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(54) **METHOD AND APPARATUS FOR LOADING A BENEFICIAL AGENT INTO AN EXPANDABLE MEDICAL DEVICE**

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Related U.S. Application Data

(63) Continuation of application No. 10/447,587, filed on May 28, 2003, now abandoned, and a continuation-in-part of application No. 09/948,989, filed on Sep. 7, 2001, now Pat. No. 7,208,010.

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A61F 2/06 (2006.01)
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(52) **U.S. Cl.** **623/1.15**

(58) **Field of Classification Search** 623/1.11, 623/1.12, 1.13, 1.14, 1.15, 1.16, 1.2, 1.21, 623/1.22; 606/192, 198
See application file for complete search history.

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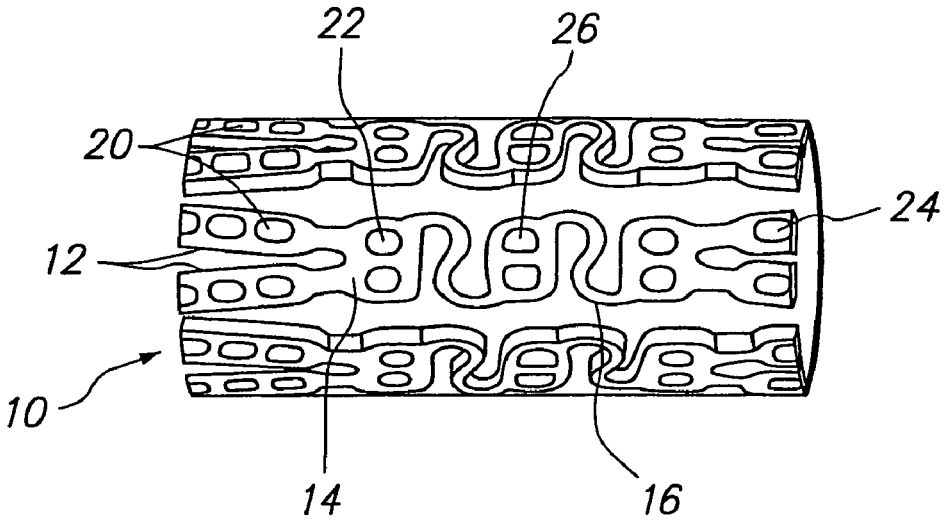
(57) **ABSTRACT**

The present invention relates to method and apparatus for dispensing a beneficial agent into an expandable medical device. The method includes the step of placing an expandable medical device on a mandrel, the medical device forming a cylindrical device having a plurality of openings and dispensing a beneficial agent into the plurality of openings.

13 Claims, 3 Drawing Sheets



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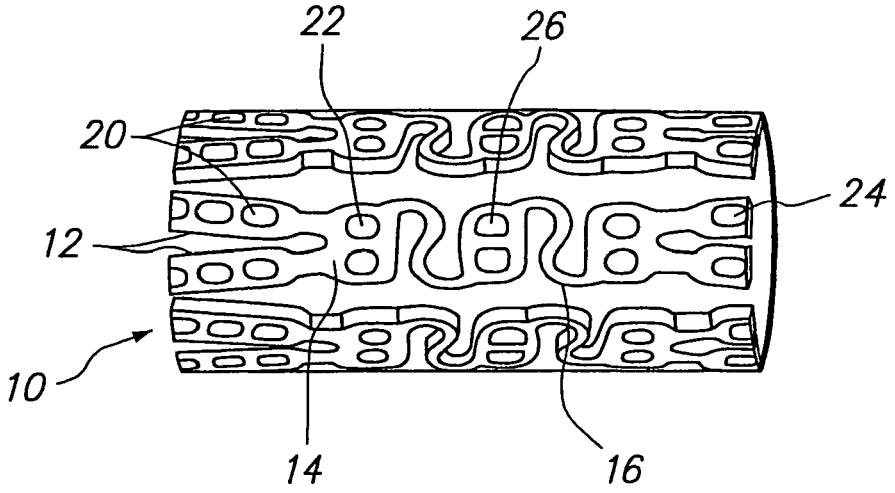

