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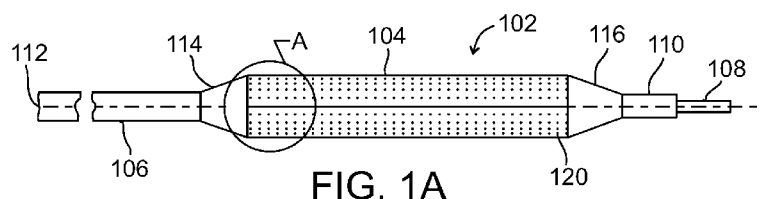


FIG. 1A

(57) Abstract: A microporous balloon catheter, and a balloon catheter drug delivery system in which the balloon catheter is formed of a semi-compliant or compliant material, and in which the pores (120) of the balloon remain substantially closed at inflation pressures below a selected threshold, and open at higher pressure to emit jets of a drug that penetrate surrounding tissue without substantial trauma. Also disclosed is an apparatus and method for perforating a balloon catheter by femtolaser pulses. The apparatus may be used for treating a variety of conditions. For example, in treating vascular obstructions, a pressure below the threshold pressure may be used for performing PTCA before drug delivery.

MICROPOROUS BALLOON CATHETER, DELIVERY SYSTEM, AND METHODS OF MANUFACTURE AND USE

CROSS-REFERENCES TO RELATED APPLICATIONS

5 The present application is based on and claims priority to U.S. provisional application 61/486,285, filed 15 May 2011, which is related to PCT/IL2009/000850, filed 2 September 2009, published as WO 2010/026578 A1 (attorney docket 47107), which claims priority of U.S. Provisional Patent Application 61/093,467, filed on 2 September 2008, and U.S. Provisional Application No. 61/193,886, filed on 10 5 January 2009. The entire disclosures of the above-identified applications are incorporated herein by reference as if fully set forth.

FIELD OF INVENTION

15 The present invention in some embodiments thereof, relates to balloon catheter technology, and more particularly, to microporous and semi-compliant or compliant balloon catheters, balloon catheter systems, to methods for dispensing medicament or other materials into a body lumen wall or cavity using such catheters and systems, and to manufacturing methods for certain components of such systems.

BACKGROUND OF THE INVENTION

20 As further elaborated in PCT/IL2009/000850, balloon catheters are widely used for opening stenotic (i.e., abnormally restricted) or occluded body lumens, for example, blood vessels. Such balloons also serve as delivery apparatus for medicaments and/or stents which mechanically keep the body lumen open.

25 Restenosis is a side effect that follows angioplasty treatments as well as any other body lumen that was mechanically forced to expand, for example, by Percutaneous Transluminal Coronary Angioplasty (PTCA). In order to prevent restenosis, a local drug delivery of special medicament is sometimes performed during or after PTCA. An anticoagulant such as heparin, or in recent years drugs that reduce 30 cell division reduction (anti-proliferative drugs), for example Paclitaxel or Sirolimus coated on drug-eluting stents, for slow release to the vessel wall to avoid cell

proliferation, are among the ways this is done, in conjunction with today's PTCA treatments.

A different method to deliver the drug to the vessel wall is the drug-eluting balloon, which is a dilatation balloon coated with a medicament such as Paclitaxel (usually in the amount of a few micrograms per a square millimeter of a balloon surface). Such devices and method of treatment are described in US patent application 2006/0020243 and in Scheller et al., "Treatment Of Coronary In-Stent Restenosis With A Paclitaxel-Coated Balloon Catheter", N Engl J Med 2006; 335:2113-24, and in Scheller et al., "Paclitaxel Balloon Coating, A Novel Method For Prevention And Therapy Of Restenosis", Circulation 2004; 110:810-814, the disclosures of which are fully incorporated herein by reference.

Sometimes, however part of the drug coating can peel off the balloon during its insertion and manipulation before the treatment site has been reached, which can make it difficult to accurately control the volume of the drug delivered to the treatment site. Sometimes this is addressed by coating the balloon with an excess amount of the drug, but this may be costly. Another potential concern is the possibility of toxic effect of drug released into the drug stream rather than the vessel wall.

Drug-dispersing balloon catheters having multiple holes or a porous surface have also been described in the art. and studied. Most of the proposed designs include a balloon catheter having a plurality of pores, through which the drug is dispersed during or after the angioplasty phase. Such technology is described, for example, in US patents 4,994,033, 5,611,775, 5,087,244, 5,232,444, 5,098,381, 5,213,576, 5,318,531, 5,498,238, 5,049,132 and 5,569,198, the disclosures of which are fully incorporated herein by reference.

Among the known prior art devices are ones that employ macroporous balloons (for example, having pore diameters of 25 micrometers, such as the Wolinsky perforated balloon catheter (of C.R. Bard, Inc.; and also described in US patent 5,087,244), and are designed to emit jets of medicament with sufficient velocity to penetrate the walls of the surrounding blood vessel. It has been suggested, however, (see, for example, Lincoff et al. *Local Drug Delivery for the Prevention of Restenosis*, Circulation, 90:4, October 1994; and Racchini U.S. Patent 5,569,198, the disclosures of

which are incorporated herein by reference), that the resulting medicament jets tend to cause vascular trauma, and in fact that medicament jetting should be avoided altogether.

Other devices employ macroporous balloons having pore sizes as large as 100 micrometers, but do not provide for delivery under high pressure within the balloon, and thus avoid the problem of jetting.

Still other known devices, including that disclosed in the Racchini patent mentioned above, employ microporous balloons, including many thousands of minute pores per balloon. These devices transfer medicament to the vessel wall by diffusion rather than by vessel wall puncture.

Other macroporous balloon designs are also known, for example as described in U.S. Patent 5,611,775, that use an inner inflation balloon and an outer perforated balloon for drug administration, to allow angioplasty and subsequent drug infusion using the same catheter, and allow drug delivery at pressures and velocities low enough to avoid jetting.

WO 2010/026578 A1 contains an extensive discussion of the prior art, including other examples of known balloon catheter technology, to which reference may be made for additional background.

SUMMARY OF THE INVENTION

Some aspects of embodiments of the present invention relate to balloon catheter devices for delivering a medicament directly into surrounding tissue,, and methods of manufacture and use relating of such devices with an acceptably low risk of tissue trauma are formed of semi-compliant material, and/or are formed with a large number of small pores.

According to an aspect of some embodiments of the present invention there is provided a balloon catheter having a plurality of micro-pores with a diameter ranging from about 1 to about 5 micrometers, wherein the balloon is made of a semi-compliant material. In some embodiments, the balloon is made of a polyamide.

In some embodiments, the pore density of the balloon is in the range of about 300 and about 600 pores/cm². In some embodiments, the pore density is about 550 pores/cm².

In some embodiments, the pores are outwardly tapered truncated cones, or alternatively, inwardly tapered truncated cones.

In some embodiments, the ratio of the larger diameter to the smaller diameter of the pores of an unexpanded balloon is in the range of about 1.33 to about 4 to 1.

5 A catheter according to any of claims 5-7, wherein the diameter of the small ends of the pores of an expanded balloon is in the range of about 1 – 5 μm . In some embodiments, the diameter at the small ends of the pores of an expanded balloon is about 1.7 μm .

10 In some embodiments, the hole diameter at the larger end of the pores of an expanded balloon is in the range of about 2 – 10 μm . In some embodiments, the hole diameter at the larger end of the pores of an expanded balloon is about 5 μm .

In some embodiments, the thickness of semi-compliant balloons is in the range of about 0.012 mm to about 0.018 mm, for balloons up to outside diameter of 3.5 mm, and the thickness in the range of 0.011 mm to about 0.025 mm for balloons having outside diameter of 4 mm to 7 mm.

15 In some embodiments, the pores may have an elliptical perimeter when the balloon is un-expanded, and a circular perimeter when the balloon is expanded. Alternatively, the pores may have a circular perimeter when the balloon is un-expanded, and an elliptical perimeter when the balloon is expanded.

20 In some embodiments, the pores are configured to be substantially closed below a predetermined balloon inflation pressure.

According to an aspect of some embodiments of the present invention there is provided a balloon catheter system which includes a microporous balloon catheter formed of a semi-compliant material, a drug reservoir, and a pressure source, wherein the pressure source is configured to transfer a drug from a drug reservoir to the interior
25 of the catheter.

In some embodiments, the drug reservoir and the pressure source are comprised in a single unit.

In some embodiments, the pressure source is manually operable. Alternatively, the pressure source is at least partially automatically operable.

30 In some embodiments, the pressure source is comprised of a barrel and a manually operable by a spring-loaded piston to transfer a drug into the balloon and to pressurize the balloon.

In some embodiments, the system includes a controller and data input and display devices.

In some embodiments, the system includes a filter between the drug reservoir and the pores of the balloon.

5 According to an aspect of some embodiments of the present invention there is provided apparatus for manufacturing a microporous balloon catheter that includes a holder for the balloon, the holder being perforated in a pattern corresponding to the desired pattern of holes in the balloon, and a laser operable to provide ultra-short duration and ultra-high intensity pulses, wherein the holder and the laser are moveable
10 relative to each other so that all the perforations in the holder are exposed in turn to the laser beam. In some embodiments, the laser is a femtosecond laser.

In some embodiments, the laser is stationary, and the holder is moved by a CNC operated driver.

15 According to an aspect of some embodiments of the present invention there is provided a method of perforating a balloon catheter according to which an un-perforated balloon is placed in a holder having a perforation pattern corresponding to a desired perforation pattern for the balloon, the balloon is expanded to desired perforation pressure, the holder with the balloon therein is located in the path of an ultra-short duration, ultra-high energy laser, the laser is activated, and the laser and the holder are
20 moved relative to each other to expose the perforation pattern of the holder to the perforation energy.

In some embodiments, the holder is moved, and the laser is stationary.

In some embodiments, the laser is a femtosecond laser.

25 In some embodiments, the balloon is attached to a catheter at the time of perforation. Alternatively, the balloon is not attached to a catheter at the time of perforation.

30 According to an aspect of some embodiments of the present invention there is provided a method of perforating a balloon catheter according to which an un-perforated balloon that is turned inside-out is placed in a holder having a perforation pattern corresponding to a desired perforation pattern for the balloon, the holder and the balloon are exposed to an ultra-short duration, ultra-high energy laser beam, and the

laser and the holder are moved relative to each other to expose the perforation pattern of the holder to the laser beam.

According to an aspect of some embodiments of the present invention there is provided an insufflator for a microporous balloon catheter having a barrel configured to receive a quantity of a drug to be delivered by the catheter, a piston moveable to lengthen and shorten the barrel whereby positive and negative pressure is created in the barrel, a connector for coupling the barrel to a catheter shaft; and a spring loaded actuator for moving the piston to shorten the barrel and to pressurize the barrel to a desired level, wherein the piston is moveable to load a drug into the barrel without compressing the spring.

In some embodiments, the actuator is operable to provide a first pressure level for PTCA and a second higher pressure level for drug delivery.

In some embodiments, the balloon is pressurized by manually compressing the spring.

In some embodiments, there are included markings to measure displacement of the spring and calibrated to provide an indication of a pressure level applied to the balloon.

According to an aspect of some embodiments of the present invention there is provided a method for treating a segment of a body lumen, in which an inflatable component formed of a semi-compliant material having a plurality of micro-pores formed in a wall thereof is located adjacent to the segment, the component is inflated with a drug to be delivered to the wall of the lumen to a first pressure not sufficient to cause effective jetting of the drug out of the pores, the component is then inflated to a second higher pressure that is sufficient to cause jetting of the drug out of the pores into the tissue of the lumen without significant trauma to the tissue.

In some embodiments, the first pressure is sufficient to widen a narrowing in the body lumen segment.

In some embodiments, the inflatable component is a balloon catheter.

In some embodiments, the first pressure is sufficient to perform PTCA.

In some embodiments, the method further includes delivering a device for implantation in the segment. In some embodiments, wherein the device for implantation is a stent.

According to an aspect of some embodiments of the present invention there is provided a balloon catheter having a plurality of micro-pores with a diameter ranging from about 1 to about 5 micrometers, wherein the pores are shaped as truncated cones.

In some embodiments, the balloon is made of a semi-compliant material.

5 Alternatively, the balloon is made of a compliant material.

In some embodiments, the pores are outwardly tapered. Alternatively, the pores are inwardly tapered.

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
10 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 are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention are herein described with reference to the accompanying drawings. However, it is to be understood that the particulars shown are by way of example for purposes of illustrative discussion of embodiments of the
20 invention, and to make apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIGs. 1A-1D illustrate schematically a microporous balloon and holes, in accordance with some embodiments of the present invention;

25 FIG. 2A-2C are enlarged cross-sectional views that illustrate features of balloons formed of semi-compliant material;

FIGs. 3A-3D illustrate exemplary balloon perforation perimeter shapes for internal pressures above and below the drug release pressure in accordance with some embodiments of the present invention;

30 FIG. 4 is a schematic showing of a catheter treatment system in accordance with some embodiments of the invention;

FIG. 5 is a flow diagram illustrating an exemplary treatment method according to some embodiments of the invention;

FIGs. 6A-6F are schematic diagrams illustrating the successive phases of the method illustrated in FIG. 5;

5 FIG. 7 is an exemplary Pressure vs. Time graph illustrating an operational sequence for a method such as that illustrated in FIG. 5;

FIG. 8 is an alternative Pressure vs. Time graph for illustrating an operational sequence for a method such as that illustrated in FIG. 5;

10 FIG. 9 is a schematic illustration of an exemplary arrangement for perforating a balloon formed of a non-compliant material according to some embodiments of the invention;

FIGs. 10A and 10B illustrate schematically an arrangement for perforating a balloon made of a semi-compliant material using a laser in accordance with some embodiments of the present invention;

15 FIGs. 11A-11B schematically illustrate some details of a balloon fixation device such as illustrated in FIGs. 10 and 10B, in accordance with some embodiments of the present invention;

FIG. 12A-12C illustrate use of the fixation device of FIGs. 11A and 11B in accordance with some embodiments of the invention;

20 FIG. 13A-13C illustrate a manually-operated insufflator, in accordance with some embodiments of the invention;

FIGs. 14A-14B illustrate another design of a manually-operated insufflator, in accordance with some embodiments of the invention;

25 FIGs. 15A and 15B are schematic illustrations of an automatically-operated insufflator, and an exemplary user interface in accordance with some embodiments of the invention; and

FIG. 16 is a graph of fluid elution rate as a function of balloon pressure in accordance with an exemplary embodiment of the invention.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS**Overview:**

The present invention, in some embodiments thereof, relates to balloon catheter technology, and more particularly, to microporous and semi-compliant or compliant
5 balloon catheters, balloon catheter systems, methods for dispensing medicament or other materials into a body lumen wall or cavity using such catheters and systems, and to manufacturing methods for certain components of such systems.

Some embodiments of the invention are based on a discovery by the inventors that pressures higher than those claimed in US Patent 5,569,198, referred to above, may
10 be beneficial for delivery of significantly higher quantities of medicament into tissue while still not causing substantial tissue damage ("jetting effect"). In some embodiments, hole (pore) size and/or density is changed as well, for example, using larger holes and/or lower density of holes to permit use of microcapsules for drug delivery.

For the purposes of the description herein, the term "jetting" is used to describe drug streams having sufficient velocity to penetrate the tissue without causing
15 unacceptable trauma. Such jets are able to penetrate the tissue to varying degrees depending on the velocity as described below, according to some aspects of the invention.

Also, for purposes of the description herein, "substantial tissue damage" or
20 "unacceptable trauma" is to be understood to include, without limitation, direct and visible tissue damage, formation of edema, rupturing of the vessel and restenosis, due, for example, to development of intimal hyperplasia.

For convenience, the medicaments or other materials delivered according to
25 some embodiments of the invention will be referred to herein simply as "drugs". Embodiments of the invention will be described mainly in the context of balloon catheters for use in treatment of vascular stenosis, but it is to be understood that catheters according to the invention may also be used for treatment of conditions of other body lumens and cavities by adjusting some or all of the diameter, length of the
30 balloon, tapered angle of the balloon, wall thickness, inflation pressure, pore size, pore density, and type of drug to be delivered. For example, embodiments of the invention can be used for treatment of the urethra, the trachea, the ureter, the prostate, the

esophagus, the ileum, the biliary duct, the fallopian tube, the tear duct, or the nasal cavity. Some embodiments can be used for local tumor treatment, local inflammation treatment, local congestion such as nasal congestion (where, for example, the balloon catheter can be used to inject steroids), local stenosis (for example, but not limited to, urethral stenosis, blood vessel stenosis), and for any other treatment where local drug delivery into tissue, to a certain depth, is desired.

An aspect of some embodiments of the present invention pertains to microporous balloon catheters formed of compliant or semi-compliant materials, for example, Nylon or other polyamide material polyolefin copolymers (POC) or acrylonitrile homopolymers and copolymers, and acrylonitrile blends in which the pores have the shape of truncated cones.

For purposes of the description herein, materials may, without limitation, be considered to be semi-compliant and within the scope of some embodiments of the invention if, by changing the pressure from 6 bar to 16 bar, the outside diameter of the a balloon having an unexpanded diameter in the range of about 3 to about 7mm (or more or less or intermediate values) will expand by about 0.3 to about 0.5mm, or more, or by intermediate values.

Again without limitation, materials that will expand less will be considered as non-compliant, and materials that expand more will be considered as compliant, but may be considered to come within the scope of some embodiments of the invention.

Further, as a matter of convenience, balloon catheters according to some embodiments of the invention will be referred to herein as "semi-compliant", or sometimes, as "balloon catheters according to some embodiments of the invention", or in similar terms. However, it is to be understood that while the focus herein is on catheters, systems and methods related to semi-compliant materials, some aspects and embodiments of the invention are also applicable to compliant materials.

An aspect of some embodiments of the invention pertains to balloon catheters formed of semi-compliant materials that are capable of delivering drugs into surrounding tissue at a high enough pressure to form jets, but through pores that are small enough, with a pore density on the balloon surface, and for a delivery time that an unacceptable level of tissue damage does not occur.

According to some embodiments, the balloon catheters can also be used at second pressure level lower than the drug delivery pressure, for angioplasty, for example, to perform PTCA, with an acceptably low drug flow rate at the PTCA pressure and below. Typically, the drug delivery pressure is higher than the PTCA pressure, but in some embodiments, there can be an overlap so that drug delivery begins below the top of the PTCA pressure range.

The pores of microporous balloons according to some embodiments of the invention are in the range of about 1 to about 5 μm in diameter, and preferably smaller than about 2 μm in diameter, for example, about 1.5 μm in diameter. Optionally, the pore diameters are less than 1 μm . With balloons having pore sizes in the range of 8-20 μm or larger (macroporous balloons), difficulty can be encountered in pressurizing the balloon sufficiently to produce jetting, and/or in controlling the depth of drug delivery.

Typically, the expanded pores are generally circular. In some embodiments, the expanded pores can be elliptical, in which case, the pore sizes represent the length of the major axis.

In some embodiments, the pores are distributed substantially uniformly over the balloon surface for example, with a density of between about 300 and about 10,000 pores/ cm^2 , and preferably between about 300 and about 600 pores/ cm^2 , for example, about 550 pores/ cm^2 . Optionally, in some embodiments, the pores are distributed non-uniformly, or on only part of the balloon surface according to particular treatment requirements. In some embodiments, at least 10 pores are provided.

Optionally, the drug delivery pressure is above 8 atmospheres, for example, at least about 15 atmospheres.

