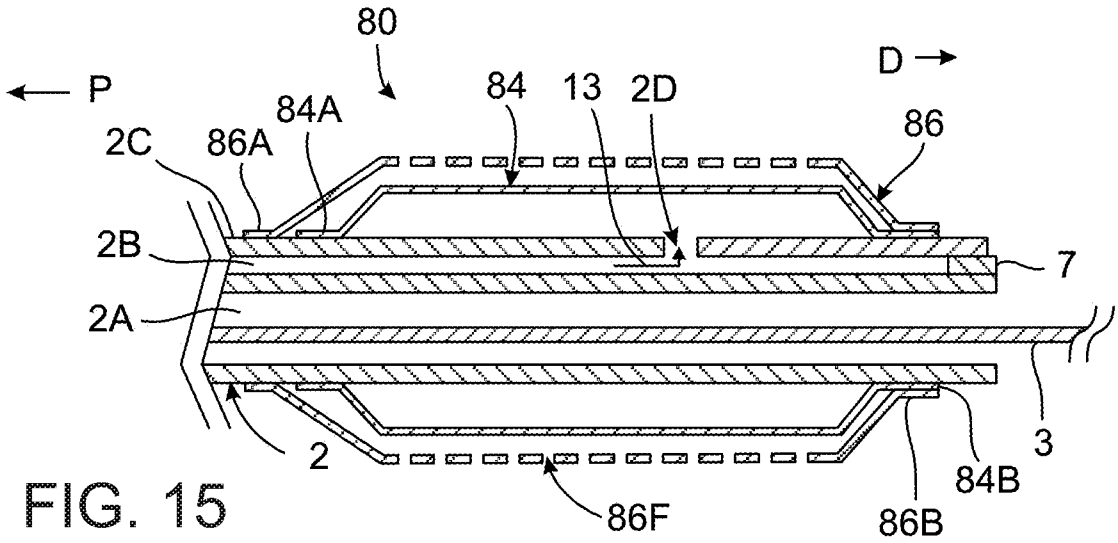

FIG. 15

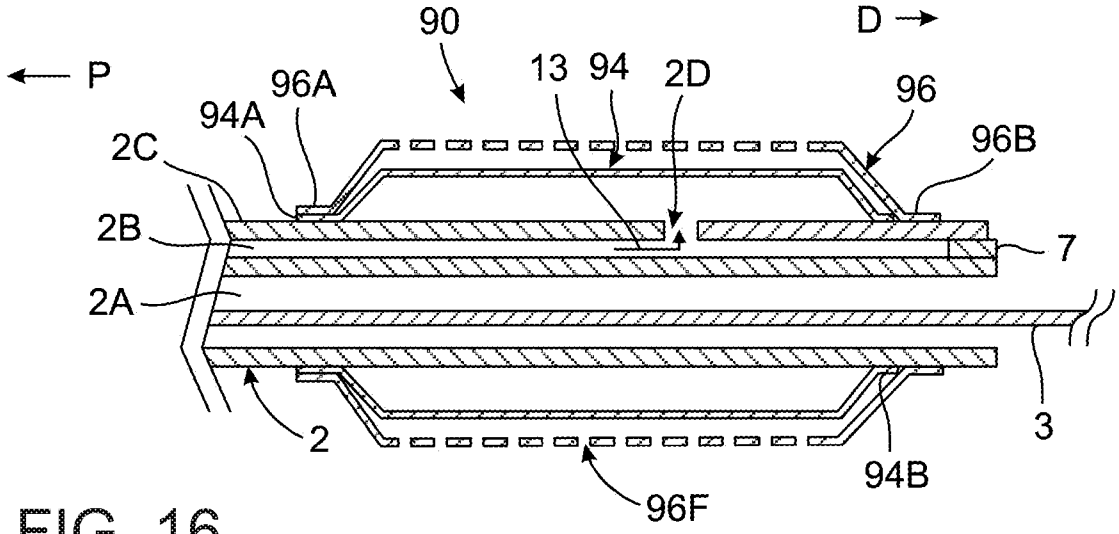

FIG. 16

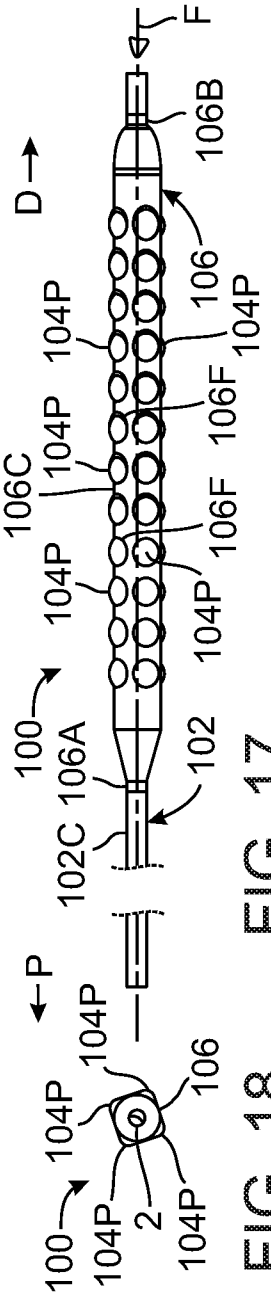

FIG. 18