FIG. 1

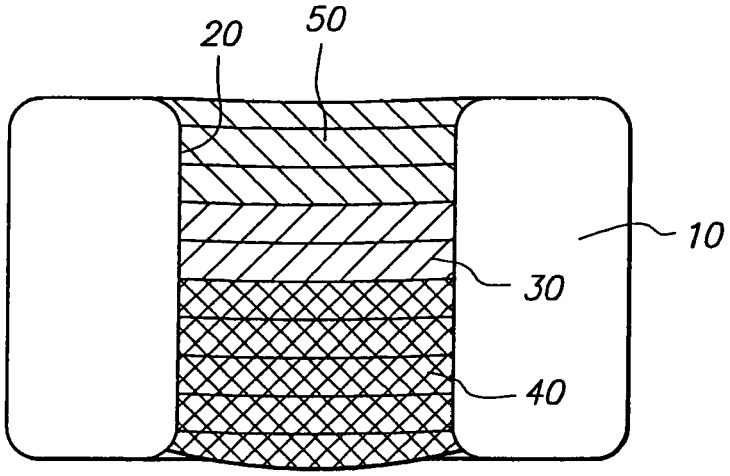

FIG. 2

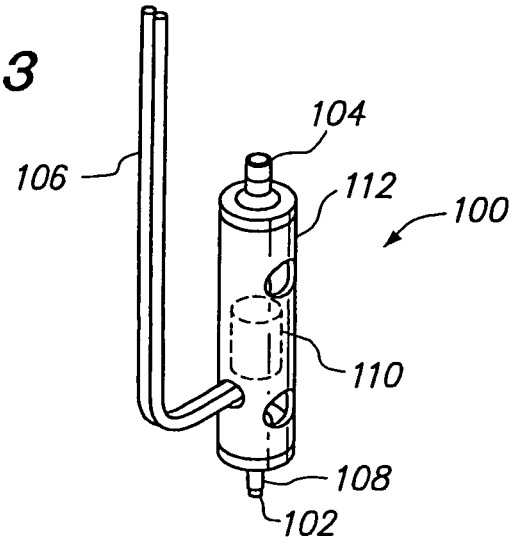

FIG. 3

FIG. 4

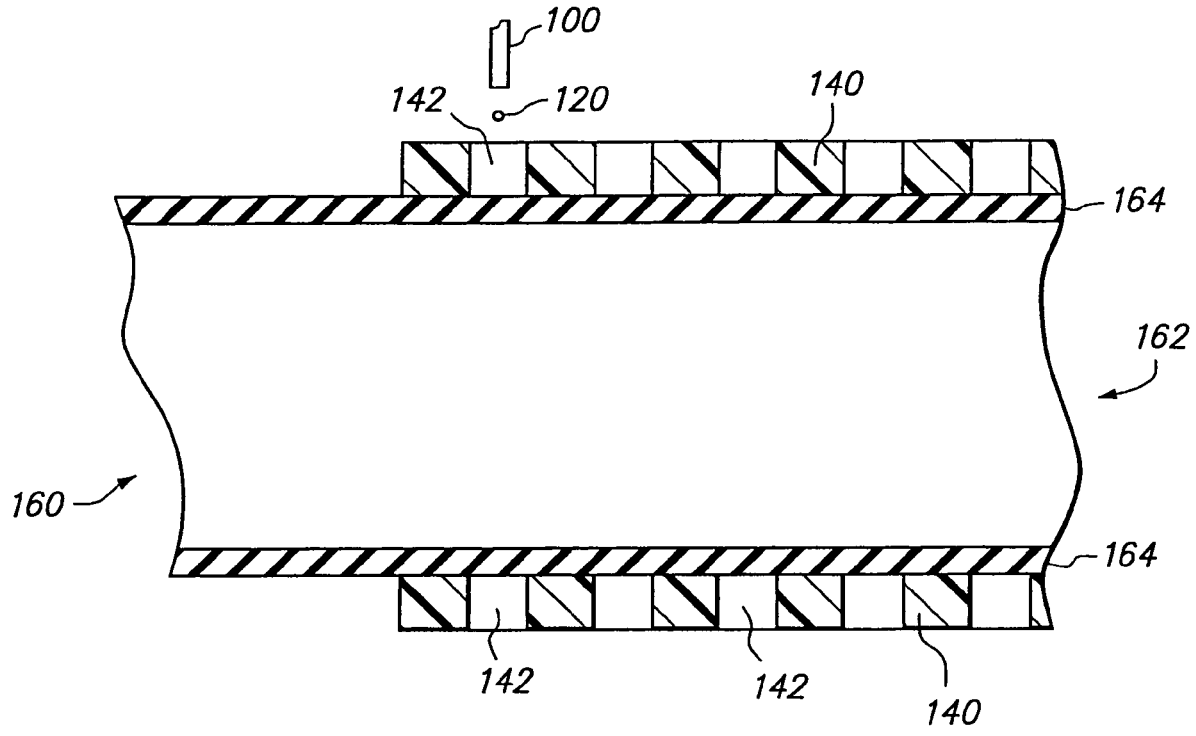

FIG. 5

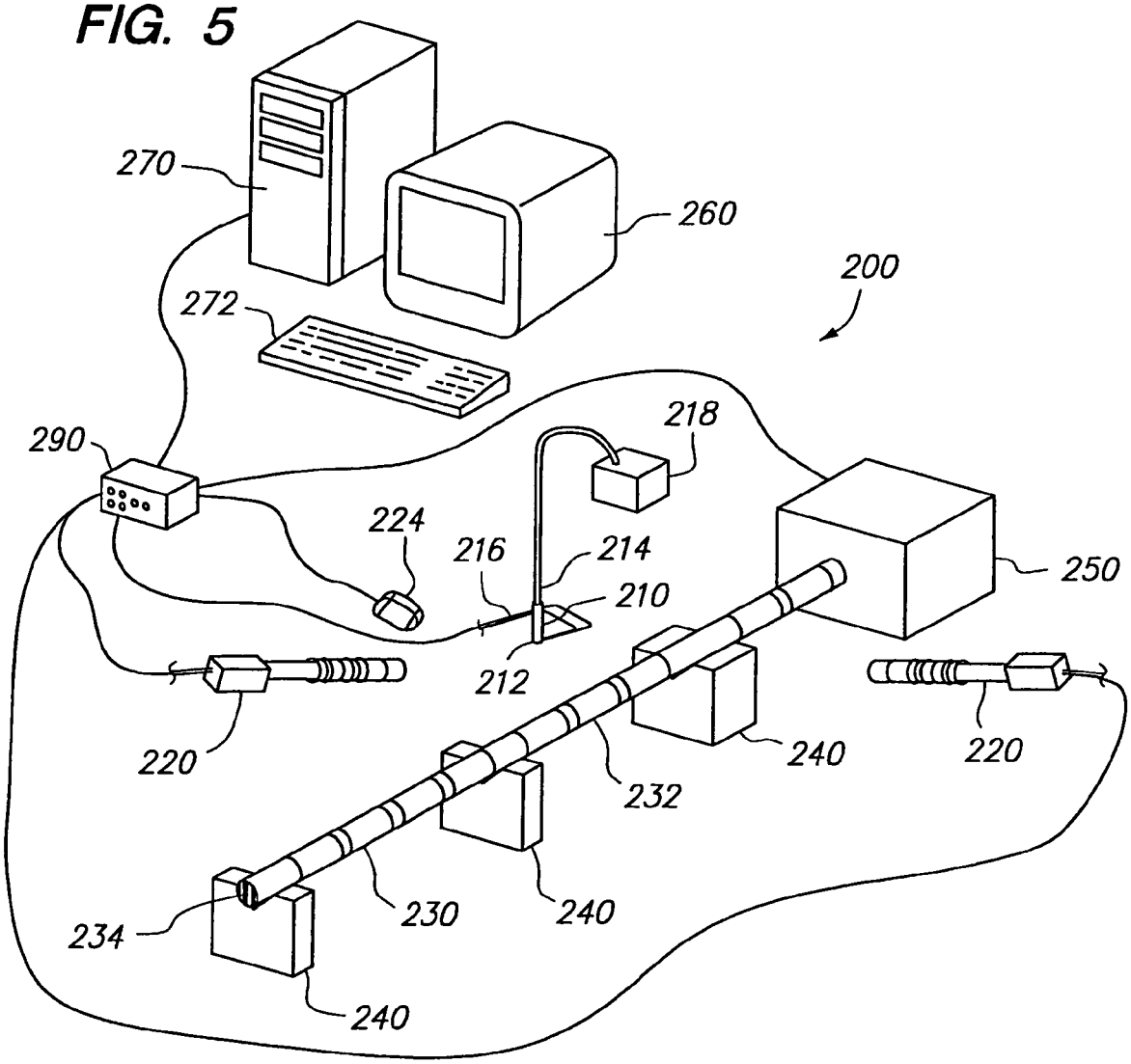
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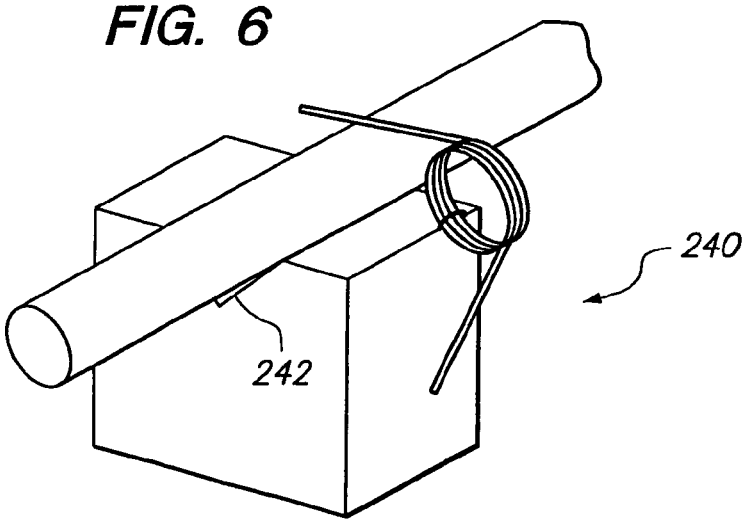
FIG. 6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METHOD AND APPARATUS FOR LOADING A BENEFICIAL AGENT INTO AN EXPANDABLE MEDICAL DEVICE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. patent application Ser. No. 10/447,587 filed May 28, 2003 which claims priority to U.S. Provisional Patent Application Ser. No. 60/412,489, filed on Sep. 20, 2002, each of which are incorporated herein by reference in its entirety. This application is also a Continuation-in-Part of U.S. patent application Ser. No. 09/948,989, filed on Sep. 7, 2001, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to a method and apparatus for loading a beneficial agent, such as a drug into an expandable medical device, and more particularly, the invention relates to a method and apparatus for dispensing a beneficial agent into an expandable medical device such as a stent.

DESCRIPTION OF THE RELATED ART

Implantable medical devices are often used for delivery of a beneficial agent, such as a drug, to an organ or tissue in the body at a controlled delivery rate over an extended period of time. These devices may deliver agents to a wide variety of bodily systems to provide a wide variety of treatments.