In some embodiments of the invention, at least one jet produces a continuous impact with magnitude and duration high enough to form an erosion hole in a body passage wall, optionally a blood vessel wall, through which the drug is delivered. Alternatively, no holes are formed, but the delivery pressure is high enough to provide active diffusion of the drug into the blood vessel wall.

An aspect of some embodiments of the invention pertains to a method of perforating microporous balloon catheters using an ultra-short duration, ultra-high intensity pulse output laser. In some embodiments, the laser is a femtosecond laser.

An aspect of some embodiments of the invention pertains to apparatus for perforating microporous balloon catheters using an ultra-short duration, ultra-high intensity pulse output laser. In some embodiments, the laser is a femtosecond laser.

In some embodiments balloon catheters according to some aspects of the invention that are perforated by laser pulses have perforations that are truncated cones that taper inwardly, i.e., the perforations are smaller on the inside of the balloon than on the outside. In some embodiments, the perforations taper outwardly. According to some embodiments, to produce laser-perforated balloons that are outwardly tapered, the balloons are turned inside out before perforation. In such embodiments, the balloon is perforated before attachment to a catheter shaft.

According to some embodiments, the ratio of the pore diameter at the larger end of the pore to the diameter at the smaller end is in the range of about 1.33 to about 4 to 1, or larger or smaller or intermediate values. For example, the diameter at the small end is in the range of about 1 – 5 μ m, preferably in the range of about 1.5 – 2.5 μ m, preferably about 1.7 μ m, and the hole diameter at the larger end is in the range of about 2 – 10 μ m, preferably about 5 μ m.

The thickness of balloons according to some embodiments of the invention is in the range of about 0.012mm to about 0.018mm, for example, in the range of about 0.014mm to about 0.016mm, for balloons up to outside diameter of 3.5 mm, and the thickness in the range of 0.011mm to about 0.025mm for balloons having outside diameter of 4mm to 7mm.

According to some embodiments, the ratio of radial compliance to the axial compliance of the balloon material determines the un-expanded and expanded shapes of the perimeters of the holes. For example, where the radial compliance of the balloon is different from the axial compliance, the un-expanded holes may be circular, and the expanded holes may be elliptical. For balloons in which for example, the radial compliance is the same as axial compliance, the un-expanded holes may be circular, and the expanded holes may stay circular.

An aspect of some embodiments of the invention pertains to fixation devices or holders to which the balloons are attached for perforation. In some embodiments, for example, used for laser perforation, the holders include tubular portions having perforation patterns matching the desired perforation patterns of the balloons. In such

embodiments, the balloons are placed in the perforated portions and expanded before perforation to press against the insides of the perforations. Optionally, the holder is rotated and translated to expose the entire perforated area of the holder to a perforating energy beam. Optionally, the balloons are made of semi-compliant or compliant materials.

In some embodiments, the holder can be used with balloons that are not attached to a catheter shaft at the time of perforation, or with balloons that are attached to a catheter shaft before perforation.

Aspects of some embodiments of the invention pertain to systems employing semi-compliant microporous balloon catheters and to methods of using such systems. Optionally, some such systems include a balloon catheter, a drug reservoir, and a pressure source for expanding the balloon, optionally by delivery of the drug to the balloon. Optionally, some such systems also include a controller and user interface and display devices.

In some embodiments, the systems are manually operated. Optionally, such systems are at least partially operated automatically by a controller.

An aspect of some embodiments of the invention pertains to insufflators for use with balloon catheters and balloon catheter systems. In some embodiments, the insufflators include a barrel into which a drug for delivery by the catheter is preloaded, and a manually operated piston by which the drug is loaded into the barrel and by which air is purged from the barrel and the catheter, and a spring-driven actuator for operating the piston to deliver the drug to the catheter and thereby inflates the balloon. Optionally, manual pressurization takes place in two stages. In the first stage, the pressure is suitable for performance of PTCA, but too low to permit the balloon perforations to open. In the second stage, the pressure is increased, and the pores open and emit jets of the drug.

In some embodiments, the insufflator is operated manually to load the drug into the balloon and to provide the PTCA pressure, and is then operated automatically to increase the pressure for drug delivery. Optionally, the insufflator is also operated automatically to deflate the balloon prior to withdrawal of the catheter.

In an exemplary embodiment of the invention, the balloon catheter system includes a filter to prevent blockage of balloon micro-pores by impurities in the

delivered solution. Optionally, the filter is placed at a proximal section of the catheter, or at a distal end, optionally, within the balloon or at an interface between the balloon and a shaft of the catheter. In other embodiments, the filter is provided outside of the catheter. In an exemplary embodiment of the invention, the filter comprises a perforated
5 film, enclosed within a housing. In an exemplary embodiment of the invention, the pores diameter of the filter may be in the range of 0.1 – 3 μm , optionally in the range of 0.5 – 1.5 μm . Optionally, the filter passes particles that are less than 80%, 60%, 30%, 10% or smaller or intermediate percentages of the pore sizes. In an exemplary embodiment of the invention, the filter passing size is between 0.2 and 0.8 microns, for
10 example, about 0.45 microns. In an exemplary embodiment of the invention, the filter area size is between 0.1 cm^2 and 4 cm^2 , for example, 2 cm^2 .

Optionally, a non-sieve filtering mechanism is used, for example, a centrifugal filter or a sorting filter where particles that are too large are washed away from apertures sized to pass correctly sized particles.

15 In an exemplary embodiment, the filter film and the filter housing are made of material to which the drug does not adhere or otherwise interact with. Optionally, the filter film and the filter housing are made of polycarbonate or other material capable of withstanding high pressure. In an exemplary embodiment of the invention, the filter is an elongate filter, for example, between 2 and 20 mm long with a diameter that is equal
20 to or less than the length, for example, less than 50%, or 30% of the length. This may be useful if the filter diameter is small, for example, if the filter fits in the catheter or the balloon.

In an exemplary embodiment of the invention, balloon visualization during the procedure is enabled by using a radiopaque material which is provided with the balloon.
25 For example, at least one thread, bar, strip, ring, dot, or other form of radiopaque material, such as Tantalum, is provided within and/or over the balloon surface or adjacent the balloon. Optionally, this allows reducing the use or avoiding the use of contrast medium. Optionally, multiple radiopaque markers are provided or a single elongate marker is positioned so that the expansion of the balloon can be measured
30 under fluoroscopy/X-rays.

In an exemplary embodiment of the invention, a catheter balloon treatment system is configured to provide a user with the information of the amount of

medicament delivered and/or other delivery parameters, such as delivery pressure and time.

In an exemplary embodiment of the invention, a physician can choose and/or control of the desired amount of drug to be delivered, for example, by adjusting the parameter(s) of pressure and/or time for each drug injection. This may be important in cases where, for example, a patient requires a higher dose of medicament. In an exemplary embodiment of the invention, the system includes a unit (e.g., calculator or printed table) that interrelates various injection parameters and the amount of medicament delivered.

In an exemplary embodiment of the invention, the system also includes a display unit, for example, a digital display of pressure and a timer.

In an exemplary embodiment of the invention, the drug delivery catheter serves for delivering an implant, for example, a balloon-mounted stent to be placed and opened in a narrowed region. In an exemplary embodiment of the invention, the medicament delivery process further includes the opening of the stent from a collapsed to a widened form before or after medicament delivery. Optionally, stent design (e.g., stent's struts design) and/or balloon design (e.g., perforation pattern and/or hole design) incorporate an improved correlativity and efficiency, for example, avoiding blocking more than, for example, 10%, 20%, 30% or intermediate percentages of pores in the balloon by the stent. It should be noted that medicament delivery can be via a device other than a balloon, for example, via one or more non-expanding porous tubes, a flat, optionally curved surface (e.g., rigid or flexible, optionally comprising a chamber covered by a membrane at least in part. Optionally, such a delivery system is thin, for example, having a thickness (e.g., minimal dimension and/or minimal trans-axial dimension) of less than 5 mm, 2 mm, less than 1 mm and/or less than 0.5 mm or intermediate sizes.

In another embodiment of the invention, the suggested balloon catheter may be used to inject a medicament following arterectomy or other treatment of a blood vessel. Optionally, a same balloon is used for vascular tissue ablation and for material delivery, for example, including both cutting wires or ridges and pores.

While in an exemplary embodiment of the invention the body part treated is a blood vessel, a medicament delivery system as described herein can be used for other body parts as well, for example, for treating a body passage or tissue adjacent such a

passage or adjacent an artificially created cavity. Example tissues include any live tissue, tumor or organ that is adjacent to a body passage, for example into a prostate or into a heart. Exemplary body passages which may be treated and/or through which treatment may be delivered to adjacent tissue include, for example, blood vessels (e.g., coronary or peripheral, veins or arteries), urethra, trachea, ureter, prostate, esophagus, ileum, biliary duct, ovaries, tear duct, and/or a nasal cavity. Optionally or alternatively, the passageway is artificial, for example, formed by a separate instrument, and/or by the drug delivery device itself (e.g., by its being pushed into tissue to form a passageway, optionally the device including a cutting tip). In an exemplary embodiment of the invention, the catheter delivery system is adapted for the passageway and/or tissue treatment. For example, the rigidity, length, or diameter of the catheter may be changed. Optionally or alternatively, the length and/or diameter of the balloon may be changed. Optionally or alternatively, the number and/or size and/or positioning and/or density of the pores may be changed. Optionally or alternatively, the pressure protocol used may be changed. Optionally or alternatively, duration and/or viscosity and/or active ingredient concentration, may be changed. Optionally or alternatively, any of these parameters may be changed to take into account the medicament being delivered.

In an exemplary embodiment of the invention, the balloon is perforated so that at least a substantial portion (e.g., 50%, 60%, 70% or more) of the perforations is perpendicular (e.g., within 30 degrees, 20 degrees, 10 degrees, and/or 5 degrees of a perpendicular) to the balloon wall at the point of perforation. This may provide more efficient delivery of medicament into tissue. Optionally or alternatively, other controlled directions can be provided, for example, a plurality of pores (e.g., more than 3, more than 4 or more than 10) selected to have jets thereof meet at a point inside the tissue (focused arrangement), or diverging away from each other. For example, at least 3, 4, 5, or more focused or diverging pore arrangements may be provided. Optionally, such directionality is provided by using a source having diverging or converging beams, for example, using a suitably shaped source and a suitable aiming mask. In an exemplary embodiment of the invention, most of the surface area of the membrane (e.g., balloon) are shielded from a perforation source (e.g., a cyclotron), while a small portion of the balloon, having a substantial part that is positioned perpendicular to the perforation source, is exposed to the perforation source. Optionally, the balloon is rotated at a

controlled rate (e.g., in steps), so that each portion of the rotated balloon is perforated separately, while most of it is approximately perpendicular to the perforation source. Optionally, the perforation is by ion beam used to weaken the membrane and then dipping in a chemical etchant, such as an acid, to remove weakened regions.

Also provided in accordance with some embodiments of the invention is the use of medicament mixtures for delivery via a small pore balloon, at a pressure sufficient to cause jets. Optionally or alternatively, such medicament includes contrast material and/or includes a desired viscosity. Optionally or alternatively, the medicament (or a kit including such medicament) is packaged with usage instructions and/or with a list of properties and/or mixing instructions relating, for example, to viscosity, treatment type and/or suitable delivery system.

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 set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Exemplary Balloon Catheter Embodiments

Figs. 1A-1D illustrate features of a microporous balloon catheter 102 with some features omitted in the interest of clarity. Fig. 1A is a side elevation. Fig. 1B is an enlarged view of Detail A indicated in Fig. 1A. Figs. 1C and 1D are fragmentary enlarged cross-sections taken along line B-B in Fig. 1B according to some embodiments of the invention.

Catheter 102 is comprised of a balloon 104, an attached catheter shaft 106, and an optional guide wire 108, the distal end of which is shown extending out of shaft distal end 110. Shaft 106 is a tubular member configured for connection at its proximal end 112 to a drug reservoir and/or pressure source as described below.

At its proximal and distal ends 114 and 116, to balloon 104 is sealed to shaft 106 in any suitable and desired manner at its ends, and shaft 106 includes openings (not shown) within the balloon to allow for inflation and drug delivery through the lumen of the shaft.

Optional guide-wire 108, when employed, is used to assist in navigation of catheter 102 to a treatment area. Guide wire 108 may be coupled with balloon catheter 102, for example, using an optional second inner lumen of shaft 106 (not shown).

In some embodiments, balloon 104 is formed of a biocompatible semi-compliant or compliant polymer.

In some embodiments, balloon membranes are perforated with a pore density in the range of about 300-10,000 holes/cm², and optionally between about 300 and about 2000 holes/cm². In an exemplary embodiment of the invention, the balloon has about 550 holes/cm².

In some embodiments, the pore density is substantially uniform over the perforated portion of the balloon surface. Optionally, however, balloons may be provided with several different or changing pore densities and/or may include specific surface areas that are not perforated. For example, a higher density may be provided on one or more angular sectors and/or axial sections.

Optionally or alternatively, the arrangement of pores and/or other properties thereof may match a target to be treated. For example, in the case of stent delivery, pores may be concentrated (and/or be larger or smaller) on parts of the balloon where greater stent pressure and/or re-stenosis are expected. In an exemplary embodiment of the invention, the pores are provided on parts of the balloon that are expected to contact a blood vessel wall (or other tissue), e.g., on parts parallel to the balloon axis. In some cases, the treated area is smaller than the stent area. Optionally, in some treatment protocols, a first balloon may be used for PTCA and then a second differently configured balloon used for drug delivery according to a desired treatment area.

According to some embodiments, the average and/or minimal and/or maximal diameter of balloon pores 120 is in the range of about 0.1-10µm, optionally 1-5µm, optionally 1-3 µm. In an exemplary embodiment of the invention, the pores are of about 1.7 µm in diameter, or less or more, for example, 1-1.7 microns, 0.1-1 microns or 1.5-5 microns. Optionally, at least about 80% of pores are of substantially equal diameter with a maximal allowed tolerance of 0.5µm or less. Pore sizes at the upper ends of the indicated ranges may be useful, for example to deliver drugs by means of microcapsules, whereby the benefit of extended drug delivery time, as well as the benefit of jetting without significant tissue trauma.

Optionally, according to some embodiments, balloon 120 includes different areas of different pore sizes (not shown). In an exemplary embodiment of the invention, different jet properties and/or pore density are provided at different parts of the balloon. Optionally, the balloon itself is asymmetric and/or non-cylindrical.

5 In general, smaller diameter holes provide a higher pressure above which jetting occurs. Thus, in some embodiments, a plurality of different size holes (e.g., having a continuous size range or selected to have sizes from a set of discrete sizes) are provided so as to provide different jetting behavior at different pressures. Optionally, the pressures are selected according to pressure levels that a blood vessel can handle, and
10 desired penetration depth. Optionally, some larger pores can be provided so that drug delivery begins toward the end of PTCA as described below. Optionally, the balloon parameters are changed or selected according to tissue limitations. The jet velocity is function of the hole diameter and the pressure.

In an exemplary embodiment of the invention, the balloon has a treatment length
15 of between 8 and 80 mm, for example, between 10 and 30 mm or intermediate lengths.

In an exemplary embodiment of the invention, the catheter/shaft on which the balloon is mounted is of a length of between 5 and 200 cm, for example, between 100 and 150 cm. Optionally, the shaft diameter is less than 10 mm, 5 mm, less than 3 mm or intermediate sizes.

20 Balloons formed of a non-compliant material such as PET may be perforated by a track etching process wherein the polymer film is bombarded by protons, ions, electrons or other radiation and then subsequently subjected to a controlled etching. The resulting perforations 112 are substantially cylindrical, as indicated at 122 in Fig. 1C.

Alternatively, the balloon may be perforated in any other suitable and desired
25 manner known to those skilled in manufacturing microfiltration and ultra-filtration membranes, for example, as described in US 5,498,238, the disclosure of which is fully incorporated herein by reference.

As noted above, in some exemplary embodiments of the invention, balloon 104 is made of a semi-compliant or a compliant material, such as a polyamide, for example,
30 Nylon, or a polyolefin copolymer (POC). Such materials are relatively elastic and therefore capable of expanding under pressure. Balloons formed of such materials may be advantageous in some instances in that they allow expansion of the obstructed lumen

to a range of diameters, as needed, comparing to just one diameter for in non-compliant balloon.

Also, semi-compliant materials are softer, and therefore after deflation, a semi-compliant balloon may fold back to a smaller profile than a non-compliant material, and in some cases, is less likely to interfere with the vessel internal surface. Semi-compliant balloons may be delivered to the treatment site in a collapsed state and is then expanded under relatively low pressures (e.g., 1 to 3 ATM), until its outer surface is in direct contact with the inner wall of the lumen being treated. The pressure may then be increased as desired for performance of PTCA and drug delivery. Optionally, in some embodiments, expansion may be limited, for example, by a non-expanding mesh embedded in the balloon.

Elasticity of polymers is nonlinear, so a specific modulus of elasticity is not readily defined, and is dependent in part, on the thickness of the material. By way of example, in some embodiments of the invention, balloons having nominal diameters in the range of fthe In general terms, for the purposes of this discussion, balloons will be considered to be semi-compliant if, by changing the pressure from 6 bar to 16 bar, the outside diameter of the balloon will expand by about 0.3 to about 0.5mm. Materials that will expand less will be considered as non-compliant, and materials that expand more will be considered as compliant. For example, balloons that exhibit diameter changes in the range of about 1.0 to about 1.3 percent or possibly more or less or which exhibit an overall effective change of diameter in the range of about 0.06 to about 0.75 mm/Bar, or possibly more or less, will be considered to be semi-compliant. Balloons experiencing greater percentage changes or greater changes in diameter per bar of pressure change will be considered to be compliant.

The Table below shows representative diameters over a range of pressures for semi-compliant balloons having a nominal diameter of 3.5 mm at a nominal pressure of 8 bar. The values given may be subject to considerable variation and are intended only as exemplary.

Pressure (ATM)	Diameter (mm)
2	3.07
4	3.2
6	3.34
8	3.5

10	3.6
12	3.69
14	3.8
16	3.9
18	3.99

Balloons according to some embodiments of the invention may have pore distribution patterns, pore densities, and pore sizes as noted above. Optionally or alternatively, the pressures are selected according to the degree of compliance of the balloon. Optionally, the diameters of balloons according to some embodiments of the invention expand less than 30%, less than 20% or less than 10% or 5% more or intermediate values when the pressure is doubled.

Semi-compliant materials do not lend themselves to perforation by conventional track etching processes, and according to some embodiments, are perforated by laser drilling. In such embodiments, the perforations 120 are of truncated conical configuration, as indicated at 124 in Fig. 1D. The perforations may be outwardly tapered, i.e., with smaller diameter on the exterior of the balloon surface as shown in Fig. 1D, or inwardly tapered, i.e., with the smaller diameter on the inside, as discussed below. The manner in which inwardly and outwardly tapered perforations are formed will be discussed in detail below. Tapered holes may be advantageous in some cases in that resistance of the hole to the flow of the drug is dependent on the length of the smallest diameter, so it may be lower than for non-tapered holes.

Outwardly tapered holes may be advantageous compared to inwardly tapered holes in some cases since the jet velocity will be maximum at the interface with the tissue.

Figs. 2A-2C are enlarged cross-sectional views that illustrate features of some balloons formed of semi-compliant material, having conical perforations formed by laser drilling. In Figs. 2A, and 2B, the holes are outwardly tapered, i.e. the small diameter openings of the conical perforations are on the outside of the balloon wall, i.e. facing the tissue being treated, and the large diameter openings are on the inside of the balloon, while in Figs. 2C, the holes are inwardly tapered with the large diameter sides of perforations on the outside of the balloon, i.e., facing the treated tissue and the small diameter sides are on the inside of the balloon.