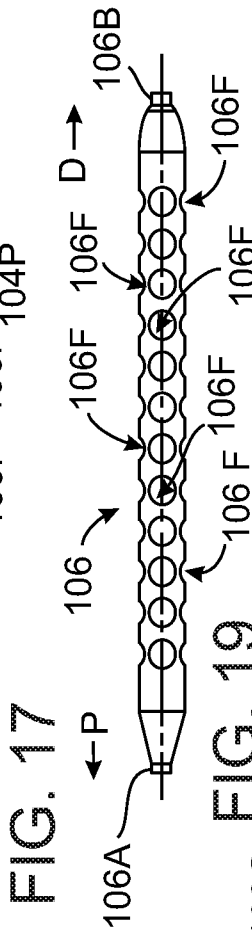

FIG. 17

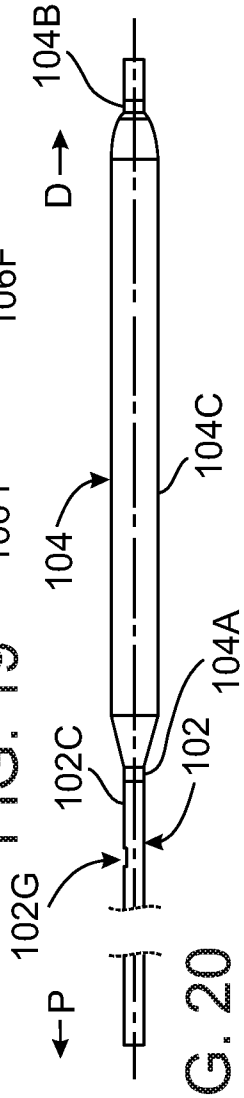

FIG. 19

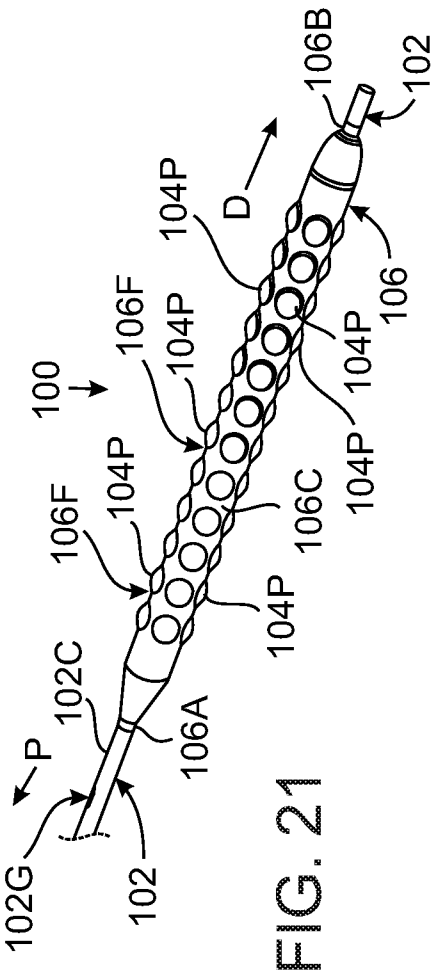

FIG. 20

FIG. 21

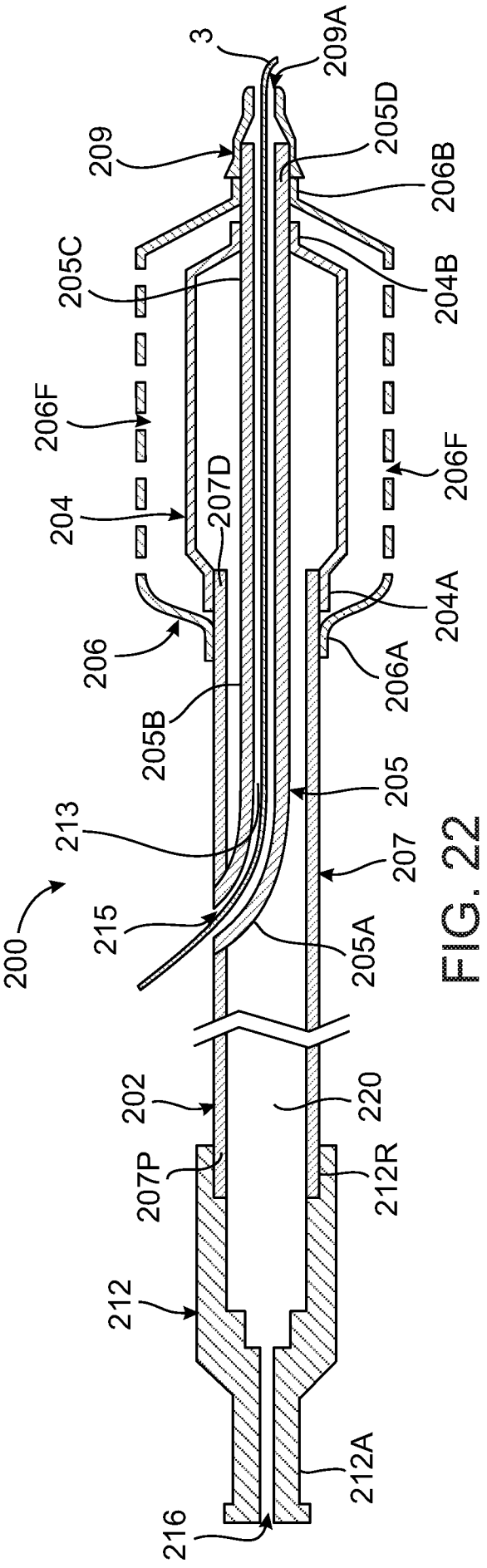