One of the many implantable medical devices which have been used for local delivery of beneficial agents is the coronary stent. Coronary stents are typically introduced percutaneously, and transported transluminally until positioned at a desired location. These devices are then expanded either mechanically, such as by the expansion of a mandrel or balloon positioned inside the device, or expand themselves by releasing stored energy upon actuation within the body. Once expanded within the lumen, these devices, called stents, become encapsulated within the body tissue and remain a permanent implant.

Known stent designs include monofilament wire coil stents (U.S. Pat. No. 4,969,458); welded metal cages (U.S. Pat. Nos. 4,733,665 and 4,776,337); and, most prominently, thin-walled metal cylinders with axial slots formed around the circumference (U.S. Pat. Nos. 4,733,665; 4,739,762; and 4,776,337). Known construction materials for use in stents include polymers, organic fabrics and biocompatible metals, such as stainless steel, gold, silver, tantalum, titanium, and shape memory alloys, such as Nitinol.

Of the many problems that may be addressed through stent-based local delivery of beneficial agents, one of the most important is restenosis. Restenosis is a major complication that can arise following vascular interventions such as angioplasty and the implantation of stents. Simply defined, restenosis is a wound healing process that reduces the vessel lumen diameter by extracellular matrix deposition, neointimal hyperplasia, and vascular smooth muscle cell proliferation, and which may ultimately result in renarrowing or even reocclusion of the lumen. Despite the introduction of improved surgical techniques, devices, and pharmaceutical agents, the overall restenosis rate is still reported in the range of 25% to 50% within six to twelve months after an angioplasty procedure. To treat this condition, additional revascularization procedures are frequently required, thereby increasing trauma and risk to the patient.

One of the techniques under development to address the problem of restenosis is the use of surface coatings of various beneficial agents on stents. U.S. Pat. No. 5,716,981, for example, discloses a stent that is surface-coated with a composition comprising a polymer carrier and paclitaxel (a well-known compound that is commonly used in the treatment of cancerous tumors). The patent offers detailed descriptions of methods for coating stent surfaces, such as spraying and dipping, as well as the desired character of the coating itself: it should "coat the stent smoothly and evenly" and "provide a uniform, predictable, prolonged release of the anti-angiogenic factor." Surface coatings, however, can provide little actual control over the release kinetics of beneficial agents. These coatings are necessarily very thin, typically 5 to 8 microns deep. The surface area of the stent, by comparison is very large, so that the entire volume of the beneficial agent has a very short diffusion path to discharge into the surrounding tissue.

Increasing the thickness of the surface coating has the beneficial effects of improving drug release kinetics including the ability to control drug release and to allow increased drug loading. However, the increased coating thickness results in increased overall thickness of the stent wall. This is undesirable for a number of reasons, including increased trauma to the vessel wall during implantation, reduced flow cross-section of the lumen after implantation, and increased vulnerability of the coating to mechanical failure or damage during expansion and implantation. Coating thickness is one of several factors that affect the release kinetics of the beneficial agent, and limitations on thickness thereby limit the range of release rates, duration of drug delivery, and the like that can be achieved.

In addition to sub-optimal release profiles, there are further problems with surface coated stents. The fixed matrix polymer carriers frequently used in the device coatings typically retain approximately 30% of the beneficial agent in the coating indefinitely. Since these beneficial agents are frequently highly cytotoxic, sub-acute and chronic problems such as chronic inflammation, late thrombosis, and late or incomplete healing of the vessel wall may occur. Additionally, the carrier polymers themselves are often highly inflammatory to the tissue of the vessel wall. On the other hand, use of biodegradable polymer carriers on stent surfaces can result in the creation of "virtual spaces" or voids between the stent and tissue of the vessel wall after the polymer carrier has degraded, which permits differential motion between the stent and adjacent tissue. Resulting problems include micro-abrasion and inflammation, stent drift, and failure to re-endothelialize the vessel wall.

Another significant problem is that expansion of the stent may stress the overlying polymeric coating causing the coating to plastically deform or even to rupture, which may therefore effect drug release kinetics or have other untoward effects. Further, expansion of such a coated stent in an atherosclerotic blood vessel will place circumferential shear forces on the polymeric coating, which may cause the coating to separate from the underlying stent surface. Such separation may again have untoward effects including embolization of coating fragments causing vascular obstruction.

In addition, it is not currently possible to deliver some drugs with a surface coating due to sensitivity of the drugs to water, other compounds, or conditions in the body which degrade the drugs. For example, some drugs lose substantially all their activity when exposed to water for a period of time. When the desired treatment time is substantially longer than the half life of the drug in water, the drug cannot be delivered by known coatings. Other drugs, such as protein or

peptide based therapeutic agents, lose activity when exposed to enzymes, pH changes, or other environmental conditions. These drugs which are sensitive to compounds or conditions in the body often cannot be delivered using surface coatings.

Accordingly, it would be desirable to provide an apparatus and method for loading a beneficial agent into an expandable medical device, such as a stent, for delivery of agents, such as drugs, to a patient.

SUMMARY OF THE INVENTION

The present invention relates to an apparatus and method for loading a beneficial agent in an expandable medical device.