Fig. 2A shows the configuration of a perforation 200 when balloon inflation pressure is below a threshold, for example, below a pressure at which injection ("jetting") begins. In this configuration, the smaller side 202 of perforation 200 has a diameter D1, and forms an angle α_1 with balloon wall 201 that depends on the thickness of balloon wall 201, and the diameters of the two openings 202 and 204.

As shown in Fig. 2B, at (and above) the threshold pressure, small end 202 of perforation 200 expands to a diameter D3 greater than D1, while the diameter D2 at the larger end 204 expands to a diameter D4. The change in the shape of perforation 200 allows a greater drug flow rate.

Conversely, in Fig. 2C, the small diameter end 202 of perforation 200 faces into the balloon. When the pressure exceeds the threshold, small diameter opening 202 again expands to a diameter D3 greater than D1, while the diameter D2 expands to D4. This again results in enlargement of the "effective" size of perforation 200 and increased drug flow rate, but the velocity will be maximum across the smaller diameter opening in 202 which is inside the balloon.

Microporous semi-compliant balloons may have pores in which the ratio of D1 to D2, i.e. of the unexpanded balloon, is in the range of about 1.33 to about 4 to 1, or larger or smaller or intermediate values. For example, the unexpanded diameter at the small end is in the range of about 1 – 5 μm , preferably in the range of about 1.5 – 2.5 μm , preferably about 1.7 μm , and the unexpanded diameter at the larger end is in the range of about 2 – 10 μm , preferably about 5 μm .

According to some embodiments, the thickness of semi-compliant balloons is in the range of about 0.012 mm to about 0.018 mm, for example, in the range of about 0.014 mm to about 0.016 mm, for balloons up to outside diameter of 3.5 mm, and the thickness in the range of 0.011mm to about 0.025 mm for balloons having outside diameter of 4mm to 7 mm.

Fig. 3A-3D illustrate exemplary balloon perforation perimeter shapes when the internal pressure is above and below the drug release pressure. Fig. 3A shows an elliptical perforation 302 when the internal pressure in the balloon is below the drug delivery pressure (for example, under 3 ATM) and the balloon is only slightly expanded, but is not sufficiently expanded to permit drug delivery. When the drug

delivery pressure is reached, the perforation enlarges and becomes substantially circular as indicated at 304 in Fig. 3B.

In the embodiment of Fig. 3C, at low pressure with the balloon slightly expanded (for example, under 3 ATM), the perimeter 306 of the perforation is substantially circular. When the balloon is expanded by the drug delivery pressure, the perimeter 408 of the perforation becomes substantially elliptical. For a given perimeter, an elliptical shape will show more resistant to flow, and round circle will show minimum resistance to flow and may sometimes be preferred for that reason. The change of hole perimeter shape in deflated and expanded balloon states results from different compliance percentages of the balloon in radial and in axial directions. Optionally, the radial compliance is greater than the axial compliance. Alternatively, the axial compliance is greater than the axial compliance. As a further option, by adjustment of the relative percentages of axial and radial compliance, the holes in the balloon may be of any desired shape.

It should be understood that for expanded pores that are elliptical, the pore sizes represent the length of the major axis.

General System Overview

Fig. 4 is a schematic diagram of an exemplary catheter treatment system 400, in accordance with some embodiments of the invention. System 400 is comprised of a balloon catheter 402 having a balloon 404 at its distal end and a shaft 404 at its proximal end as described in connection with Figs. 1-3 above. System 400 further includes a drug reservoir 408, a pressure source 410, for example, a pump, a controller 412, for example, a microprocessor, a user interface 414, for example, a keyboard, mouse and/or touch screen, and a display unit 416.

In some embodiments, drug reservoir 408 and pressure source 410 may be a single unit. Optionally, reservoir 408 may be a separate unit, and the drug may be pumped to catheter 402, for example, through a conduit 418.

As mentioned above, pressure source 410 may be a pump. A suitable pump may be a peristaltic pump, a syringe pump, a shockwave source, an electric pump, and/or a hydraulic pump. Optionally or alternatively, pressure creating means such as described in U.S. patent application 11/335,317, published as 2006-0190022-A1 may be

employed. The disclosure of this application is fully incorporated herein by reference are used to generate a pressure pulse.

Controller 412 may optionally perform one or more functions including control of the pressure profile provided by pressure source 410, provision of step-by-step instructions to a user for system set-up of treatment parameters for system 400, calculation and/or control of drug dosages, and other desired functions. Controller 412 may be a dedicated unit part of system 400, or a suitably programmed computer.

In an exemplary embodiment of the invention, system 400 (e.g., via controller 406) calculates an actual delivered dosage. Optionally, such delivery is presented in real time for a physician to follow. Optionally, the system integrates the rate of fluid delivery over time. Optionally or alternatively, the system takes into account initial leakage of fluid and/or fluid delivered at pressures too low to enter tissue. For example, the system may only take into account delivery when pressure is above a threshold. Optionally or alternatively, instead of measuring flow, the system measures pressure and estimates delivery according to known delivery rates at different pressures. Optionally or alternatively, the system presents estimated leakage into the blood stream. Optionally or alternatively, the system stops delivery and/or generates and alerts the user when a desired amount of medicament is estimated to have been delivered or, possibly, a short time before such estimated delivery is completed.

Optionally, a visual and/or auditory display 416 may be used to inform the surgeon of treatment progress or other information. In some embodiments, the display unit is a digital display showing pressure and a timer. The controller 412 may be programmed to integrate the pressure and time parameters to give real time drug flow rate, which can be translated to the delivered amount of the drug. Optionally, corrections may be computed for elasticity effects in the delivery catheter and balloon. Optionally, the controller can be programmed for display of any desired treatment parameter, intended and/or actually occurring, for example, a total amount of drug delivered, a sequence of pressure pulses to be applied and/or a sequence of such pulses that was actually applied.

Optionally, system 400 includes a filter as described below. For example, a filter 422 may be located in conduit 418, or a filter 424 may be located at a distal end of catheter shaft 404, or within balloon 404 at 426.

When used for PTCA and for drug delivery, balloons according to some embodiments of the invention are advantageously expandable, rather than just inflatable, as is the case of balloons formed of a non-compliant material. Alternatively, only part of the balloon may be expandable, for example, an axial portion, or a sector).

5 As a further alternative, balloon 404 can be non-expandable, for example if used only for drug delivery.

Also, for example as described below, catheter 404 may be used to deliver a stent or provide other treatment to a vessel. In some embodiments, for example, for treating coronary vessels, shaft 406 is flexible. In other applications, for example in the
10 urethra shaft 406 may be rigid or semi-rigid as it may facilitate insertion.

In some embodiments of the invention, catheter 402 includes one or more radio-radiopaque markers 420, for example, mounted on shaft 406 or on the balloon membrane or inside the balloon. Optionally, a plurality of markers 420 (or an elongated marker) may be positioned at either end of the porous areas of the balloon.

15 By way of example, at least one thread, bar, strip, ring, dot or other form of radiopaque material, such as Tantalum, is provided within and/or over the balloon surface or adjacent the balloon. Optionally, this allows reducing or avoiding the use of contrast medium. Optionally, multiple radiopaque markers are provided or a single elongate marker is positioned so that the expansion of the balloon can be measured
20 under fluoroscopy/X-rays.

In an exemplary embodiment of the invention, some or all of system 400, for example, the balloon, the catheter, the pressure source, and the conduit may be disposable and/or may be provided as a kit. Optionally, controller 412, display unit 416, and/or UI 414 are reusable. Optionally, if pressure source 410 does not contact the drug,
25 except through conduit 418 or other interface so it can also be reused.

Exemplary Treatment Method

Fig. 5 is a schematic flow diagram of an exemplary method 500 for treating a narrowed segment of a body passage using, for example, the semi-compliant
30 microporous balloon catheters described above. This should be considered in conjunction with Figs. 6A-6D which show schematically an exemplary course of treatment of a vascular stenosis, and with Fig. 7, which shows an exemplary pressure

profile for the treatment. Also, in connection with the following description, the benefits of both micro-porosity and semi-compliance of the balloon material as explained above should be recalled.

In an exemplary embodiment of the invention, prior to treatment, a physician selects treatment parameters, for example, including one or more of a particular drug, desired amount, desired concentration, desired release profile, desired in-tissue concentration, desired penetration depth, maximal allowed penetration depth, vessel diameter, vessel length to be treated and/or angular sector to be treated. The physician can then determine, for example, which medicament and which balloon design to use. Optionally, a plurality of different balloons with different properties as described above are available. Optionally, in the determination of treatment parameter, the physician uses a table or is guided by instructions provided by controller 412 and display 416, and enters the required information into controller 412 by means of UI 414.

Once the initial steps described above are completed, at S502, a balloon catheter 402 is positioned with balloon 404 within a stenosis 602 in a blood vessel 600 or other tissue to be treated (see Fig. 6A). In this position, balloon 404 is substantially collapsed and/or deflated to facilitate maneuverability within body passages until the area to be treated is reached. Catheter 402 may be advanced to the desired location by any means known to the art, including or excluding the use of guide-wire 604 (see Fig. 6B). If the stenosis is asymmetric, for example, on only one side of the vessel, the balloon may be selected to be a balloon with asymmetric treatment/penetration profile and then oriented as needed.

S504 is the initial stage of inflation of balloon 402. Here, the balloon is subjected to an internal pressure that rises to at level P1 (see Fig. 7), for example, less than 6 ATM for the case of treatment of a coronary artery. In some embodiments, the balloon is inflated by delivery of the drug to fill the interior of the balloon. The resulting internal pressure causes the balloon to expand and to press outwardly on obstruction 602 (see Fig. 6B), but the pressure is insufficient to cause significant drug release through the pores in the balloon.

Sometimes, a minimal pressure may be needed at S504 before expansion begins, for example, when an initial resistance is encountered from the balloon surroundings. In another exemplary case, when a stent is delivered and disposed in narrowing 602, a

higher inflation pressure P1 may be needed, for example, about 6 ATM or more or less. The buildup of pressure to level P1 during S504 (i.e., the time between t0 and t1 in Fig. 7), can be very short, for example, 1-5 seconds, or more, or less).

S506 is an optional angioplasty stage during which, for example, PTCA is performed. Here, balloon 404 is pressurized to a pressure P2 during a time interval t2-t1. During this interval, the balloon expands to a degree that narrowing 602 is opened to an extent chosen by the physician, optionally to the general diameter of the adjacent unobstructed segments of body passage 600 (see Fig. 6C). As an example, a pressure P2 in the range of about 8 to about 18 atmospheres may be used for angioplasty of a stenotic coronary artery, while lower pressures (e.g., 3-9 atmospheres) may be used for opening stenotic peripheral arteries. Higher or lower pressure may be applied for different body lumens according to the vessel mechanical properties, the procedural protocol and/or according to the physician's discretion.

The duration t1...t2 of the angioplasty stage S506 may also be relatively short, for example, 10-30 seconds or up to a minute or more or less, according to standard angioplasty protocol and/or the physician's discretion.

S508 is the drug delivery stage. Here, balloon 404 is further pressurized to a pressure level P3 (see Fig. 7). At this pressure, pores 606 in balloon wall 808 open, and the drug is released as a plurality of medicament jets 610 with a velocity sufficient to penetrate the adjacent tissue 212. Exemplary jets 610 are schematically illustrated in Fig. 6E, which is an enlargement of a portion of Fig. 6D.

In an exemplary embodiment of the invention, P3 is between 10 and 80 atmospheres, optionally between 15 and 50 atmospheres. Optionally, the pressure build-up duration t2...t3 is less than 3-5 seconds, optionally less than a second or less than 200 ms, after which the pressure remains constant for a drug delivery duration t3...t4. In some embodiments, t3...t4 is longer than 3 seconds, 8 seconds, 15 seconds, 30 seconds, 45 seconds or 60 seconds or shorter or intermediate durations.

Optionally, instead of a constant pressure P3 during drug delivery, the pressure source can be operated to provide a train of pressure pulses. In that event, the duration is even longer (e.g., 1-10 minutes, for example, about 5 minutes or intermediate durations). Optionally, t3...t4 is determined (optionally predetermined) according to

treatment type, location and severity of the lesion, specific balloon design and/or applied pressure P3.

In some exemplary embodiment of the invention, jets 610 travel into the stenosis tissue at narrowing 602. Optionally, the penetration depth is maintained within the stenosis layer (e.g., lipids and/or fibrotic tissue), but alternatively it may be desired to apply injection pressures that will promote penetration into deeper layers of passage 600 (e.g., the intima layer and/or the media layer of a blood vessel).

Optionally, balloon 404 can be fabricated so that the pore opening pressure is slightly below P2, i.e. the pores open before the balloon has completely expanded. This allows at least some jetting during the final stages of PCTA.

Optionally, by varying the size of the balloon perforations, it may be arranged that some of the delivered drug does not penetrate into the tissue in the form of jets, but instead enter the vessel wall by diffusion

Alternatively, or additionally, balloon 410 may be kept in place for a short time to assist in adhesion.

S510, beginning at time t_4 , is the termination stage. Here, pressure is reduced and jetting stops. The balloon may be collapsed, for example by vacuum and withdrawn. Optionally, the pressure during time period ($t_3...t_4$) can be varied, for example to alternate eroding and non-eroding jetting and/or to massage fluid into the tissue and/or otherwise manipulate the tissue. Optionally or alternatively, pressure alternation is used to allow tissue to rest between injections. For example, a series of 1-5 second injections may be spaced out over several minutes. Optionally, such alternation is used to allow intermittent blood flow past the treatment region. Optionally or alternatively, blood flow past is allowed by a bypass tube (not shown) which may or may not be part of the catheter system.

It should be noted that while the description herein focuses on using a balloon, which has the potential advantage that it can self expand to ensure contact with tissue, in some embodiments, medicament delivery is via an expanding element other than a balloon or via a non-expanding element. In one example, the delivery is via a membrane attached to a delivery system, which is urged against a tissue to be treated, but the membrane does not appreciably expand. In another example, delivery is via thin tubes, for example, with a diameter of 300-1000 microns and pores along their sides.

Optionally, such tubes are urged against tissue to be treated using a balloon. Optionally or alternatively, systems with small pores as described in the art (possibly with a higher or lower surface density thereof) are used, albeit with pressures higher than suggested, for the express purpose of causing a desired jetting effect.

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Stent Delivery

As mentioned above, in some embodiments of the invention, the catheter is also used for delivering an implant, for example, a balloon-mounted stent to be placed and opened in a narrowed region. Optionally, the initial expansion of the balloon also serves to open the stent from a collapsed to a widened form. Optionally, the stent is opened after or during drug delivery. Optionally, the configuration of the struts of the stent, and balloon perforation pattern and/or hole design are selected to avoiding blockage of more than, for example, 10%, 20%, 30% or intermediate percentages of pores in the balloon by the stent.

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It should be noted that drug delivery can be via a device other than a balloon, for example, via one or more non-expanding porous tubes, a flat, optionally curved surface (e.g., rigid or flexible, optionally comprising a chamber covered by a membrane at least in part. Optionally, such a delivery system is thin, for example, having a thickness (e.g., minimal dimension and/or minimal trans-axial dimension) of less than 5 mm, 2 mm, less than 1 mm and/or less than 0.5 mm or intermediate sizes.

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Exemplary Medicament Flow Parameters

As noted above, Fig. 7, shows an exemplary pressure profile for treatment that includes angioplasty (PTCA) and drug delivery. As the pressure is measured at a pressure source, it is noted that there can be a pressure drop of, for example, 10%, 30%, 50% or intermediate or greater amounts between the source and the balloon. It is also noted that under sufficient pressure the drug jets penetrate tissue by forming an erosion hole. Different situations will reflect different desired erosion properties.

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In an exemplary embodiment of the invention, the erosion hole has a depth between 0.001mm and 0.2mm, optionally between 0.01mm and 0.05mm. In an exemplary embodiment of the invention, the erosion hole extends from an inner wall of a blood vessel into the endothelial layer, optionally into the area between the intima and

media layers, and/or optionally extends into the media layer and/or beyond. Erosion hole depths may be controlled, for example, by setting fluid velocity, selecting pore size and/or selecting pressure and/or presence of eroding particles in the medicament.

In an exemplary embodiment of the invention, the average and/or maximal velocity of a single jet exceeds 0.1m/s, optionally 0.5m/s, optionally 5 m/s, or optionally exceeds 15 m/s, or is intermediate in velocity. An exemplary low flow rate per hole may be lower than 0.0001 cc/sec. As a function of balloon area, the flow rate may be, for example, lower than 0.1 cc/min/cm², and/or lower than 0.005 cc/sec/cm². In an exemplary embodiment of the invention, the flow rate is the maximal flow rate achieved during maximal injection pressure.

As noted above, in some embodiments of the invention, the intention is to achieve a desired minimal flow volume, without causing unacceptable trauma to the tissue being treated. For example, pressure and/or jet velocity may be reduced after it is estimated that there is a sufficient depth for erosion. In an exemplary embodiment of the invention, pressure and application duration are calculated according to a desired delivery amount and an allowed amount of tissue damage, for example, using tables or a function which inter-relates such parameters.

In some embodiments of the invention, the entire duration of the jetting forms a hole in the adjacent tissue. In other embodiments, a first part of the jetting forms a hole and a second part either only slowly increases the hole depth and/or size or does not affect the hole depth and/or diameter, but rather serves to provide additional material into the tissue. Optionally or alternatively, the jetting includes a series of one or more hole forming periods interspersed with periods during which there is only drug delivery. Optionally, the process is terminated with a hole forming act. Optionally, the acts being hole forming or material injection depends on the jet parameters which may be set, for example, by controlling the pressure (e.g., higher pressure for hole forming, for example, 300%, 200%, 100%, 50%, 30% or intermediate or higher percentages more pressure for hole forming).

In an exemplary embodiment of the invention, the duration of the hole-formation stage may be higher than 0.5 ms, optionally higher than 5ms, optionally higher than 20ms, optionally higher than 100ms, optionally higher than 1 second or may be of any intermediate value. Alternatively, the hole forming stage is very long and may

take over 5 seconds, optionally over 10 seconds. The duration of the medicament dispersion stage may be higher than 1ms, optionally higher than 10ms, optionally higher than 100ms, optionally higher than 1 second, optionally higher than 10 seconds, or may be of any intermediate value. In an exemplary embodiment of the invention, most of the medicament is dispensed out of the balloon in a period between 1 to 60 seconds, optionally 5 to 30 seconds, optionally about 15 or 20 seconds. Times smaller than and/or intermediate the times described herein may be used for some embodiments.

In an exemplary embodiment of the invention, an exemplary procedure total leakage prior to jetting is less than 40%, 30%, 20%, 1%, 0.5% or intermediate percentages of the amount of fluid exiting the balloon during jetting into tissue.

In an exemplary embodiment of the invention, at least 20%, at least 50%, at least 80%, at least 90% or intermediate percentages of provided medicament are ejected from the balloon during the jetting phase. Optionally, remaining medicament is sucked out of the catheter and/or washed out (e.g., ejected optionally as jets) using saline or other washing fluid.

Optionally, the maximal injection pressure is in the range of 10-100 atmospheres, optionally in the range of 15-50 atmospheres.

Optionally, the suggested exemplary balloon is capable of producing a continuous stream of fluid medication that with sufficient impact for active diffusion of the medication to the passage wall (e.g., to provide drug diffusion volume which is substantially higher than passive diffusion, resulting in better adhering to- and/or penetration and/or absorption of medicament into tissue).