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FIG. 22

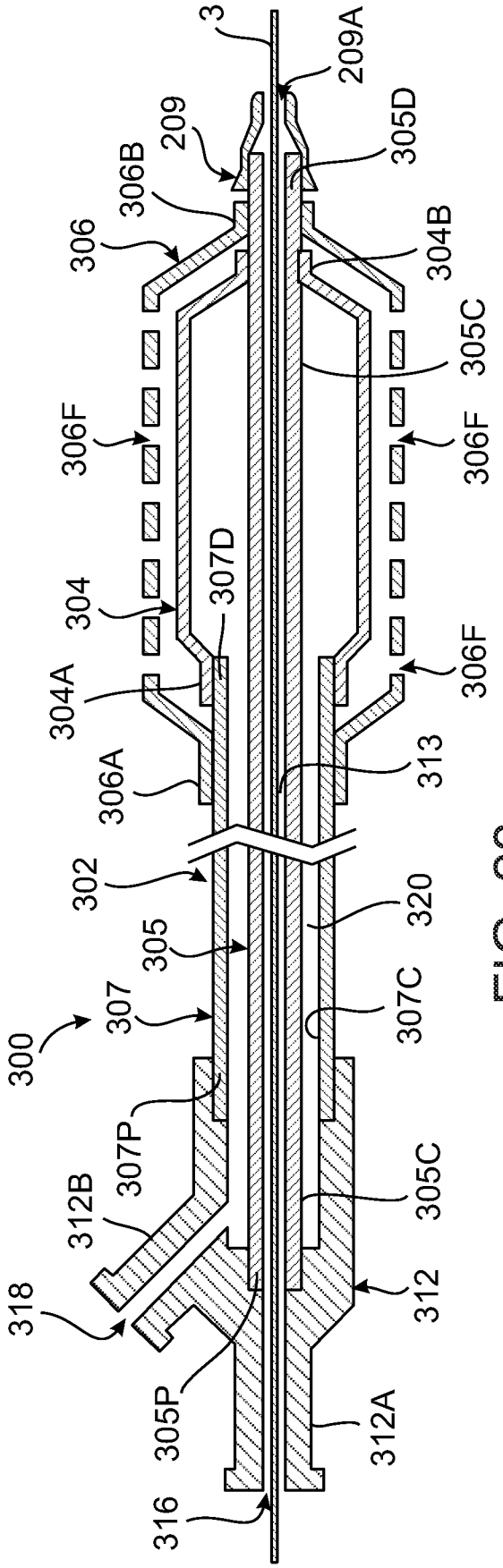
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FIG. 23