In accordance with one aspect of the invention, a method for dispensing a beneficial agent into an expandable medical device includes the steps of placing an expandable medical device on a mandrel, the medical device forming a cylindrical device having a plurality of openings; and dispensing a beneficial agent into at least a portion of the plurality of openings.

In accordance with another aspect of the invention, a method for loading a beneficial agent in an expandable medical device includes the steps of dispensing a beneficial agent through a dispenser into a first opening in an expandable medical device; providing relative movement between the dispenser and the expandable medical device such that the dispenser is moved from alignment with the first opening in the expandable medical device to alignment with a second opening in the expandable medical device; and dispensing the beneficial agent into the second opening in the expandable medical device.

In accordance with a further aspect of the invention, an apparatus for loading a beneficial agent in an expandable medical device includes a mandrel; an expandable medical device having a plurality of openings, the expandable medical device mounted on the mandrel; and a dispenser configured to dispense a beneficial agent into the plurality of openings in the expandable medical device.

In accordance with a further aspect of the invention, a method for loading a stent with a beneficial agent includes the steps of providing a stent with a plurality of holes; and dispensing a beneficial agent through a piezo-electric micro-jet into the plurality of holes.

In accordance with an additional aspect of the invention, an apparatus for loading a beneficial agent in a medical device comprises a dispenser configured to dispense a beneficial agent into the plurality of openings in the medical device; an observation system configured to locate and identify the plurality of openings; and a central processing unit for controlling the dispensing of the beneficial agent into the openings of the medical device, wherein an amount and location of droplets of beneficial agent dispensed into each of the openings in the medical device is determined by the central processing unit based information obtained from the observation system.

In accordance with another aspect of the invention, a system for controlling a delivery of a beneficial agent into a plurality of openings of a medical device includes an observation system for mapping a medical device to obtain an actual position of a plurality of openings of the medical device; a central processing unit for comparing the actual position of the plurality of openings of the medical device to an anticipated position from a manufacturing specification; and a dispenser for dispensing a fluid beneficial agent into the plurality of openings.

In accordance with a further aspect of the invention, a system for controlling a delivery of a beneficial agent into an opening includes a mandrel having a plurality of expandable medical devices; a dispenser configured to dispense a first layer and a second layer of a beneficial agent into a plurality of openings in the expandable medical device; and a central processing unit for controlling the dispensing of the beneficial agent into the openings of the expandable medical device.

In accordance with another aspect of the invention, a method of removing stents from a mandrel includes the steps of radially expanding the stents by injecting air into at least a portion of the mandrel to inflate the mandrel and expand the stents; deflating the mandrel; and sliding the expanded stents off the mandrel.

In accordance with another aspect of the invention a method of obtaining a quantity of a dry, solid form of an agent of interest comprises the steps of providing a liquid which comprises an agent of interest dissolved or dispersed in a volatile liquid medium, depositing a microquantity of the liquid onto a pre-selected site of a substrate, and drying the microquantity by volatizing the volatile liquid medium to produce a dry, solid form of the agent of interest.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

The invention will now be described in greater detail with reference to the preferred embodiments illustrated in the accompanying drawings, in which like elements bear like reference numerals, and wherein:

FIG. **1** is a perspective view of a therapeutic agent delivery device in the form of an expandable stent.

FIG. **2** is a cross-sectional view of a portion of a therapeutic agent delivery device having a beneficial agent contained in an opening in layers.

FIG. **3** is a cross-sectional view of a piezoelectric micro-jetting dispenser for delivery of a beneficial agent.

FIG. **4** is a cross-sectional view of a piezoelectric micro-jetting dispenser and an expandable medical device on a mandrel.

FIG. **5** is a perspective view of a system for loading an expandable medical device with a beneficial agent.

FIG. **6** is a perspective view of a bearing for use with the system of FIG. **5**.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method and apparatus for loading a beneficial agent into an expandable medical device. More particularly, the invention relates to a method and apparatus for loading a beneficial agent in a stent.

First, the following terms, as used herein, shall have the following meanings:

The term "beneficial agent" as used herein is intended to have its broadest possible interpretation and is used to include any therapeutic agent or drug, as well as inactive agents such as barrier layers, carrier layers, therapeutic layers or protective layers.

The terms "drug" and "therapeutic agent" are used interchangeably to refer to any therapeutically active substance that is delivered to a bodily conduit of a living being to produce a desired, usually beneficial, effect. The present invention is particularly well suited for the delivery of antineoplastic, angiogenic factors, immuno-suppressants, anti-inflammatories and antiproliferatives (anti-restenosis agents) such as paclitaxel and Rapamycin for example, and antithrombins such as heparin, for example.