Fig. 8 illustrates another pressure profile according to some embodiments of the invention. With reference again to Fig. 5, after catheter 402 has been prepared for use, and correctly located against treated lesion (S502), at the initial balloon pressurization (dilatation) stage S504, the internal pressure is brought to a level P1. When P1 has been attained, PTCA stage S506 commences, for a time period T1...T2 during which the pressure is held constant.

After time T2, the balloon pressure is increased to a level P2 (over a time interval T2...T3). At T3, drug delivery stage 508 commences, during which the pressure is held at P2 for in interval T3...T4. Then, at T4, stage S510 commences, during which the balloon is deflated and withdrawn.

It should be noted that the methods and devices described herein may be used for the treatment of in-stent restenosis, where only angioplasty and local drug administration is preferred. In another exemplary embodiment of the invention, the method described herein is useful for bent or torturous blood vessels and/or for vessel junctions where placing a stent can be difficult or impossible.

Exemplary Methods and Apparatus for Balloon Perforation

Perforation of Non-compliant Balloon Materials

As previously noted, for balloons made of non-compliant materials such as PET, conventional track etching procedures may be employed for balloon perforation. Fig. 9 illustrates schematically a track-etch process for production of a perforated balloon in which most of the pores are approximately perpendicular to balloon wall.

Here, a thin polymer film which forms the balloon membrane is bombarded by charged particles (protons, ions, electrons or other radiation), and then subsequently subjected to a controlled etching, during which the tracks left by the particles are preferentially etched, optionally to form uniform, cylindrical pores of predetermined size.

In Fig. 9, balloon 900 is rotated, for example by connecting one or both ends of balloon to a dedicated apparatus (not shown), that turns the balloon in a controlled, optionally predefined, rate, as required. Balloon portion 904 that is positioned substantially perpendicular to the perforation source (e.g., a nuclear reactor/cyclotron; not shown in Fig. 9) remains exposed, while other portions (906, 908) which do not face the perforation source are shielded from the perforation source (for example, by metal such as a lead shield 912, 914).

The perforation source is activated, and the unshielded portion 904 of the balloon surface is bombarded, to create the pores that are angled at approximately 90 degrees to balloon surface at the perforation point. Optionally, a perforated mask is used to set the location, pattern, size and/or other properties of the pores.

Then, balloon 900 is rotated to expose a portion of the surface that was previously shielded to the perforation source, and to shield other portions of the balloon surface that have already been perforated. The perforation source is re-activated and the newly-exposed area is bombarded to perforate it at approximately 90 degrees. The

balloon 900 is rotated again, and the procedure is repeated until all, or the desired part of the balloon has been perforated.

Optionally or alternatively, axial masking may be used as well. In an exemplary embodiment of the invention, the beam of the radiation source comprises a plurality of
5 beams (e.g., formed by masking a wide aperture beam with a mask and/or by relative movement of a narrow beam and the balloon), optionally parallel, but alternatively non-parallel, for example, diverging or converging in one or two dimensions.

Perforation of Semi-compliant Balloon Materials

Figs. 10A and 10B illustrate an arrangement for laser perforation which may be
10 used for balloons according to some embodiments of the invention and optionally, for non-compliant materials as well. As shown, an assembled but un-perforated balloon catheter 1000 is inserted into a balloon holder or fixation device 1002 through an opening 1004 (with balloon 1006 fully deflated) and with catheter 1000 positioned so that balloon portion 1006 is inside fixation device 1002 and aligned with holes 1008 in a
15 tubular portion 1010, and with catheter shaft 1011 extending out through an opening 1012 at the opposite end. Optionally, catheter 1000 is held in place, and the correct placement of balloon 1006 within fixation device 1002 is determined using restrictor element (not shown) on the balloon catheter or within holder 1002.

Fig. 10B shows an exemplary perforation device 1014 including a driving
20 device 1015, to which fixation device 1002 is connected to, for example, via grabbing arms shown schematically at 1016. Before perforation, balloon 1006 is expanded, so that its diameter matches internal diameter (ID) of tubular portion 1010 of the fixation device.

Perforation is achieved by activating a laser source 1018 to provide a beam 1020
25 that passes through the holes 1008 in fixation device tube 1010. Preferably, laser 1018 is an ultra-short, ultra-high energy pulse laser, for example, a femtosecond laser.

Use of a femtosecond laser has been found to result in unexpected advantages. Apparently due to the short pulse duration and high energy level, the perforations are formed by the effect of impingement of the intense stream photons causing dissolution
30 of the chemical bonds at the perforation sites, and with only limited conduction of heat into the balloon material away from the perforation sites. The result is a neat and

sharply defined perforation with almost no loss of resilience and reduced compliance in the surrounding balloon material.

Beam 1020 may be scanned longitudinally while fixation device 1002 is rotated by driver 1014 to provide perforation over the desired portion of the balloon surface.

5 Alternatively, beam 1020 may be held stationary, and holder scanned longitudinally and rotated.

It should be understood that the perforation device may be designed to operate in a fully automated manner or may be operated manually, at least in part. For fully automated operation, there may be provided suitable arrangements for loading the
10 catheter into the holder, for removing it after perforation, and for controlling the sequence of operations. Alternatively, the catheter may be loaded and unloaded manually by an operator, and driver 1015 and laser 1018 activated by the operator as well.

It should further be understood that the track etching and laser perforation
15 processes described herein are intended to be exemplary. Any other suitable methods of perforation, whether now known, or developed hereafter, should be considered as being within the scope of the present invention.

An Exemplary Fixation Device

20 Figs. 11A and 11B present an exemplary design for balloon fixation device 1002 which may be used with any of the perforation arrangements described above. Referring to Fig. 11A, fixation device 1002 comprises two tubular sections 1010 and 1100. Section 1100 provides for connection of balloon fixation device 1002 to driving device 1015 (see Fig. 10B). Section 31 is perforated, with perforations 1008, configured
25 according to the pattern of perforations required for the balloon. Openings 1004, and 1012 of fixation device 1002 are used for passing the balloon into and out of the fixation device. The un-perforated balloon is placed within tube 1102 (see Fig. 11B) with the part of the balloon to be perforated (balloon "effective length"/"shoulder-to-shoulder" section) located against perforations 1008.

30 It should be noted that the laser drilling process results in truncated conical perforations that have a larger diameter opening on the outside of the balloon than on the inside. Thus, in the embodiment just described in which the perforation process is

performed with the balloon already connected to a catheter shaft, the resulting perforations are outwardly tapered so the large diameter ends are oriented adjacent to the tissue into which medicament dispersion is desired.

5 With continued reference to Figs. 10 and 11, and to Figs. 12A–12C, there is shown an alternative arrangement of balloon 1006 within fixation device 1002 in which balloon 1006 is perforated before assembly with the catheter shaft. This can be used to form either inwardly or outwardly tapered perforations.

10 Here, balloon 1006 is placed over a thin tube (e.g., hypo-tube) 1202, by a suitable connector 1204. Distal end 1206 of balloon 1006 is sealed (e.g., with medical glue). Then, balloon 1006, connected to tube 1202, is inserted into fixation device 1002 via opening 1004. Balloon 1006 is fully deflated during insertion into fixation device 1002.

15 Balloon 1006 is positioned within fixation device 1002 such that the fixation device holes 1008 are placed against the effective length area 1206 of the balloon. Optionally, correct placement and anchoring of balloon 1006 within fixation device 1002 is determined using a restrictor element (not shown) located, for example, on the distal section of balloon 1006. Tube 1202 is passed through opening 1012 of fixation device 1002.

20 Fixation device 1002 is connected to perforator 1014 as previously described. Balloon 1006 is expanded to conform to the internal diameter (ID) of tube 1010 of fixation device 1002 and perforation is performed also as described above. Following perforation the balloon is separated from tube 1202 and attached to the catheter shaft, for example, using, for example, implant-grade medical glue.

25 In this embodiment, since perforation is performed with the balloon not connected to the catheter. The perforations can be oriented either inwardly or outwardly tapered. To form outwardly tapered perforations, with the smaller end of the perforation located against the tissue, the balloon is turned inside-out prior to placement in the fixation device, such that its inner portion is placed against the balloon fixation device. Following perforation, the balloon is again turned inside-out and restored to its original condition.

30

Inflation Apparatus

Fig. 13A – 13C illustrate an exemplary design of a manually-operated insufflator 1300 which may be used as the pressure source for filling the balloon with the drug to be delivered, for angioplasty, and/or drug delivery. Insufflator 1300 may be
5 balloon-size-specific, or may be adapted for use with catheters of different sizes or configurations.

Insufflator 1300 is comprised of a barrel 1302 designed to be filled with a desired quantity of the drug to be delivered, and a piston or plunger 1306 located within the barrel, and an actuator generally indicated at 1308. Barrel 1302 is equipped with a
10 connector (e.g., a conventional Luer type connector) 1328 for connecting the barrel to a balloon catheter, and includes a collar or a finger grip 1310 at its proximal end by which insufflator 1300 is held, typically, between the user's pointer and the middle finger, or between the middle finger and the ring finger during pressurization of the balloon.

In some embodiments, actuator 1308 is comprised of a tubular body 1304, a
15 compression spring 1320 located in body 1304, and a coupling rod 1322 located between spring 1320 and piston 1306, and a shoulder 1326 at its proximal end that rests, for example, against the user's thumb during balloon pressurization.

Coupling rod 1322, is marked with graduations, for example circumferential lines (not shown), and calibrated to indicate the pressure used for balloon inflation. The
20 distal end of body 1304 indicates the pressure level when observed against the markings. Alternatively, markings 1322 may be located on piston shaft 1306; in which case, an o-ring (not shown) may optionally be provided on piston shaft 1306, to indicate the pressure reached at each stage.

These markings take advantage of Hooke's Law and the measured properties of
25 the spring to provide a convenient pressure gauge which can be incorporated in a disposable unit and which does not have to come in contact with the drug, and thereby avoids a risk of possible contamination

All the parts are formed of biocompatible materials, and are suitable for sterilization by one or more customary methods, for example, steam sterilization, EtO
30 sterilization, gamma sterilization, etc. Alternatively, insufflator 1300 may be disposable and provided as part of a kit with a catheter. Optionally, when delivered as a kit, barrel 1302 may be preloaded with a desired quantity of the drug to be delivered. In an

exemplary embodiment of the invention, barrel 1302 and, optionally, handle assembly 1308 are formed of a transparent polymer, for example, polycarbonate. Optionally, the handle assembly is made of translucent material (for example, polycarbonate). Piston 1306 is made, for example, of stainless steel, or a rigid polymer.

5 Barrel 1302 is optionally marked with lines 1312, 1314, and 1316 to indicate injection stages. As will be appreciated, for balloon-specific insufflators, a single set of markings is provided. For use with multiple size balloons, more than one set of markings may be provided. The most distal tip 1318 of piston 1316 indicates injection stage when observed against markings 1312, 1314, and 1316.

10 As will be understood, barrel 1302 is filled in the manner of a hypodermic syringe, i.e., by attaching connector 1328 handle to a drug container and withdrawing piston 1306 to provide a negative pressure in the barrel. In the illustrated embodiment, piston 1306 is long enough to extend out of the proximal end of barrel 1302 when fully inserted in the barrel, and can be grasped to fill the barrel and to purge air from the
15 barrel and the catheter as described below. Alternatively, if actuator rod 1322 extends all the way to the proximal end of barrel 1302 when piston 1302 is fully inserted in the barrel, the barrel may be loaded and the purging may be performed by grasping rod 1322.

When insufflator 1300 is used for PTCA and/or drug delivery, barrel connector
20 1328 is attached to a catheter, and handle assembly 1308 is compressed between shoulder 1326 and finger grip 1310 against spring 1320. The displacement imposed on the spring determines the pressure applied to the catheter.

Figs. 14A and 14B illustrate another exemplary design of a manually-operated insufflator 1400. Insufflator 1400 is also optionally balloon-size-specific. Insufflator
25 1400 is similar to that described in connections with Figs. 13A and 13B, and is comprised of a barrel 1402 including a finger grip 1404 at its proximal end, a piston 1406 and a handle assembly 1408 connected to piston 1406. Handle assembly 1408 includes a body 1408 within which is positioned an open ring 1412 that defines a thumb grip. Suitable marking lines calibrated to indicate the pressure used for balloon inflation
30 (not shown) may also be provided.

Insufflator 1400 differs from insufflator 1300 mainly in that spring 1410 is contained in an enclosure 1416 located at the proximal end of the handle assembly

1408. Pressure is applied to barrel 1402 by squeezing thumb grip 1412 and finger grip 1004 together, with the user's pointer and middle fingers on the distal side of finger grip 1404. The embodiment of Fig. 14 may be preferred in some instances since it allows for a shorter distance between the thumb and finger grips.

5 Insufflators 1300 and 1400 have several desirable features. For example, they are of simple construction which facilitates disposability. Further, disposable insufflators can economically be sized to match a particular application which can facilitate accurate filling and may reduce drug waste. Additionally, the need for a pressure gage in contact with the drug is avoided, which reduces or avoids the risk of
10 contamination.

Reverting to the description given in connection with Fig. 5, insufflators 1300 and 1400 may be used in the following exemplary manner:

a) the barrel is filled with a quantity of a prepared drug and the piston is pushed a sufficient distance (as indicated, for example, by a mark on the barrel) to evacuate air
15 from the barrel;

b) the insufflator is connected to a microporous balloon catheter;

c) the piston is pushed an additional distance (also indicated by a mark on the barrel) sufficient to evacuate air from the catheter shaft. Optionally, the balloon is provided with a protective tubing cover which is remains in place during these steps;

20 d) the piston is then pushed an additional marked distance to evacuate air from the balloon;

e) the balloon catheter is positioned at the area to be treated;

f) the balloon is then pressurized by further operation of the piston to transfer the drug from the barrel of the insufflator to the balloon at a PTCA pressure sufficient to
25 widen the constricted area of the segment being treated but not sufficient to cause jetting of the drug out of balloon pores;

g) the balloon is then further pressurized to a level sufficient to open the pores in the balloon and cause jetting of the drug out of the balloon pores;

h) the treatment process is completed by deflating and withdrawing the
30 catheter.

Figs. 15A and 15B illustrate an exemplary design of an automatic insufflator 1500. Insufflator 1500 comprises an enclosure (not shown) that houses a motor 1502, a

force sensor 1504, encoders, a programmable controller an input device (not shown), and user interface 1506 (see Fig. 15B).

Insufflator 1500 also comprises a barrel 1508 and a piston 1510. Barrel 1508 connects to the distal end 1512 of a frame 1514. A connector (e.g., a Luer type connector) 1516 at the distal end of barrel 1508 is provided for connecting the barrel to a balloon catheter. Optionally, a flexible extension tube (not shown) formed of a substantially non-compliant material is assembled between connector 1516 and the balloon catheter input to facilitate positioning of the balloon catheter against the target tissue.

Piston 1510 fits into frame 1518, with its most distal end 1520 in contact with sensor unit 1504. A handle 1522 provides manual input to insufflator system 1500, for example, by means of a built-in encoder (not shown).

Turning handle 1522 provides input via system controller (not shown) to motor 1502 which operates a pair of gears 1524. Gears 1524 cause movement of a rod 1526, thereby moving frame 1518 against frame 1514, and applying pressure on piston 1510.

Force sensor 1504 includes, for example, a load cell and encoders, and is arranged to provide feedback to the controller indicating pressure within barrel 1508 (e.g., by interpreting the force on the load cell) and injected amount of medicament (e.g., by interpreting location of the sensor).

Reverting again to Fig. 5, in an exemplary embodiment of the present invention, the initial inflation stage S504 and angioplasty stage S506, are performed manually, optionally using insufflator 1300, or 1400 or handle 1522 of insufflator 1500. Inflation to the drug delivery pressure P2, the actual drug delivery, and post delivery deflation are performed manually when using insufflator 1300 or insufflator 1400, and automatically when using insufflator 1500. In the latter case, automatic operation at time T2 may be initiated (e.g., pressing a button on the insufflator enclosure. At any time point pressure within microporous balloon can be reduced; optionally, by releasing the pressure on handle 1308 of insufflator 1300 or handle 1412 of insufflator 1400, or by turning handle 1522 of insufflator 1500 in a direction counter to that used for pressure elevation.

Referring to Fig. 15B, the user interface 1506 is located on the enclosure of insufflator 1500. In an exemplary embodiment of the present invention user interface 1506 is designed to provide continuous numerical information of inflation pressure in a

window 1530, and controls 1532 and 1534 for setting injected volume, as displayed in window 1536. As will be appreciated, other forms of display of the inflation pressure and injected volume, and other mechanisms for data entry may be provided.

Optionally, injected volume is calculated by insufflator 1500 controller based on
5 information provided by the user of microporous balloon dimensions.

With continued reference to Figs. 5, 15A and 15B, after barrel 1508 has been filled with the prepared drug, piston 1510 is pushed manually to evacuate air from the barrel. The piston and barrel assembly is installed on the frame portions 1514 and 1518. The volume of drug to be delivered and/or the balloon dimensions are programmed into
10 the controller by means of user interface 1506, and the insufflator is connected to the balloon catheter

Handle 1522 is then turned manually to move frame portions 1514 and 1418 toward each other as indicated by a mark on the barrel (not shown), or until indicated by user interface 1506, to evacuate air from balloon catheter (while balloon protective
15 tubing is still in place).

The balloon catheter is then positioned adjacent a narrowed segment of the vessel being treated, and handle 1522 is turned again to transfer the drug to the balloon and to pressurize the balloon to the desired pressure for PTCA., but not sufficient to cause jetting out of balloon pores;

20 a control is activated to automatically cause further inflation of the balloon to the drug delivery pressure, followed by automatic balloon deflation.

Filtration

In some embodiments of the invention, the drug, which may be is filtered during
25 manufacture, is also filtered during delivery to prevent blockage of balloon micropores by impurities in the delivered solution. The filter may be located at 422, 424, or 426 as described above. Alternatively, the filter may be located entirely outside the catheter.

According to some embodiments, a filter may be employed to prevent blockage of the balloon pores that only allows passage of particles smaller than the dimensions of
30 the balloon pores, for example, particles smaller than 3 μm , or 0.5 μm , or 0.1 μm or smaller, or larger or intermediate size particles. Optionally, the filter passes particles

that are less than 80%, 60%, 30%, 10% or smaller or intermediate percentages of the pore sizes.

Any suitable and desired filter may be used which is capable of withstanding high pressure i.e. of drug delivery. In an exemplary embodiment of the invention, the filter comprises a perforated film, enclosed within a housing. In an exemplary embodiment of the invention, the filter area size is between 0.1 cm^2 and 4 cm^2 , for example, 2 cm^2 .

Optionally, a non-sieve filtering mechanism is used, for example, a centrifugal filter or a sorting filter where particles that are too large are washed away from apertures sized to pass correctly sized particles.

In an exemplary embodiment, the filter film and the filter housing are made of material to which the drug does not adhere or otherwise interact with. Optionally, the filter film and the filter housing are made of polycarbonate or other material capable of withstanding high pressure. In an exemplary embodiment of the invention, the filter is an elongate filter, for example, between 2 and 20 mm long with a diameter that is equal to or less than the length, for example, less than 50%, or 30% of the length. This may be useful if the filter diameter is small, for example, if the filter fits in the catheter or the balloon.