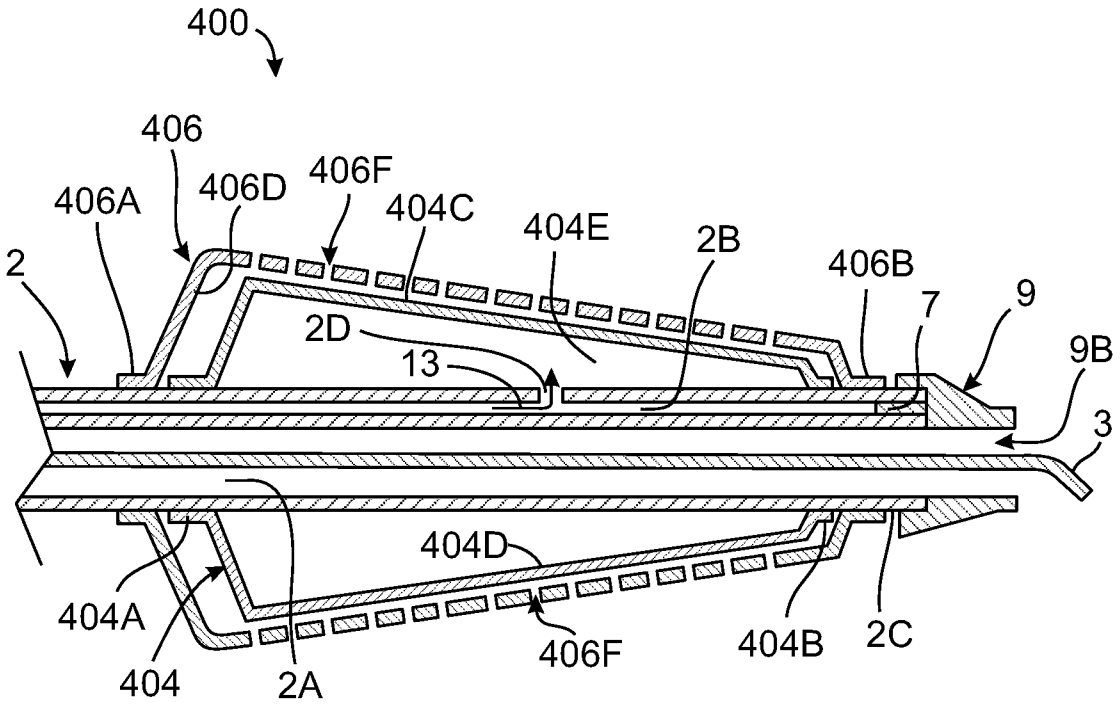
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FIG. 24