The therapeutic agents used in the present invention include classical small molecular weight therapeutic agents commonly referred to as drugs including all classes of action

as exemplified by, but not limited to: antiproliferatives, antithrombins, antiplatelet, antilipid, anti-inflammatory, and anti-angiogenic, vitamins, ACE inhibitors, vasoactive substances, antimitotics, metello-proteinase inhibitors, NO donors, estradiols, anti-sclerosing agents, alone or in combination. Beneficial agent also includes larger molecular weight substances with drug like effects on target tissue sometimes called biologic agents including but not limited to: peptides, lipids, protein drugs, enzymes, oligonucleotides, ribozymes, genetic material, prions, virus, bacteria, and eucaryotic cells such as endothelial cells, monocyte/macrophages or vascular smooth muscle cells to name but a few examples. Other beneficial agents may include but not be limited to physical agents such as microspheres, microbubbles, liposomes, radioactive isotopes, or agents activated by some other form of energy such as light or ultrasonic energy, or by other circulating molecules that can be systemically administered.

The term "matrix" or "biocompatible matrix" are used interchangeably to refer to a medium or material that, upon implantation in a subject, does not elicit a detrimental response sufficient to result in the rejection of the matrix. The matrix typically does not provide any therapeutic responses itself, though the matrix may contain or surround a therapeutic agent, a therapeutic agent, an activating agent or a deactivating agent, as defined herein. A matrix is also a medium that may simply provide support, structural integrity or structural barriers. The matrix may be polymeric, non-polymeric, hydrophobic, hydrophilic, lipophilic, amphiphilic, and the like.

The term "bioresorbable" refers to a matrix, as defined herein, that can be broken down by either chemical or physical process, upon interaction with a physiological environment. The bioresorbable matrix is broken into components that are metabolizable or excretable, over a period of time from minutes to years, preferably less than one year, while maintaining any requisite structural integrity in that same time period.

The term "polymer" refers to molecules formed from the chemical union of two or more repeating units, called monomers. Accordingly, included within the term "polymer" may be, for example, dimers, trimers and oligomers. The polymer may be synthetic, naturally-occurring or semisynthetic. In preferred form, the term "polymer" refers to molecules which typically have a M_w greater than about 3000 and preferably greater than about 10,000 and a M_w that is less than about 10 million, preferably less than about a million and more preferably less than about 200,000.

The term "openings" refers to holes of any shape and includes both through-openings and recesses.

Implantable Medical Devices with Holes

FIG. **1** illustrates a medical device **10** according to the present invention in the form of a stent design with large, non-deforming struts **12** and links **14**, which can contain openings (or holes) **20** without compromising the mechanical properties of the struts or links, or the device as a whole. The non-deforming struts **12** and links **14** may be achieved by the use of ductile hinges which are described in detail in U.S. Pat. No. 6,241,762 which is incorporated hereby by reference in its entirety. The holes **20** serve as large, protected reservoirs for delivering various beneficial agents to the device implantation site.

As shown in FIG. **1**, the openings **20** can be circular **22**, rectangular **24**, or D-shaped **26** in nature and form cylindrical, rectangular, or D-shaped holes extending through the width of the medical device **10**. It can be appreciated that the openings **20** can be other shapes without departing from the present invention.

The volume of beneficial agent that can be delivered using openings **20** is about 3 to 10 times greater than the volume of a 5 micron coating covering a stent with the same stent/vessel wall coverage ratio. This much larger beneficial agent capacity provides several advantages. The larger capacity can be used to deliver multi-drug combinations, each with independent release profiles, for improved efficacy. Also, larger capacity can be used to provide larger quantities of less aggressive drugs and to achieve clinical efficacy without the undesirable side-effects of more potent drugs, such as retarded healing of the endothelial layer.

FIG. **2** shows a cross-section of a medical device **10** in which one or more beneficial agents have been loaded into the opening **20** in layers. One method of creating such layers is to deliver a solution comprising beneficial agent, polymer carrier, and a solvent into the opening and evaporating the solvent to create a thin solid layer of beneficial agent in the carrier. Other methods of delivering the beneficial agent can also be used to create layers.

According to another method for creating layers, a beneficial agent may be loaded into the openings alone if the agent is structurally viable without the need for a carrier. The process can then be repeated until each opening is partially or entirely filled. Examples of some methods of creating such layers and arrangements of layers are described in U.S. patent application Ser. No. 09/948,989, filed on Sep. 7, 2001, which is incorporated herein by reference in its entirety. Although the layers are illustrated as discrete layers, the layers can also mix together upon delivery to result in an inlay of beneficial agent with concentration gradients of therapeutic agents but without distinct boundaries between layers.

According to one example, the total depth of the opening **20** is about 100 to about 140 microns, typically 125 microns and the typical layer thickness would be about 2 to about 50 microns, preferably about 12 microns. Each typical layer is thus individually about twice as thick as the typical coating applied to surface-coated stents. There would be at least two and preferably about ten to twelve such layers in a typical opening, with a total beneficial agent thickness about 25 to 28 times greater than a typical surface coating. According to one preferred embodiment of the present invention, each of the openings have an area of at least 5×10^{-6} square inches, and preferably at least 7×10^{-6} square inches. Typically, the openings are filled about 50% to about 75% full of beneficial agent.

Since each layer is created independently, individual chemical compositions and pharmacokinetic properties can be imparted to each layer. Numerous useful arrangements of such layers can be formed, some of which will be described below. Each of the layers may include one or more agents in the same or different proportions from layer to layer. The layers may be solid, porous, or filled with other drugs or excipients. As mentioned above, although the layers are deposited separately, they may mix forming an inlay without boundaries between layers.