Exemplary Drugs and Other Materials

As described earlier, the methods and apparatus described herein may be used for delivery of a variety of drugs and/or other materials and/or for treatment of a variety of disorders. In some exemplary embodiments of the invention one or more anti-proliferative agents is used to treat a blood vessel wall in order to prevent or lower the possibility of re-stenosis. Optionally, one such agent is Paclitaxel (Taxol), optionally provided as an active ingredient in a solution (for example, Medixel[®], by Medison Pharma Ltd, Israel). Alternatively, Sirolimus (Rapamycin) or a Sirolimus derivative (such as Tacrolimus) is used.

In an exemplary embodiment of the invention, one of the ingredients for the drug is an injectable Paclitaxel solution, with a concentration of 30mg /5ml Paclitaxel, commercially available as Medixel[®] from Medison Pharma Ltd, Israel. The drug solution is then diluted with saline and optionally with contrast medium (e.g.,

VISIPAQUE™ by Amersham Health Ireland, for example, iodixanol) in an exemplary volumetric ratio of 1:3:1 or 1:3.25:0.75 (Taxol:Saline:Contrast Medium). Optionally, after dilution, in each 1cc of prepared drug, there will be 1-1.4 mg, optionally about 1.2mg Paclitaxel. Optionally, the solution also includes approximately 10% Cremophor EL and/or approximately 10% Dehydrate Ethanol. Optionally, 10%-15% of the medicament is contrast material.

The drug may also contain a suitable diluent, such as saline. Optionally, different dilutions may be used for different applications and/or different balloon designs. For example, when using a balloon with larger hole diameters a more viscous medicament may be used (e.g., by increasing the volumetric percentage of a contrast media material), optionally calibrated so as to achieve similar hole erosion properties as with a more diluted medicament that is delivered through a balloon having smaller hole diameters. Optionally, the overall delivered quantity may change in correlation to the change of medicament dilution, in order to set a requested dose of the active ingredient.

In some circumstances, a higher viscosity of delivered material may be used in order to achieve unique parameters in a specific tissue. Optionally, other material (e.g., not a contrast medium) that changes medicament solution viscosity may be used, for example, a sufficient. Optionally or alternatively, an effective amount of a material that improves tissue adhesion is provided.

Different saline:contrast-medium ratios may be prepared according to the required viscosity of the drug. Generally, the contrast medium material is substantially more viscous than saline and can be used to control the viscosity of the resulting medicament. The physician optionally prepares the preferred volumetric ratio according to a table of ratios-vs.-viscosities provided to him with the drug ingredients and/or the balloon catheter kit. Optionally or alternatively, the physician (or a technician or other user) is provided with several packs of different pre-mixed drug ingredients having different ratios, which will be differentiated according to final mixture viscosity and/or other desired properties. Optionally, the use of contrast material allows the monitoring the progress of the procedure and/or allows to consider and/or monitor tissue migration and/or drug diffusion over time.

In an exemplary embodiment of the invention, it is noted that even in a solution, aggregates can form. Optionally, the sizes of the particles (e.g., of Paclitaxel) and/or

aggregates delivered with the drug influences the minimal pores diameter chosen for the perforated balloon. Optionally, an effective injection of a Paclitaxel-based drug is met with minimal and/or average pores diameter of 0.5 μm or more, optionally 0.8 μm or more, optionally 1 μm or more, optionally 1.5 μm or more, optionally 2 μm or more, or
5 higher or lower or intermediate diameters.

In another exemplary embodiment of the invention, one of the ingredients for the drug is an injectable Sirolimus (Rapamycin) solution, with Sirolimus concentration of 1-1.4 mg/ml. The drug bulk substance (raw material, as, for example, is commercially available from Chunghwa Chemical Synthesis & Biotech Co. Limited,
10 Taiwan) is optionally dissolved with 100% Ethanol and 15% Tween 80 to form a stock solution, which is further diluted with Saline at a ratio of 1:49 (Saline:Stock solution). Rapamycin solution may be prepared using different solvents, for example, as described in US Patent Application 2005/0222191.

In tests performed by the inventors it was determined that a balloon having pores
15 with diameter of 1.7-2 μm , enables delivery of Taxol solution or saline as jets via its pores.

In accordance with exemplary embodiments of the present invention, the administered material may consist, for instance, of compounds or drugs selected for one or more of reducing cell division activity (e.g., Paclitaxel, Rapamycin, and/or their
20 derivates), vasomotor action (calcium antagonists) and inflammatory response (steroids) as well as anticoagulants. Calcium antagonists may include materials such as diltiazem HCl, nifedipine and verapamil HCl, steroids such as dexamethasone and specific nonsteroidal anti-inflammatory agents. Anticoagulants may include materials such as heparin, hirudin, dipyridamole, papaverine HCl, ethaverine HCl and prostacyclin
25 inhibitors. It is also contemplated that agents (e.g., antisense, growth inhibitor, or gene therapy) inhibiting smooth muscle proliferation, which is, apparently, a primary factor in restenosis, or agents tending to reduce collagen response to injury could also be used. Fibroblast proliferation inhibiting agents may also be included as well as collagen response reduction agents. It is still further contemplated that compounds that reduce
30 platelet aggregation may also be beneficial to administer. Also, antitumor or other antimitogenic agents can be used for prevention of restenosis. Optionally, a combination of more than one drug/material may be administered.

In case of tumors treatment the medicament may include, for example, a drug such as mechlorethamine, cyclophosphamide, chlorambucil (leukeran), melphalan (alkeran), busulfan (myleran), dacarbazine (DTIC), cisplatin (Platinol), methotrexate, 6-mercaptopurine 6-MP, thioguanin 6-TG, 5-fluorouacil (5-FU), vinblastine (velban),
5 dactinomycin, doxorubicin, daunorubicin, mitomycin (mutamycin), diethylstilbestrol, and retinoic acid and analogues. Some embodiments of the present invention are suited to delivery of sensitizer and immunomodulator drugs. Optionally, more than one drug/material listed above and/or other material may be administered.

10 In an exemplary embodiment of the invention, medicament may be provided for performance of gene therapy. In another exemplary embodiment, medicament may include angiogenesis factors.

In an exemplary embodiment of the invention, the medicament is a structure affecting medicament, for example a material which stiffens, softens and/or makes tissue more or less elastic. Optionally, the medicament is a tissue adhesive.

15 In an exemplary embodiment of the invention, the medicament is an ablating material, for example, which kills tissue, for example, a high concentration of ethanol.

It should be noted that in some embodiments of the invention, tissue modifying effects are achieved using injection of saline.

In an exemplary embodiment of the invention, the medicament is provided
20 encapsulated and/or attached and/or adsorbed with particles, to provide for its slow release following administration. Optionally, the microencapsulation particles (for example, PGA, PLA, PGLA, PCL), are smaller than the size of balloon pores. In an exemplary embodiment of the invention, Paclitaxel is delivered encapsulated within particles having a diameter smaller than 1 μ m. Optionally, particle diameter is in the
25 range of 50-300 nm. Optionally, the particles aggregate to form larger particles, having a diameter smaller than 3 μ m, optionally smaller than 1 μ m. Optionally, the particles are smaller than 70%, 50%, 30%, 20%, 10% or smaller or intermediate percentages of the pore diameter. Optionally or alternatively, some pores are smaller than particles and do not pass particles, only jets. Alternatively, only part of the drug, for example Paclitaxel,
30 is provided encapsulated and is slow released, while the rest of the drug is free and immediately penetrates into- and/or adheres to the tissue following administration. Optionally, a total volume of 0.01-0.3 cc is injected throughout the complete procedure,

optionally 0.03-0.20 cc, for example, for a treatment area of 1-2 cm², for example, about 1.8 cm². Optionally, the resulting concentration by volume in the target tissue is between 0.1% and 30%, for example, between 1% and 10% or intermediate percentages. Optionally, the volume which penetrates into the body passage wall is at least 1%, optionally at least 5%, optionally at least 20%, optionally at least 50% of the total injected volume.

In an exemplary embodiment of the invention, the drug used is Rapamycin (Sirolimus), encapsulated within biodegradable particles, which optionally have a diameter smaller than, for example, 400 nm, 200 nm, 100 nm and/or intermediate diameters and/or are optionally made of a polymer, such as PLLA (poly, L lactic acid) or PLGA (poly lactic glycolic acid). Optionally, the particles are prepared using a solvent evaporation technique.

In an exemplary embodiment of the invention, the drug is released from the particles in a slow release manner (for example, over 3-4 weeks for restenosis or over other time periods for other applications, which can be, for example, 1-4 days, 5 weeks, 3 months or shorter, intermediate or longer periods. Optionally, the initial delivery is delayed, for example, for 2-3 days, to allow healing of the jet-caused wounds and/or stents or PTCA caused damage.

In an exemplary embodiment of the invention, the encapsulated particles are supplied as a powder, which is mixed with and suspended in sterile distilled water/glucose solution immediately prior to use. Optionally, drug concentration (in the mixture) is in the range of about 100µg/ml to about 1mg/ml. Optionally, such particles with drug are manufactured by Southwest Research Institute, San Antonio, Texas, USA.

A potential advantage of using particles rather than a solution of a drug is that a drug in the solution may be more susceptible to reaction and/or aggregation than particles within which a drug is encapsulated and not immediately available for reaction.

Optionally, the delivered material or medicament has lipophilic and/or tissue adhering properties (optionally selectable by changing the formulation) so at least part of the injected volume can coat the inner wall surface of the body passage. Optionally, at least part of the injected material is attached to- and/or penetrates the body passage wall for at least 5 seconds, optionally at least 30 seconds, optionally at least 1 minute,

optionally at least 1 hour, optionally at least 1 day, optionally at least 10 days. Optionally, the material is degraded over time and/or is biodegradable, while preserving residual quantity for few hours or a few days, or in any lesser or higher or intermediate values.

- 5 In an embodiment, the medicament is coupled/bound to a carrier, suitable for the delivery of the medicament to/into the target site (e.g., endothelial cells of blood vessel wall). In an exemplary embodiment of the invention, a protein, such as Albumin, which is a natural carrier of lipophilic molecules, serves as a delivery vehicle for the drug (as done by Abraxis Bioscience, for example, using ABRAXANE™ or Nab™ technology).
- 10 Optionally, an insoluble or poorly soluble drug may be combined with such a protein, to form a nanoparticle and to facilitate drug solubility and delivery. Optionally, no toxic agents that are normally being used as solvents are required for the process.

- In an exemplary embodiment of the invention, the medicaments and/or delivery systems are packaged with instructions and/or labeled for specific applications and/or
- 15 usage protocols. Optionally, a label on the medicament and/or a label on the delivery catheter are read by the delivery system and this information (e.g., medicament properties and/or balloon properties) is used to configure, optionally automatically, the pressure profile used for delivery.

- Where it is desired to deliver multiple drugs in a sequence, this can be done, for
- 20 example, by emptying the catheter, optionally washing with low pressure saline and then refilling the catheter with a different drug, optionally at a high pressure. Optionally or alternatively, the balloon is partially collapsed and repositioned to a new region to be treated which is then treated with a same or different medicament.

25 **Exemplary Urethral and other treatment**

- Numerous conditions may be treated using the exemplary methods and apparatus in accordance with the present invention, including treatments of narrowed or non-narrowed body lumens. These may include: treatment for the prevention of restenosis or any other possible narrowing of a lumen, delivery of drugs to treat cancer
- 30 (that may be evolving in, for example, biliary duct, trachea, esophagus), delivery of drugs to prevent hyperplasia (e.g., in the case of BPH treatments; such drugs may include anti-androgen to prevent prostate hyperplasia, Botox for tonus relaxation, and

cytotoxic drugs for local treatment of hyperplasia and/or cancer), delivering anesthetics to a target area before a treatment (e.g., as needed in some invasive treatments in the urethra).

In an exemplary embodiment of the invention, the microporous balloon of the invention is used to open a urethral stricture as well as drug injection into the urethra wall at the stricture site. Optionally, balloon is introduced transurethrally. Optionally, balloon is introduced into the urethra via a working channel of an endoscope. Optionally or alternatively, the procedure is performed under fluoroscopy, and balloon visualization is enabled by the addition of a contrast medium to the drug solution.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below may find experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions, illustrate some embodiments of the invention in a non limiting fashion.

Example 1 – Balloon with 0.8 μ m Diameter Holes

A first exemplary balloon includes pores with a 0.8 μ m diameter and a density of 5,000 pores/cm². The balloon is based on a PET membrane perforated using track-etching technique. The balloon diameter in expanded form is approximately 3mm and has a wall thickness of possibly 20 microns.

Two in-vitro tests were performed with this balloon type on tissue (domestic pig coronary arteries), using different injection parameters (as detailed below). All injections used same drug composition of 1:3:1 (taxol:saline:CM) ratio with 1.2 mg/ml Paclitaxel concentration. The tissues were then deep frozen and underwent HPLC examination for evaluation of the penetrated Paclitaxel quantities of each injection.

Test No. 1 included a continuous drug delivery with pressure (P3) of 10 atmospheres during 60 seconds (t4-t3); and Test No. 2 had a P3 of 18 atmospheres and t4-t3 of 15 seconds. The HPLC results showed that in Test No. 1 the total amount of Paclitaxel found in the tissue was 392.8 ng (nanogram) (about 0.49 weight% of the total injected medicament), and in Test No. 2 a quantity equal to 2,520.4 ng was traced

in the tissue (about 5.6 weight% of the total injected medicament). For both tests, no substantial damage to tissue was revealed in histological examination. These test results suggest that there is a correlation between the magnitude of the drug delivery pressure (P3) and the effectiveness of the treatment (e.g., the amount of drug adheres and/or penetrates into tissue), at least with respect to the specific balloon perforation design (e.g., 0.8 micron holes and 500 holes/cm²). Drug delivery at a higher pressure of 18 atmospheres resulted in a significantly higher (non-linear) drug penetration level into tissue. This can be useful, for example, in that if a higher rate of delivery is desired and/or if delivery to a nearby tissue is desired, pressure can be increased (e.g., temporarily). Optionally, depth of penetration is controlled using a table linking pressure to penetration and selection of a pressure according to a desired penetration depth.

Example 2 – Comparison between Exemplary Microporous and Macroporous Balloons

The following is a comparison between microporous and macroporous balloons made of a biocompatible semi-compliant material, for example, Nylon, perforated using a laser, whereby the perforations ("holes", "pores") created in the balloon were truncated cones. Pressurized balloons in which the holes were circular and conical were tested.

The pores of the microporous balloon were of 1.5µm diameter at the large end with density of 1,000 pores/cm² (a total of 1,880 pores). The chosen macroporous balloon included 88 pores of 20µm (microns) in diameter at the large end.

The use of the macroporous balloon with the particular pressure source used did not enable elevation of the pressure to 10 atmospheres, due to the relatively large diameter pores of the balloon, compared to the catheter lumen diameter.

A second macroporous balloon having a double balloon design (with the inner balloon serving as a valve to the outer balloon) was then tested. These balloons included 88-160 pores, each having a diameter of 8-20µm at the large end, and pore density of 62-113 pores/cm²). Using these balloons, a volume of 0.025cc saline solution was injected in a pulse of 0.02 seconds. The injection pressure (pulse) was approximately

22 - 25 atmospheres. The derived overall flow rate was 1.25 cc/sec and the derived jet speed was 45.2 m/sec.

Exemplary in-vitro tests performed with the macroporous balloons having the above parameters for injection into the walls of coronary arteries of domestic pigs.

5 These tests showed more difficulty with controlling penetration depths and distribution of the drug.

When injecting a quantity of 0.15cc drug solution with the exemplary microporous balloon (for example, with an injection pressure of 18 atmospheres and an injection time of 60 seconds), the overall flow rate is 0.0025 cc/sec (or 0.00133
10 cc/(secxcm²)), and the jet velocity is approximately 0.75 m/sec. Histological examination following the injection did not detect damage to tissue, while HPLC results indicated drug presence in tissue.

Example 3 – Balloon with 1.7 µm Diameter Holes

15 Additional tests were performed with another exemplary microporous balloon, having 1.7µm diameter pores with pore density of 550 pores/cm² (a total of 1,036 pores). When injecting a quantity of 0.185cc Taxol solution (with concentration of 1.2 mg/ml and 15% contrast medium as described above) using this exemplary balloon, under P3 = 18 atmospheres and t4-t3 = 20 seconds, the overall flow rate is 0.00925
20 cc/sec (and a flow rate of 0.00000892 cc/sec for a hole), and the jet velocity is approximately 3.93 m/sec.

Additional Exemplary Tests

25 The following table (Table 1) presents flow rate and velocity results obtained while injecting various amounts of Taxol solution (in concentration of 1.2 mg/ml), using microporous balloons, under various pressures and durations. The tests were performed with balloons having 20 mm length and 3 mm diameter, with various pore size and pore density, as specified in the table below. The flow rate and pore flow rate are calculated based on the other columns.

Table 1

Pore Size [μm]	Pore Density [Pore/cm²]	Delivery Pressure [Atm]	Delivery Time [sec]	Delivery Volume [cc]	Total Flow Rate [cc/sec]	Pore Flow Rate [cc/sec]
0.8	5000	15	60	0.055	0.000916667	0.0000000931
2.5	400	16	15	0.253	0.016866667	0.0000223815
2	550	16	15	0.12	0.008	0.00000772052
2	550	12	15	0.11	0.00733333	0.00000707714
2	550	20	15	0.27	0.018	0.0000173712
2	550	12	30	0.19	0.00633333	0.00000611208
2	550	20	30	0.6	0.02	0.0000193013
1.9	550	12	15	0.0726	0.00484	0.00000467091
1.9	550	20	15	0.2	0.01333333	0.0000128675
1.7	550	8	20	0.0037	0.000185	0.00000017853
1.7	550	18	20	0.185	0.00925	0.00000892685
1.7	550	20	20	0.216	0.0108	0.0000104227

5 Table 2) presents test results of the amount of delivered drug (Taxol with 15% contrast medium) from a 20 mm long, 3 mm diameter balloon, with 1.7 μm diameter pore and pore density of 550 pore/cm². The drug amount is presented as function of pressure and time. In the table, only the pressure, time and amount were measured and the other columns were calculated/estimated.

Table 2 - Delivered Drug Amount [μg]

Pressure [Atm] Time [sec]	8	12	16	18	20
1	0.2	1	1	12	14
2	0.5	2	2	23	27
3	1	3	3	35	41
4	1	4	5	47	55
5	1	5	6	59	68
6	1	6	7	70	82
7	2	7	8	82	96
8	2	8	9	94	109
9	2	9	10	105	123
10	2	10	11	117	137
11	3	11	12	129	151
12	3	12	14	141	164
13	3	13	15	152	178
14	3	14	16	164	192
15	4	15	17	176	205
16	4	16	18	187	219
17	4	17	19	199	233
18	4	18	20	211	246
19	4	19	22	222	260
20	5	20	23	234	274
21	5	21	24	246	287
22	5	22	25	258	301
23	5	23	26	269	315
24	6	24	27	281	328
25	6	25	28	293	342
26	6	26	29	304	356
27	6	28	31	316	370
28	7	29	32	328	383
29	7	30	33	340	397
30	7	31	34	351	411

Fig. 16 shows the dependence of flow on the pressure. As can be seen, there is a sudden change in flow rate between 16 atmospheres and 18 atmospheres pressure, for a 3x20 mm balloon. The following table summarizes the data shown in the graph. It is expected that the change in rate can be controlled, for example, by controlling the fluid viscosity and/or pore size.

pressure (atm)	Weight after 20 seconds (gr)	volume after 20 seconds (ml)	flow rate (est) ml/sec	drug rate (est) mg/sec
8	0.0037	0.0039035	0.000195175	0.00023421
12	0.0161	0.0169855	0.000849275	0.00101913
16	0.0179	0.0188845	0.000944225	0.00113307
18	0.185	0.195175	0.00975875	0.0117105
20	0.2162	0.228091	0.01140455	0.01368546

In additional series of tests, the inventors evaluated the potential damage to the treated tissue following the use of the discussed microporous balloon system.