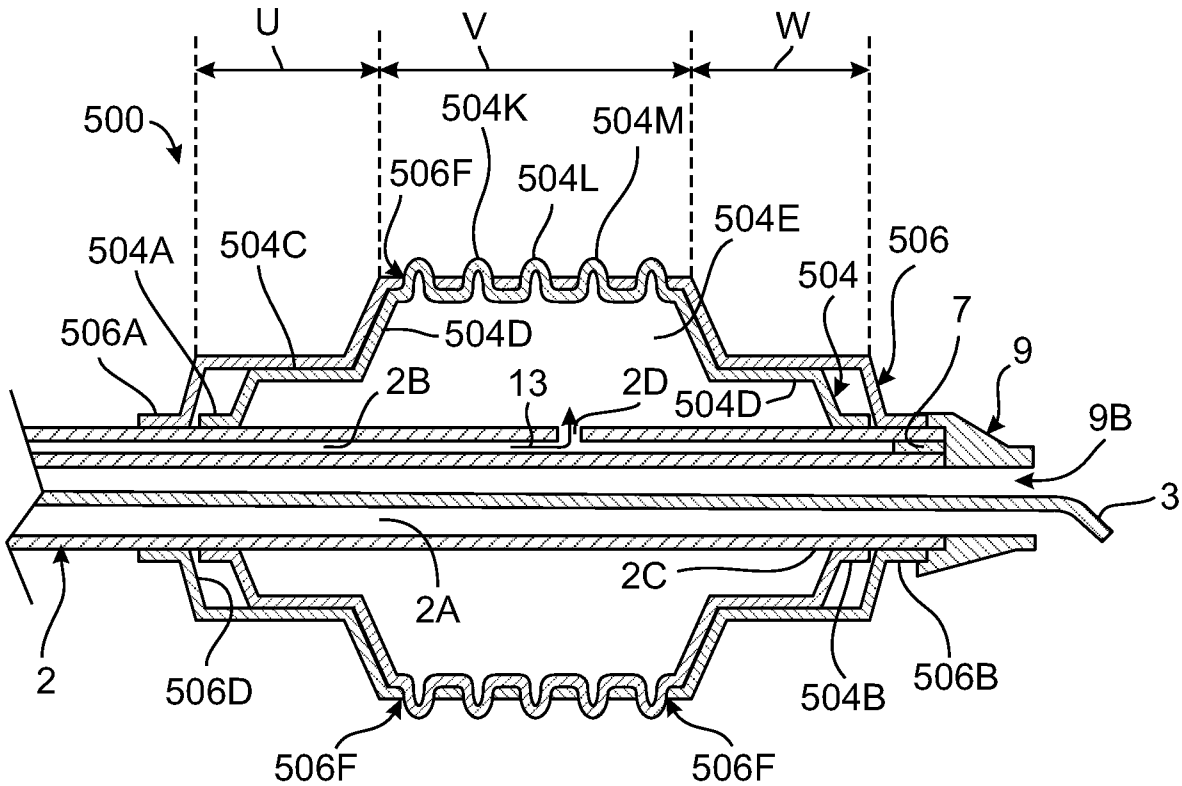
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FIG. 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2017/050911

A. CLASSIFICATION OF SUBJECT MATTER
IPC (2017.01) A61M 25/10

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)
IPC (2017.01) 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)
Databases consulted: Esp@cenet, Google Patents, Derwent Innovation
Search terms used: Inner, inside, internal, interior, coat, cover, disposed, applied, drug, medicament, agent, substance, outer, outside, external, exterior, balloon, sleeve, inflate, expand, perforated, holes, apertures, pores

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012143054 A1 EATON et al. 07 Jun 2012 (2012/06/07) para.[0009], [0012], [0037], [0040], [0041], [0043], [0057], [0068], [0085]-[0091]; fig. 1, 1A, 2C	1-43
X	US 2010069900 A1 COOK INC. 18 Mar 2010 (2010/03/18) para.[0008], [0009], [0018], [0019], [0020], [0026], [0028]; fig. 1-3	1,2,18-20,22,23,26, 30,32,39,42
A	US 2015306361 A1 ANGIOSLIDE LTD. 29 Oct 2015 (2015/10/29) * the whole document *	1-43

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"E" earlier application or patent 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 Nov 2017	30 Nov 2017
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	Authorized officer AHARONY Meytal Telephone No. 972-2-5657820

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2017/050911

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 2012143054 A1	07 Jun 2012	US 2012143054 A1	07 Jun 2012
		US 8740843 B2	03 Jun 2014
		EP 2419167 A1	22 Feb 2012
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		US 8672919 B2	18 Mar 2014
US 2015306361 A1	29 Oct 2015	US 2015306361 A1	29 Oct 2015
		CN 105025968 A	04 Nov 2015
		EP 2928537 A1	14 Oct 2015
		EP 2928537 A4	03 Aug 2016
		JP 2016503330 A	04 Feb 2016
		WO 2014087395 A1	12 Jun 2014