As shown in FIG. **2**, the opening **20** is filled with a beneficial agent. The beneficial agent includes a barrier layer **40**, a therapeutic layer **30**, and a cap layer **50**.

Alternatively, different layers could be comprised of different therapeutic agents altogether, creating the ability to release different therapeutic agents at different points in time. The layers of beneficial agent provide the ability to tailor a delivery profile to different applications. This allows the

medical device according to the present invention to be used for delivery of different beneficial agents to a wide variety of locations in the body.

A protective layer in the form of a cap layer **50** is provided at a tissue contacting surface of a medical device. The cap layer **50** can block or retard biodegradation of subsequent layers and/or blocks or retards diffusion of the beneficial agent in that direction for a period of time which allows the delivery of the medical device to a desired location in the body. When the medical device **10** is a stent which is implanted in a lumen, the barrier layer **40** is positioned on a side of the opening **20** facing the inside of the lumen. The barrier layer **40** prevents the therapeutic agent **30** from passing into the lumen and being carried away without being delivered to the lumen tissue.

Typical formulations for therapeutic agents incorporated in these medical devices are well known to those skilled in the art.

Uses for Implantable Medical Devices

Although the present invention has been described with reference to a medical device in the form of a stent, the medical devices of the present invention can also be medical devices of other shapes useful for site-specific and time-release delivery of drugs to the body and other organs and tissues. The drugs may be delivered to the vasculature including the coronary and peripheral vessels for a variety of therapies, and to other lumens in the body. The drugs may increase lumen diameter, create occlusions, or deliver the drug for other reasons.

Medical devices and stents, as described herein, are useful for the prevention of amelioration of restenosis, particularly after percutaneous transluminal coronary angioplasty and intraluminal stent placement. In addition to the timed or sustained release of anti-restenosis agents, other agents such as anti-inflammatory agents may be incorporated into the multi-layers incorporated in the plurality of holes within the device. This allows for site-specific treatment or prevention any complications routinely associated with stent placements that are known to occur at very specific times after the placement occurs.

Methods and Systems for Loading a Beneficial Agent in a Medical Device

FIG. **3** shows a piezoelectric micro-jetting dispenser **100** used to dispense a beneficial agent into the opening of a medical device. The dispenser **100** has a capillary tube **108** having a fluid outlet or orifice **102**, a fluid inlet **104**, and an electrical cable **106**. The piezoelectric dispenser **100** preferably includes a piezo crystal **110** within a housing **112** for dispensing a fluid droplet through the orifice **102**. The crystal **110** surrounds a portion of the capillary tube **108** and receives an electric charge that causes the crystal to vibrate. When the crystal vibrates inward, it forces a tiny amount of fluid out of the fluid outlet **102** of the tube **108** to fill an opening **20** in a medical device. In addition, when the crystal vibrates outward, the crystal pulls additional fluid into the tube **108** from a fluid reservoir connected to the inlet **104** to replace the fluid that has been dispensed into the opening of the medical device.

In one embodiment as shown in FIG. **3**, the micro-jetting dispenser **100** includes an annular piezoelectric (PZT) actuator **110** bonded to a glass capillary **108**. The glass capillary **108** is connected at one end to a fluid supply (not shown) and at the other end has an orifice **102** generally in the range of about 0.5 to about 150 microns, and more preferably about 30 to about 60 microns. When a voltage is applied to the PZT actuator, the cross-section of the capillary glass **108** is reduced/increased producing pressure variations of the fluid enclosed in the glass capillary **108**. These pressure variations propagate in the glass capillary **108** toward the orifice **102**. The sudden change in cross-section (acoustic impedance) at the orifice **102**, causes a droplet to be formed. This mode of producing droplets is generally called drop on demand (DOD).

In operation, the micro-jetting dispenser **100**, depending on the viscosity and contact angle of the fluid, can require either positive or negative pressure at the fluid inlet **104**. Typically, there are two ways to provide pressure at the fluid inlet **104**. First, the pressure at the fluid inlet **104** can be provided by either a positive or a negative head by positioning of the fluid supply reservoir. For example, if the fluid reservoir is mounted only a few millimeters above the dispenser **100**, a constant positive pressure will be provided. However, if the fluid reservoir is mounted a few millimeters below the dispenser **100**, the orifice **102** will realize a negative pressure.

Alternatively, the pressure of the fluid at the inlet **104** can be regulated using existing compressed air or vacuum sources. For example, by inserting a pressure vacuum regulator between the fluid source and the dispenser **100**, the pressure can be adjusted to provide a constant pressure flow to the dispenser **100**.

In addition, a wide range of fluids including beneficial agents can be dispensed through the dispenser **100**. The fluids preferably have a viscosity of no greater than about 40 centipoise. The droplet volume of the dispenser **100** is a function of the fluid, orifice **102** diameter, and actuator driving parameter (voltage and timing) and usually ranges from about 50 picoliters to about 200 picoliters per droplet. If a continuous droplet generation is desired, the fluid can be pressurized and a sinusoidal signal applied to the actuator to provide a continuous jetting of fluids. Depending on the beneficial agent dispensed, each droplet may appear more like a filament.