As an initial determination, in vitro tests were performed using a 20 mm long, 3 mm diameter balloon, with pore diameter of 1.7 microns and pore density of 550 pore/cm². The balloon, mounted on a PTCA catheter, was introduced into pig coronary arteries, and the pressure was elevated to about 10-12 ATM (with over-dilatation of 10%), to simulate an angioplasty procedure. Then, the pressure was elevated to 18 ATM for about 30 seconds, and a volume of about 0.15 cc of saline solution with ink was injected. The ink dye indicated the material penetrates into the blood vessel wall, into the intima and further into part of the media layer.

Following the in vitro tests, an in vivo procedure was performed in pigs, under the same protocol (i.e., initial pressure of about 10-12 ATM with over-dilatation of 10%, and then elevation of the pressure to 18 ATM for about 30 seconds, with the exception that ink was not added to the saline solution). The same balloon was used. After a week, the animals were sacrificed, and the treated tissue was histological assessed in a certified laboratory. The histological examination did not detect any significant damage, inflammation signs or injury to the vessel wall. This result suggests that it is possible to inject material into a vessel wall without causing damage that would be problematic or encourage re-stenosis.

It is expected that during the life of a patent maturing from this application many relevant medicaments for affecting tissue structurally and/or functionally will be developed and the scope of the term medicament is intended to include all such new technologies *a priori*.

As used herein the term “about” refers to $\pm 10\%$. Such limitation is optionally applied to any numerical value described herein.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to". This term encompasses the terms "consisting of" and "consisting essentially of".

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

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
10 least one compound" may include a plurality of compounds, including mixtures thereof.

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.

15 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.

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
20 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 subranges 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 subranges such as
25 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
30 between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein

interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

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 subcombination 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.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

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.

CLAIMS

1. A balloon catheter having a plurality of micro-pores with a diameter ranging from about 1 to about 5 micrometers, wherein the balloon is made of a semi-compliant material.
2. A catheter according to claim 1, wherein the balloon is made of a polyamide.
3. A catheter according to claim 1, wherein the pore density is in the range of about 300 and about 600 pores/cm².
4. A catheter according to claim 1, in which the pore density is about 550 pores/cm².
5. A catheter according to claim 4 in which the pores are outwardly tapered truncated cones.
6. A catheter according to claim 4 in which the pores are inwardly tapered truncated cones.
7. A catheter according to claim 5 or claim 6, wherein the ratio of the larger diameter to the smaller diameter of the pores of an unexpanded balloon is in the range of about 1.33 to about 4 to 1.
8. A catheter according to any of claims 5-7, wherein the diameter of the small ends of the pores of an expanded balloon is in the range of about 1 – 5 μm.
9. A catheter according to any of claims 5-8, wherein the diameter at the small ends of the pores of an expanded balloon is about 1.7 μm.
10. A catheter according to any of claims 5-9 wherein the hole diameter at the larger end of the pores of an expanded balloon is in the range of about 2 – 10 μm.

11. A catheter according to any of claims 5-9, wherein the hole diameter at the larger end of the pores of an expanded balloon is about 5 μm .
12. A catheter according to any of the preceding claims, wherein the thickness of the balloon is in the range of about 0.012 mm to about 0.018 mm, for balloons up to outside diameter of 3.5 mm, and the thickness in the range of 0.011 mm to about 0.025 mm for balloons having outside diameter of 4 mm to 7 mm.
13. A catheter according to any of the preceding claims in which the pores have an elliptical perimeter when the balloon is un-expanded, and a circular perimeter when the balloon is expanded.
14. A catheter according to any of claims 1-13, in which the pores have a circular perimeter when the balloon is un-expanded, and an elliptical perimeter when the balloon is expanded.
15. A balloon catheter according to any of the preceding claims, wherein the pores are configured to be substantially closed below a predetermined balloon inflation pressure.
16. A balloon catheter system comprising:
 - a balloon catheter as described in any of the preceding claims;
 - a drug reservoir; and
 - a pressure source,wherein the pressure source is configured to transfer a drug from a drug reservoir to the interior of the catheter.
17. A device according to claim 16, wherein the drug reservoir and the pressure source are comprised in a single unit.
18. A device according to claim 16, wherein the pressure source is electrically operated.

19. A device according to claim 16, wherein the pressure source is manually operable.
20. A device according to claim 16, wherein the pressure source is at least partially automatically operable.
21. A device according to claims 16, 19 or 20, wherein the pressure source is comprised of a barrel and a manually operable by a spring-loaded piston to transfer a drug into the balloon and to pressurize the balloon.
22. A device according to any of claims 16-21, further including a controller and data input and display devices.
23. A device according to any of claims 16-22, further including a filter between the drug reservoir and the pores of the balloon.
24. Apparatus for manufacturing a microporous balloon catheter as described in any of the preceding claims comprising:
 - a holder for the balloon, the holder being perforated in a pattern corresponding to the desired pattern of holes in the balloon; and
 - a laser operable to provide ultra-short duration and ultra-high intensity pulses, wherein the holder and the laser are moveable relative to each other so that all the perforations in the holder are exposed in turn to the laser beam.
25. A device according to claim 24, wherein the laser is a femtosecond laser.
26. A device according to claim 24 or claim 25, wherein the laser is stationary, and further including a CNC operated driver for the holder.
27. A method of perforating a balloon catheter comprising:
 - placing an un-perforated balloon in a holder having a perforation pattern corresponding to a desired perforation pattern for the balloon;

expanding the balloon to desired perforation pressure;
locating the holder with the balloon therein in the path of an ultra-short duration, ultra-high energy laser;
activating the laser; and
moving the laser and the holder relative to each other to expose the perforation pattern of the holder to the perforation energy.

28. The method of claim 27, further comprising moving the holder while maintaining the laser stationary.

29. The method of claim 27 or claim 28, wherein the laser is a femtosecond laser.

30. The method of any of claims 27-29, wherein the balloon is attached to a catheter at the time of perforation.

31. The method of any of claims 27-29, wherein the balloon is not attached to a catheter at the time of perforation.

32. A method of perforating a balloon catheter comprising:

placing an un-perforated balloon that is turned inside-out in a holder having a perforation pattern corresponding to a desired perforation pattern for the balloon;

exposing the holder and the balloon an ultra-short duration, ultra-high energy laser beam; and

moving the laser and the holder relative to each other to expose the perforation pattern of the holder to the laser beam.

33. An insufflator for a microporous balloon catheter comprising:

a barrel configured to receive a quantity of a drug to be delivered by the catheter;

a piston moveable to lengthen and shorten the barrel whereby positive and negative pressure is created in the barrel;

a connector for coupling the barrel to a catheter shaft; and

a spring loaded actuator for moving the piston to shorten the barrel and to pressurize the barrel to a desired level,

wherein the piston is moveable to load a drug into the barrel without compressing the spring.

34. A device according to claim 33, wherein the actuator is operable to provide a first pressure level for PTCA and a second higher pressure level for drug delivery.

35. A device according to claim 33 or claim 34, wherein the balloon is pressurized by manually compressing the spring.

36. A device according to any of claims 33-35, further including markings to measure displacement of the spring and calibrated to provide an indication of a pressure level applied to the balloon.

37. A method for treating a segment of a body lumen, comprising:

locating an inflatable component formed of a semi-compliant material having a plurality of micro-pores formed in a wall thereof adjacent to the segment;

inflating the component with a drug to be delivered to the wall of the lumen to a first pressure not sufficient to cause effective jetting of the drug out of the pores;

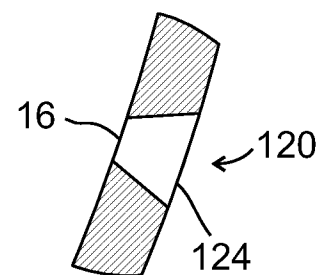
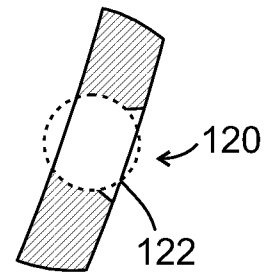
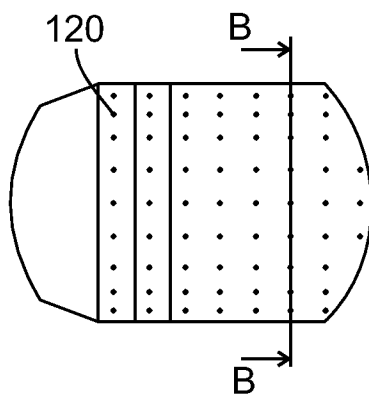
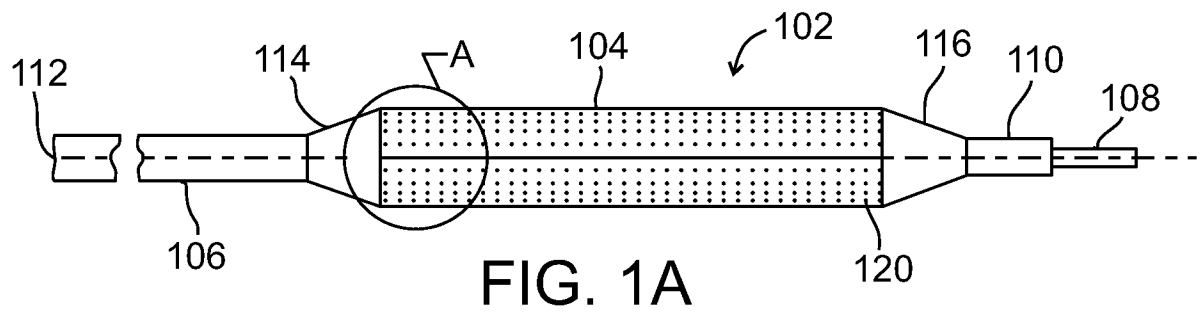
further inflating the component to a second higher pressure that is sufficient to cause jetting of the drug out of the pores into the tissue of the lumen without significant trauma to the tissue.

38. The method of claim 37, wherein the first pressure is sufficient to widen a narrowing in the body lumen segment.

39. The method of claim 37, wherein the inflatable component is a balloon catheter.

40. The method of any of claims 37-39, wherein the first pressure is sufficient to perform PTCA.

41. The method of any of claims 39-40 further including delivering a device for implantation in the segment.
42. The method according to claim 41, wherein the device for implantation is a stent.
43. A balloon catheter having a plurality of micro-pores with a diameter ranging from about 1 to about 5 micrometers, wherein the pores are shaped as truncated cones.
44. A catheter according to claim 43, wherein balloon is made of a semi-compliant material.
45. A catheter according to claim 43, wherein the balloon is made of a compliant material.
46. A catheter according to any of claims 43-45, in which the pores are outwardly tapered.
47. A catheter according to any of claims 43-45, in which the pores are inwardly tapered.



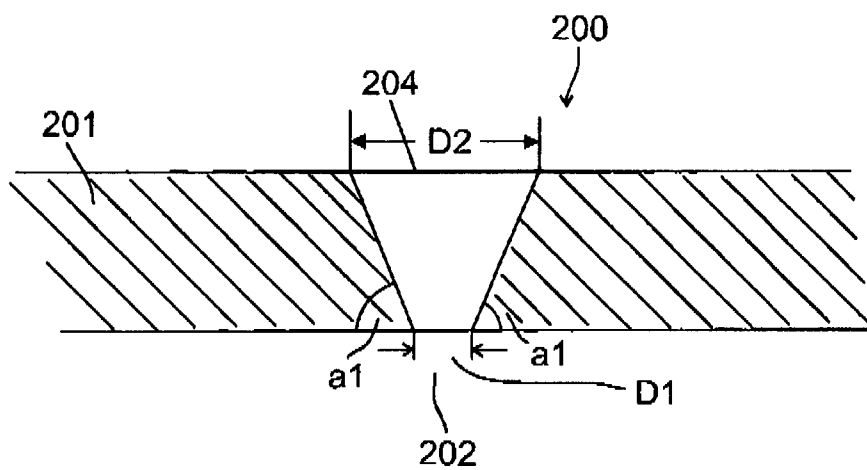


FIG. 2A

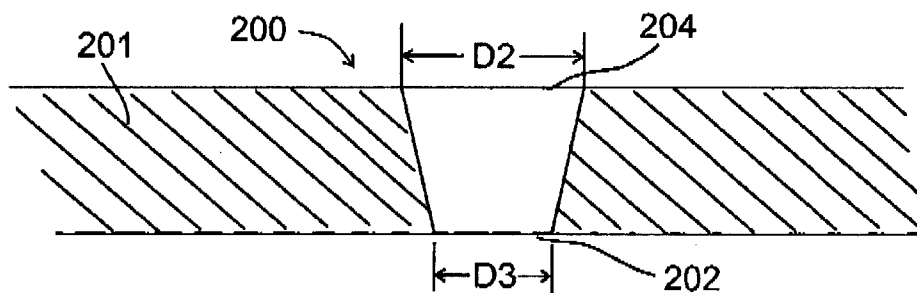


FIG. 2B

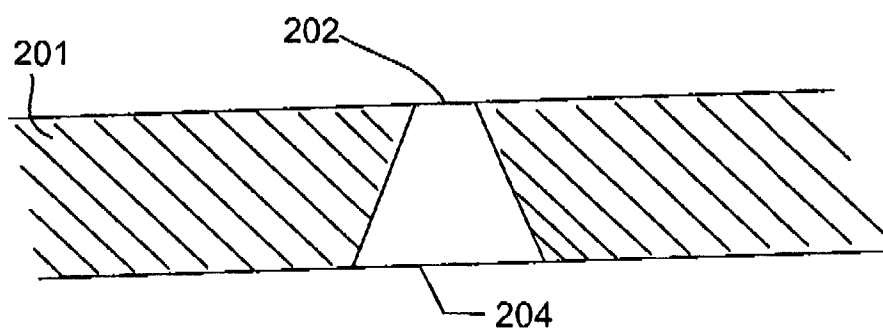


FIG. 2C

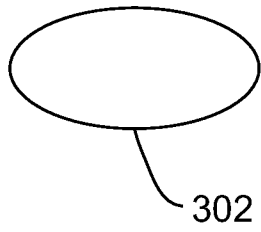


FIG. 3A

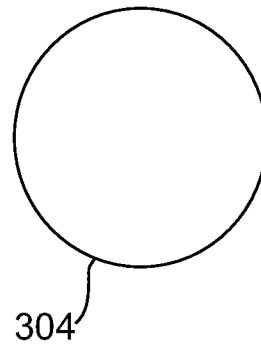


FIG. 3B

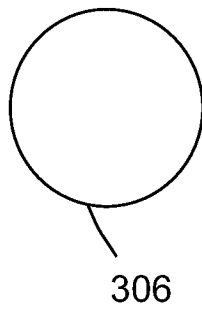


FIG. 3C

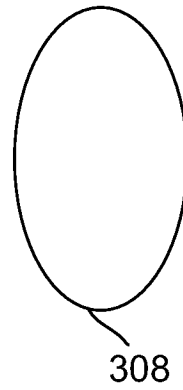


FIG. 3D

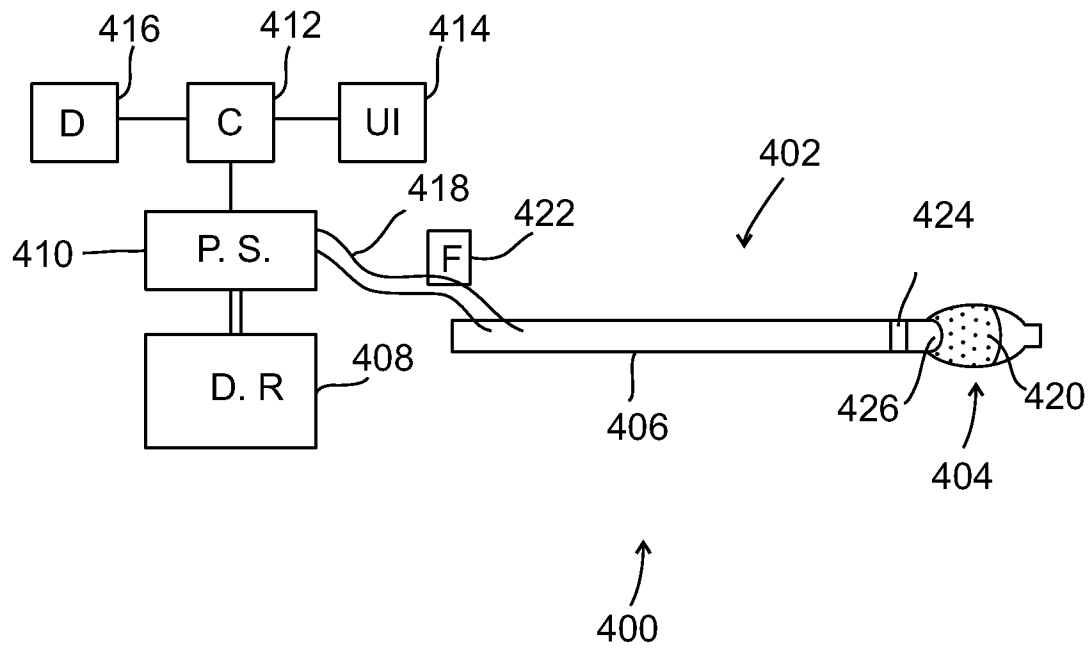


FIG. 4

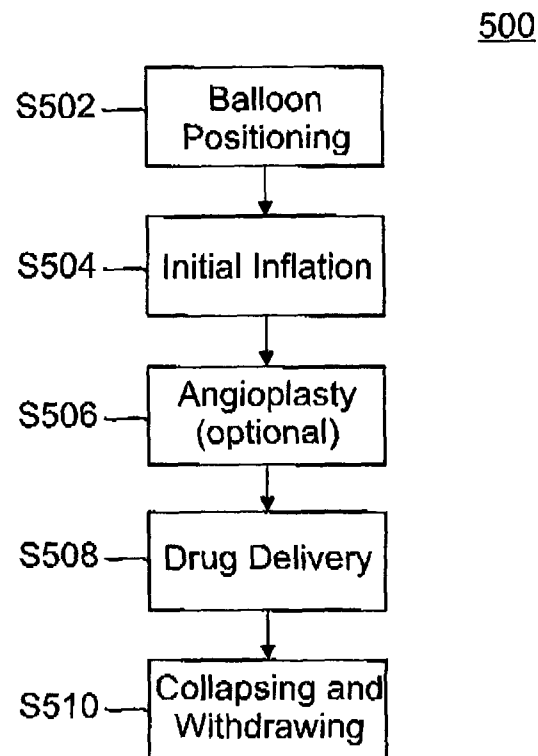
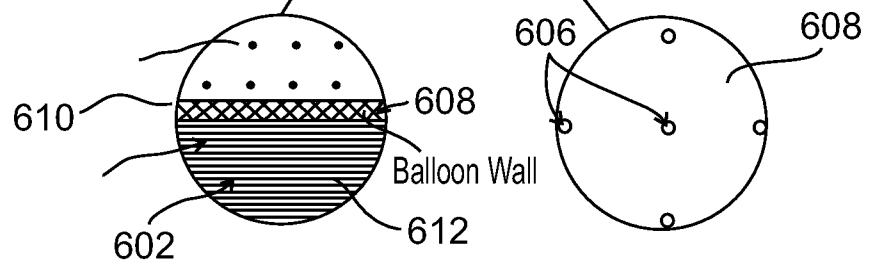
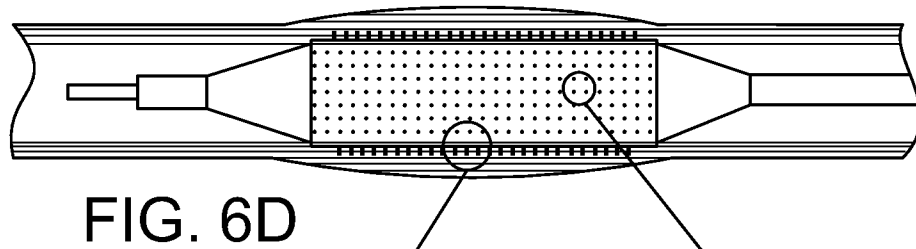
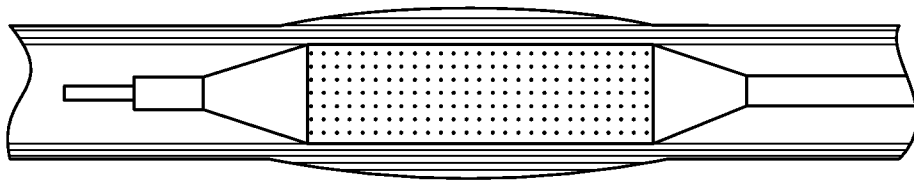
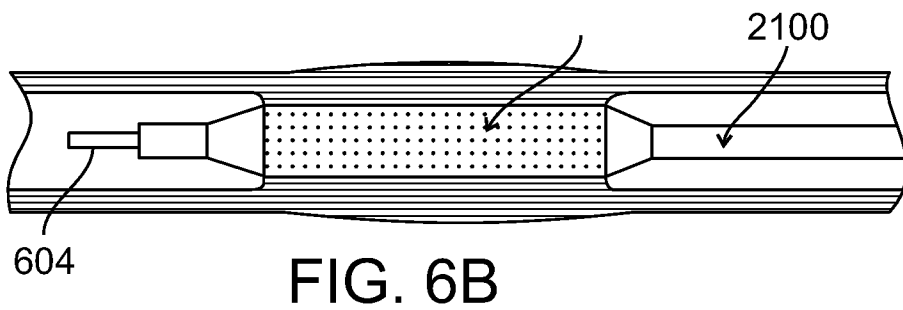
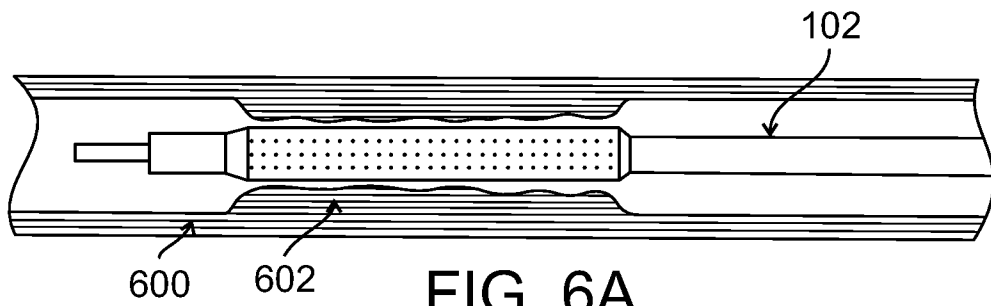


FIG. 5



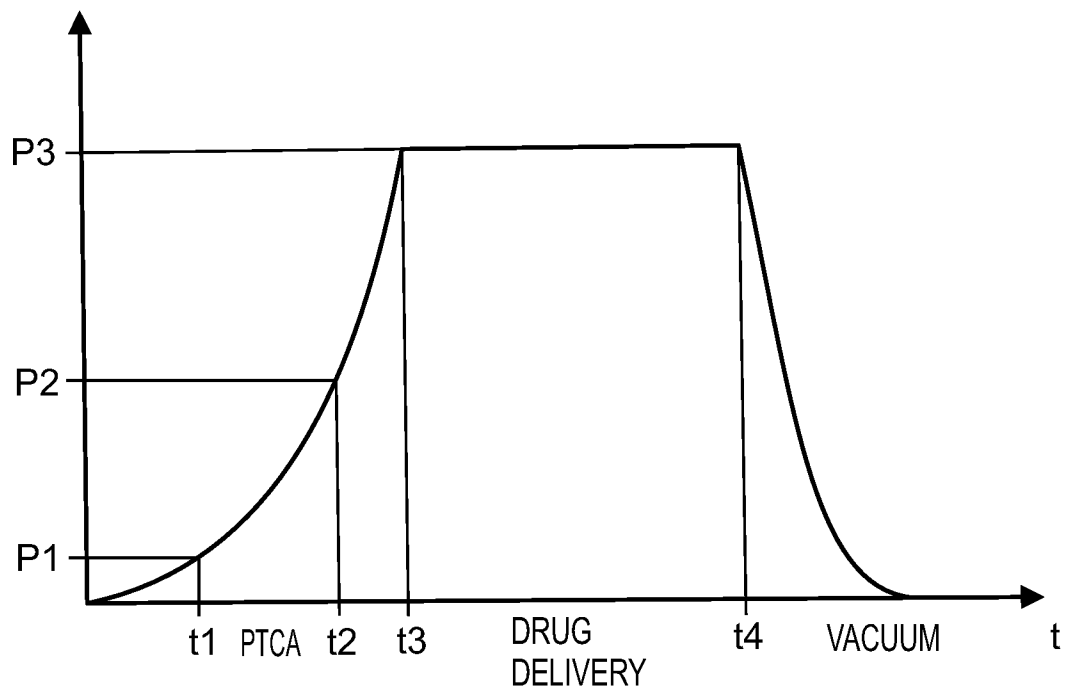


FIG. 7

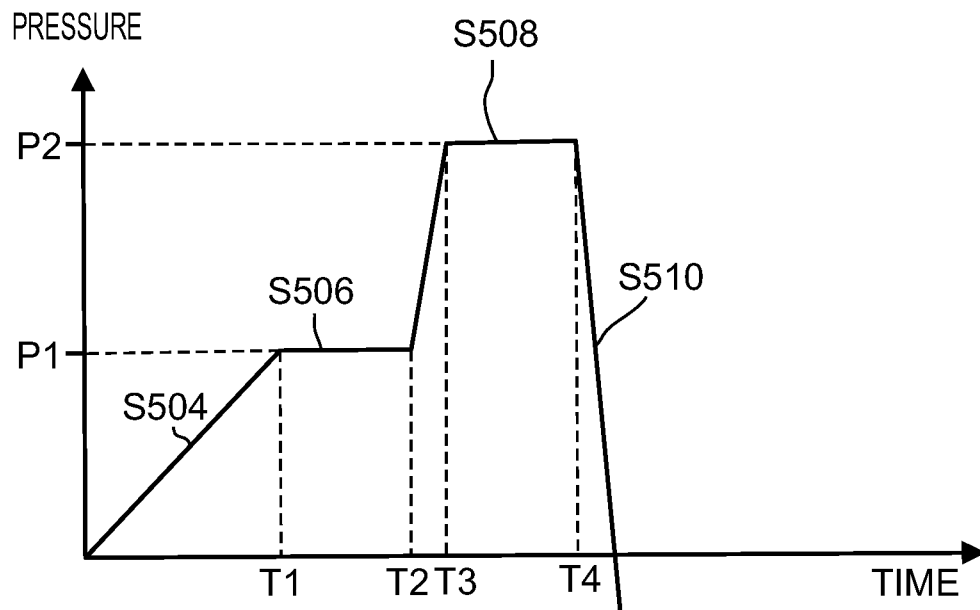


FIG. 8

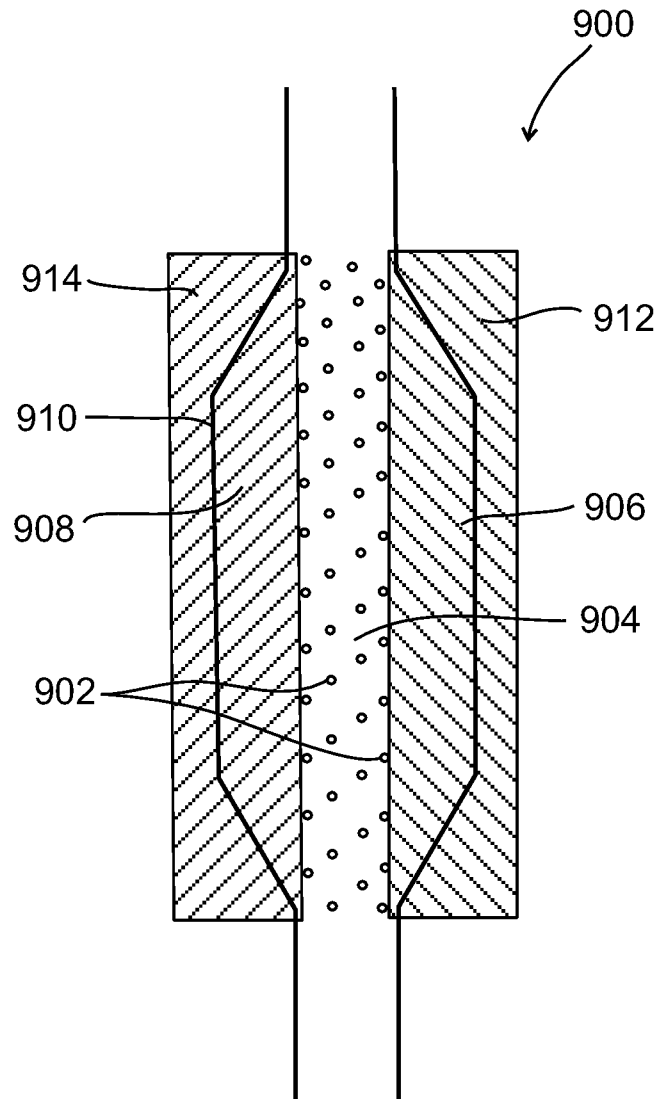


FIG. 9

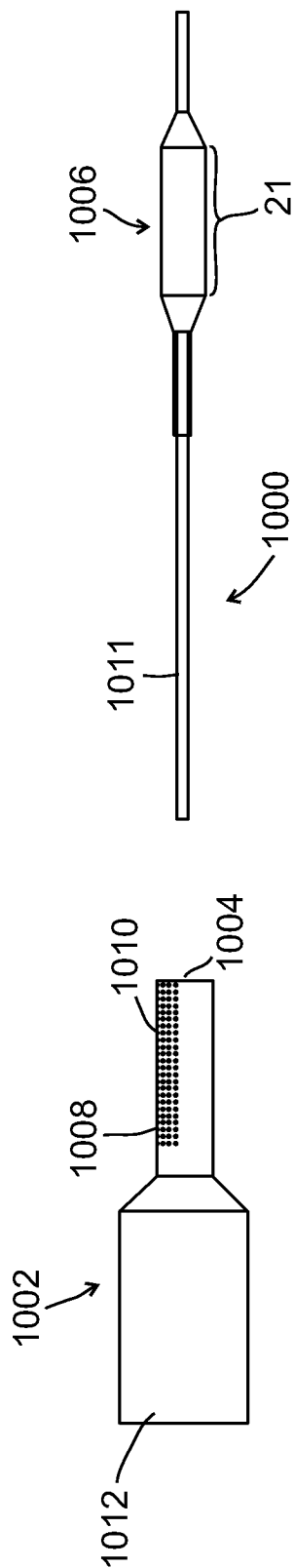


FIG. 10A

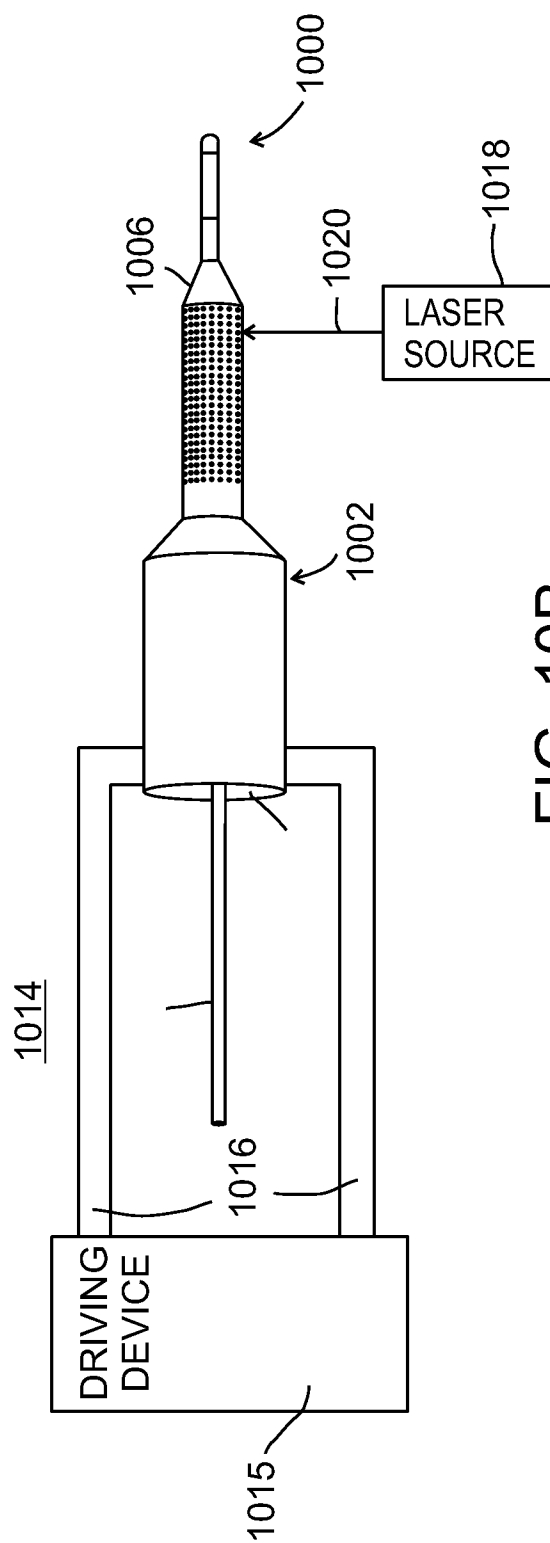


FIG. 10B

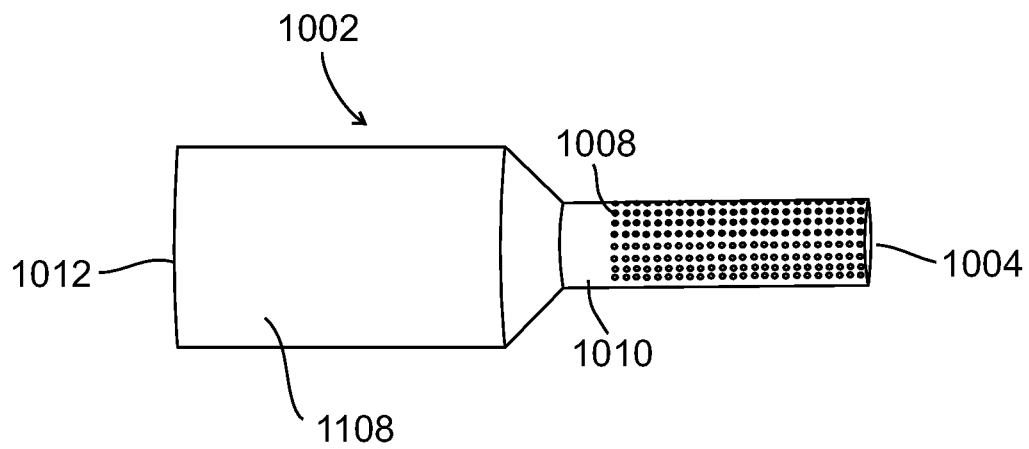


FIG. 11A

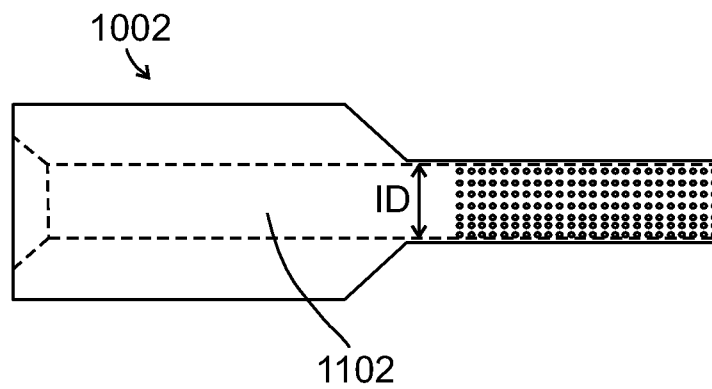


FIG. 11B

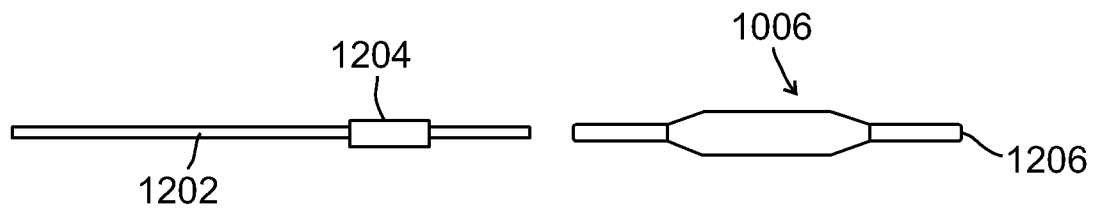


FIG. 12A

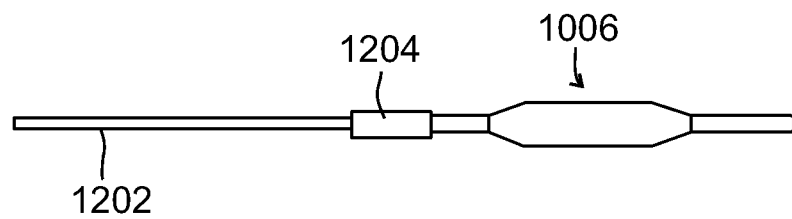


FIG. 12B

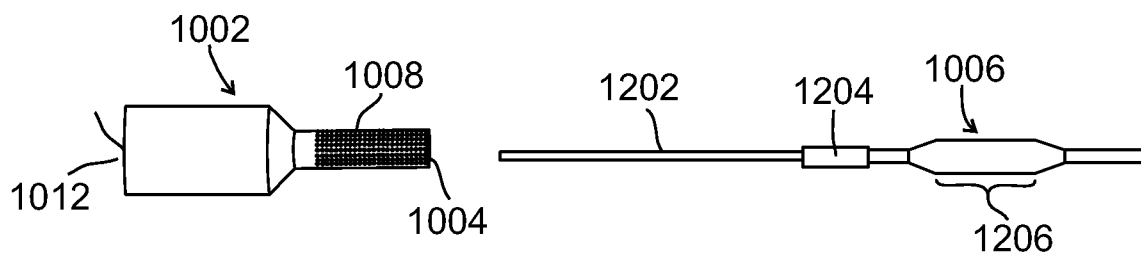
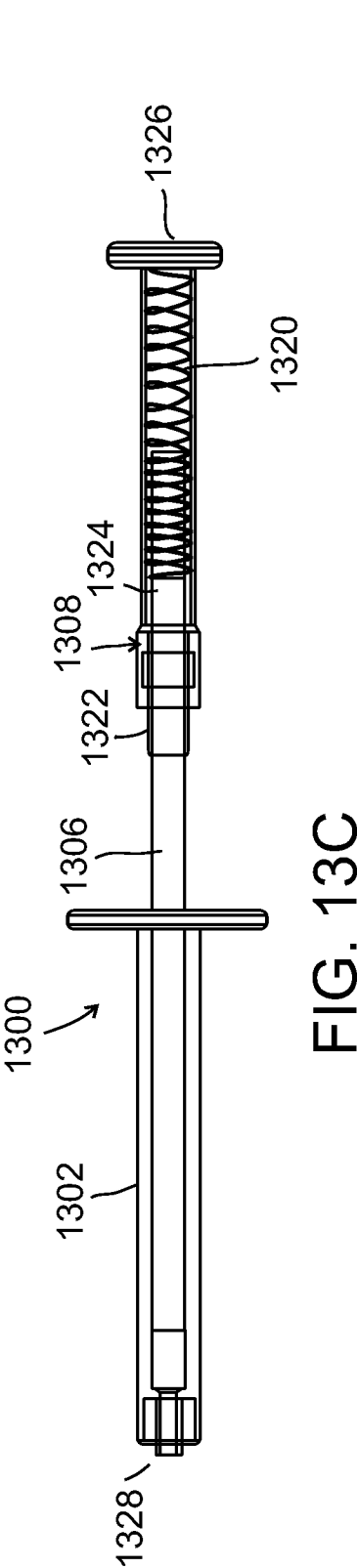
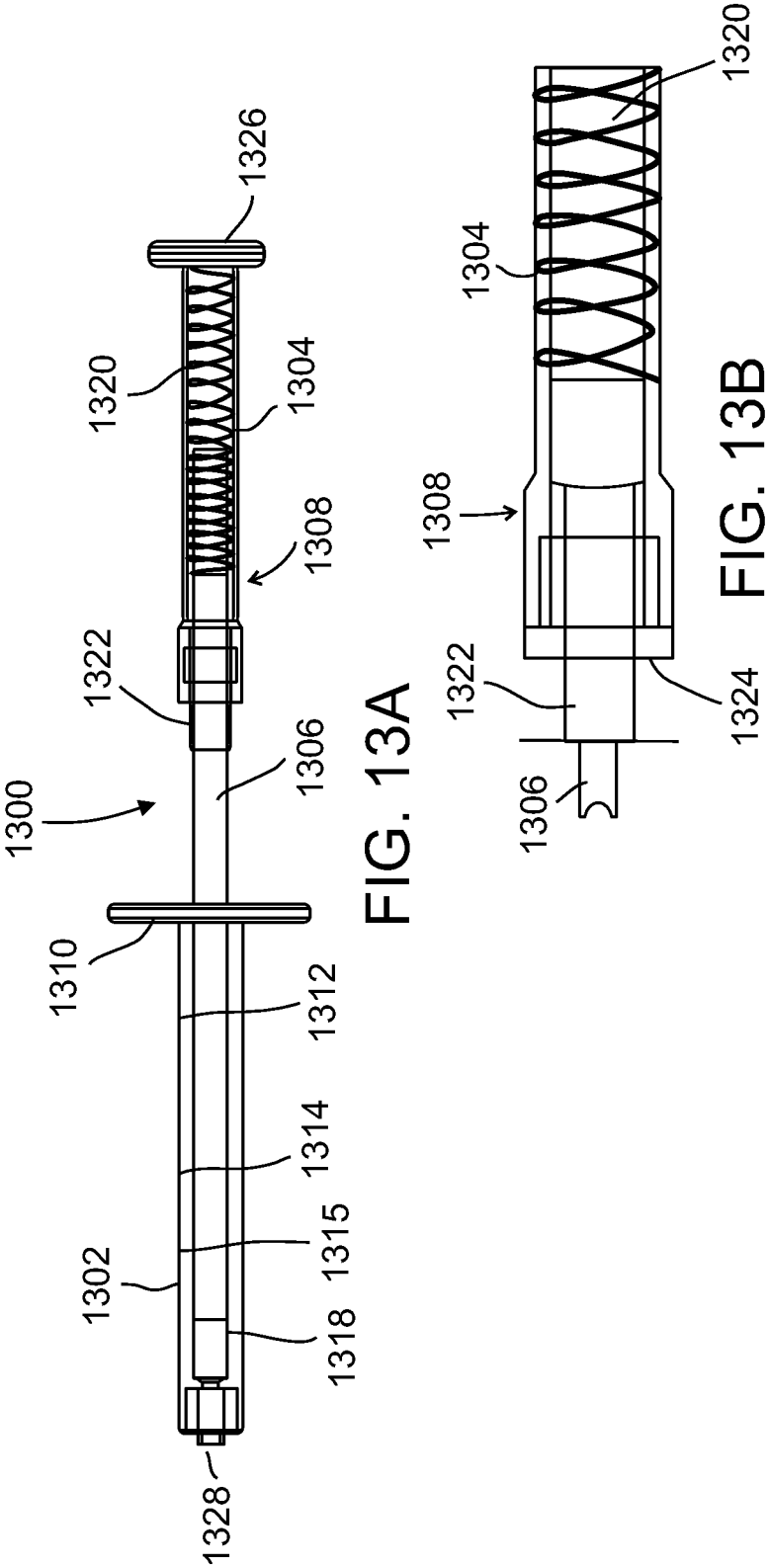


FIG. 12C



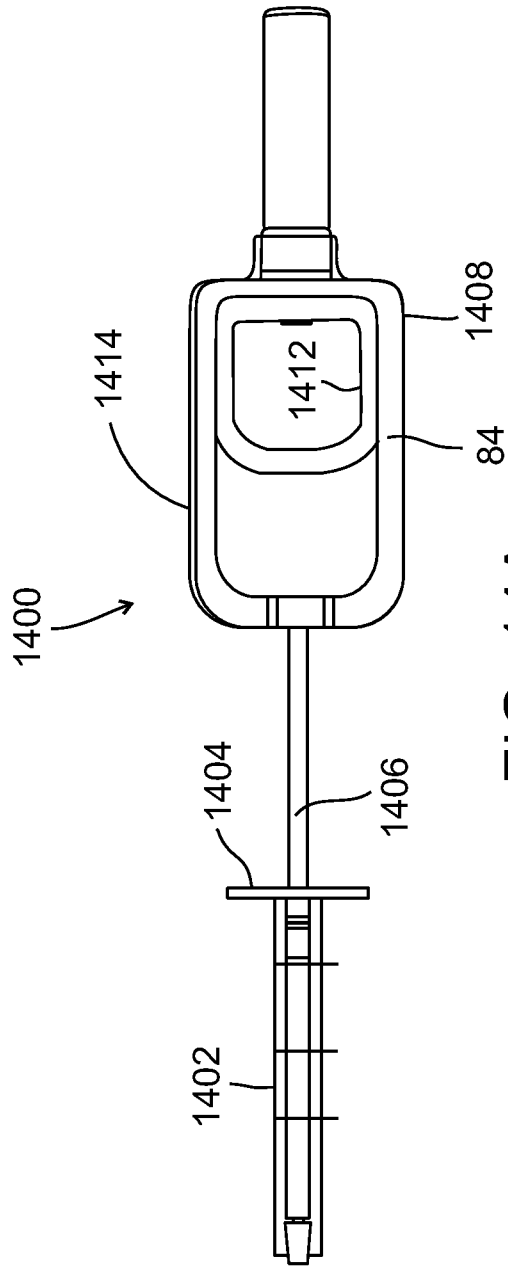


FIG. 14A

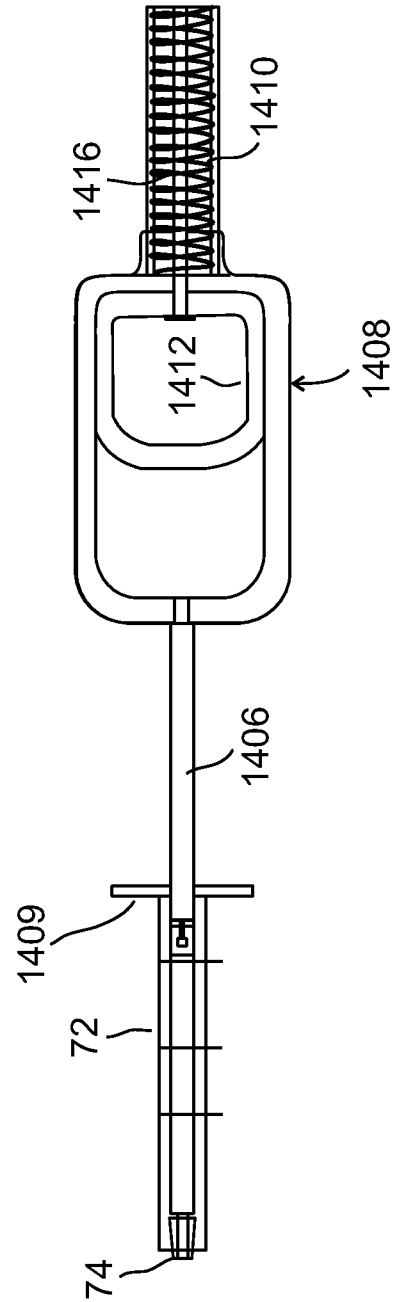
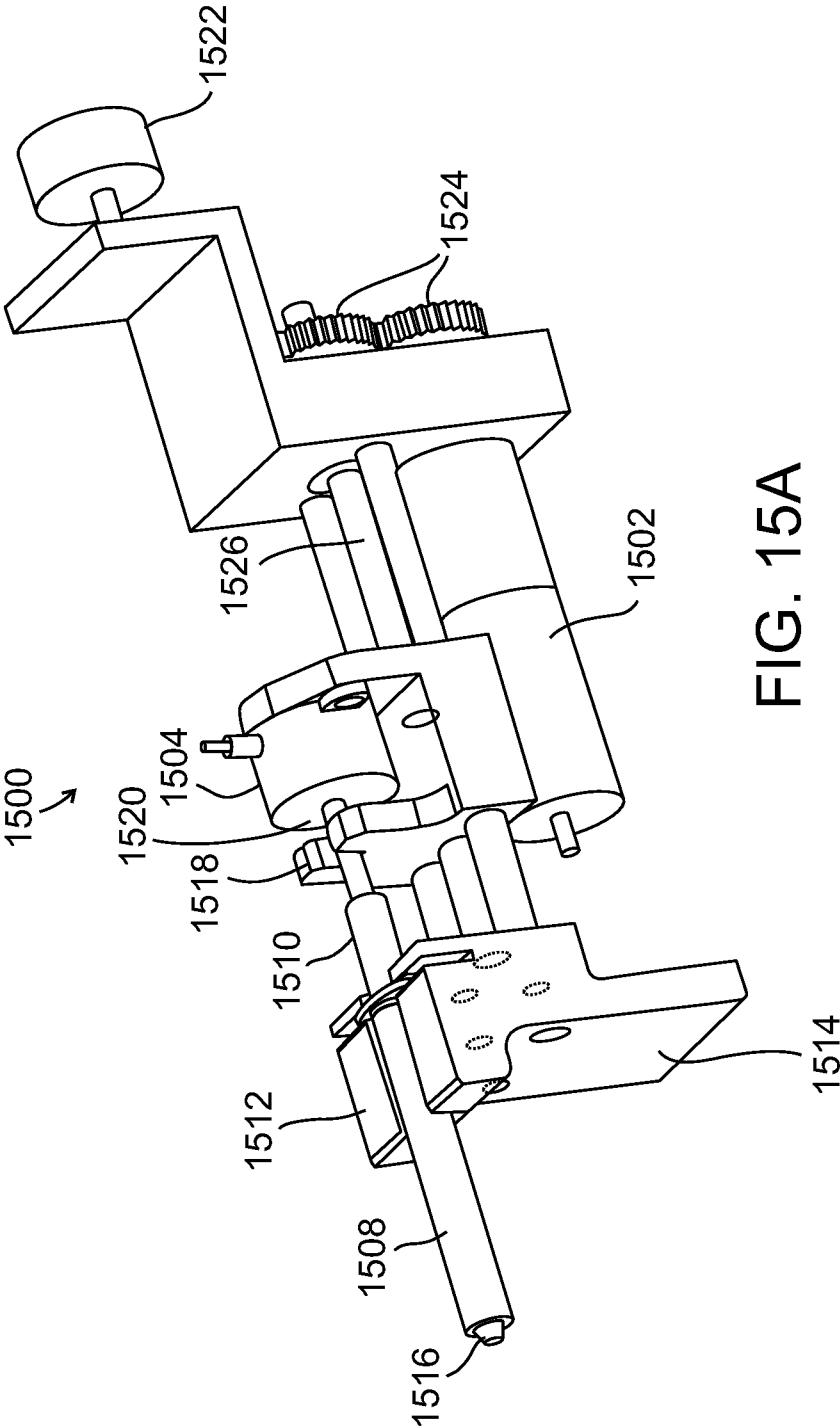


FIG. 14B



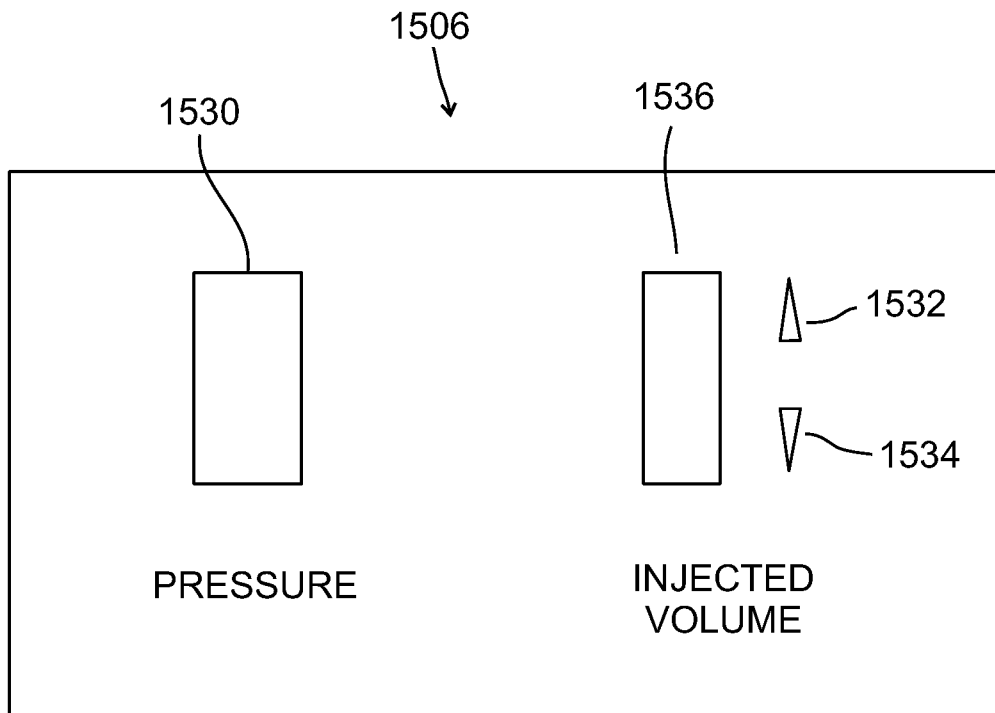


FIG. 15B

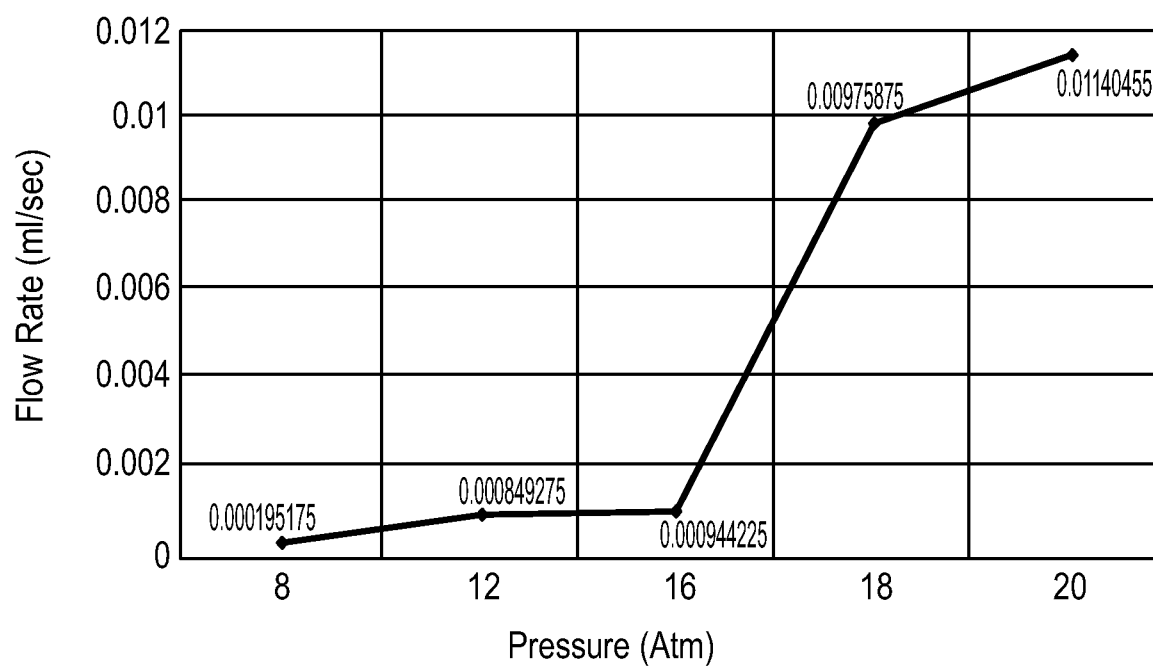


FIG. 16

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2012/052436

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61M25/10

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61M

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/079923 A1 (CHHABRA MANIK [US] ET AL) 13 April 2006 (2006-04-13)	1,15
Y	paragraph [0025] paragraph [0043] paragraph [0059] figure 1	2
Y	----- US 2006/229552 A1 (SLAZAS ROBERT [US] ET AL) 12 October 2006 (2006-10-12) paragraph [0013] paragraph [0023] figure 1	2
A	----- WO 2010/026578 A1 (BY PASS INC [US]; BEYAR MORDECHAY [IL]; GLOBERMAN OREN [IL]; WACHSLER-) 11 March 2010 (2010-03-11) page 23, line 13 - line 16 page 23, line 29 - page 24, line 2 figures 2A-2D -----	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

"E" earlier 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

13 September 2012

Date of mailing of the international search report

15/11/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Amaro, Henrique

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/052436

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006079923	A1	13-04-2006	NONE
US 2006229552	A1	12-10-2006	CA 2541144 A1 30-09-2006 EP 1752169 A2 14-02-2007 JP 2006280942 A 19-10-2006 US 2006229552 A1 12-10-2006
WO 2010026578	A1	11-03-2010	EP 2331187 A1 15-06-2011 US 2011160575 A1 30-06-2011 WO 2010026578 A1 11-03-2010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/052436

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 37-47
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 15

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 15

A balloon catheter made of a semi-compliant material having a plurality of micro-pores with a diameter ranging from about 1 to about 5 micrometers and a density in a range from about 300 to about 600 pores/cm²

2. claims: 3-14

A balloon catheter having a membrane with a defined thickness including pores with defined density and shape.

3. claims: 16-23

A balloon catheter system comprising a balloon catheter, a drug reservoir and a pressure source

4. claims: 24-26

Apparatus for manufacturing a microporous balloon catheter

5. claims: 27-32

A method of perforating a balloon catheter

6. claims: 33-36

An insufflator for a microporous balloon catheter