It can be appreciated that other fluid dispensing devices can be used without departing from the present invention. In one embodiment, the dispenser is a piezoelectric micro-jetting device manufactured by MicroFab Technologies, Inc., of Plano, Tex.

The electric cable **106** is preferably connected to associated drive electronics (not shown) for providing a pulsed electric signal. The electric cable **106** provides the electric signal to control the dispensing of the fluid through the dispenser **100** by causing the crystal to vibrate.

FIG. **4** shows an expandable medical device in the form of a stent **140** receiving a droplet **120** of a beneficial agent from a piezoelectric micro-jetting dispenser **100**. The stent **140** is preferably mounted to a mandrel **160**. The stent **140** can be designed with large, non-deforming struts and links (as shown in FIG. **1**), which contain a plurality of openings **142** without compromising the mechanical properties of the struts or links, or the device as a whole. The openings **142** serve as large, protected reservoirs for delivering various beneficial agents to the device implantation site. The openings **142** can be circular, rectangular, or D-shaped in nature and form cylindrical, rectangular or D-shaped holes extending through the width of the stent **140**. In addition, openings **142** having a depth less than the thickness of the stent **140** may also be used. It can be appreciated that other shaped holes **142** can be used without departing from the present invention.

The volume of the hole **142** will vary depending on the shape and size of the hole **142**. For example, a rectangular shaped opening **142** having a width of 0.1520 mm (0.006 inches) and a height of 0.1270 mm (0.005 inches) will have a volume of about 2.22 nanoliters. Meanwhile, a round opening having a radius of 0.0699 mm (0.00275 inches) will have a

volume of about 1.87 nanoliters. A D-shaped opening having a width of 0.1520 mm (0.006 inches) along the straight portion of the D, has a volume of about 2.68 nanoliters. The openings according to one example are about 0.1346 mm (0.0053 inches) in depth having a slight conical shape due to laser cutting.

Although a tissue supporting device configuration has been illustrated in FIG. **1**, which includes ductile hinges, it should be understood that the beneficial agent may be contained in openings in stents having a variety of designs including many of the known stents.

The mandrel **160** can include a wire member **162** encapsulated by an outer jacket **164** of a resilient or a rubber-like material. The wire member **162** may be formed from a metallic thread or wire having a circular cross-section. The metallic thread or wire is preferably selected from a group of metallic threads or wire, including Nitinol, stainless steel, tungsten, nickel, or other metals having similar characteristics and properties.

In one example, the wire member **162** has an outer diameter of between about 0.889 mm (0.035 inches) and about 0.991 mm (0.039 inches) for use with a cylindrical or implantable tubular device having an outer diameter of about 3 mm (0.118 inches) and an overall length of about 17 mm (0.669 inches). It can be appreciated that the outer diameter of the wire member **162** will vary depending on the size and shape of the expandable medical device **140**.

Examples of rubber-like materials for the outer jacket **164** include silicone, polymeric materials, such as polyethylene, polypropylene, polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), polyurethane, polyamides, polyethylene terephthalate (PET), and their mixtures and copolymers. However, it can be appreciated that other materials for the outer jacket **164** can be implemented, including those rubber-like materials known to those skilled in the art.

In one embodiment, the wire member **162** is encapsulated in a tubular outer jacket **164** having an inner diameter of about 0.635 mm (0.25 inches). The outer jacket **164** can be mounted over the wire member **162** by inflating the tubular member to increase to a size greater than the outer diameter of the wire member **162**. The tubular member can be inflated using an air pressure device known to those skilled in the art. The wire member **162** is placed inside of the outer jacket **164** by floating the outer jacket **164** of silicon over the wire member **162**. However, it can be appreciated that the wire member **162** can be encapsulated in an outer jacket of silicon or other rubber-like material by any method known to one skilled in the art.

In one embodiment for loading stents having a diameter of about 3 mm (0.118 inches) and a length of about 17 mm (0.669 inches), a wire member **162** having an outer diameter of 0.939 mm (0.037 inches) is selected. In one example, the wire member **162** is about 304.8 mm (12 inches) in length. The outer jacket **164** has an inner diameter of about 0.635 mm (0.025 inches).

The expandable medical device or stent **140** is then loaded onto the mandrel **160** in any method known to one skilled in the art. In one embodiment, the stents **140** and the mandrel **160** are dipped into a volume of lubricant to lubricate the stents **140** and the mandrel **160**. The stents **140** are then loaded onto the mandrel **160**. The drying of the stents **140** and the mandrel **160** create a substantially firm fit of the stents **140** onto the mandrel **160**. Alternatively, or in addition to drying, the stents **140** can be crimped onto the mandrel by a method known to one skilled in the art onto the mandrel **160**. The crimping ensures that the stents **140** will not move or rotate during mapping or filling of the openings.

FIG. **5** shows a system **200** for loading a beneficial agent in an expandable medical device. The system **200** includes a dispenser **210** for dispensing a beneficial agent into an opening of an expandable medical device, a reservoir of beneficial agent **218** at least one observation system **220**, and a mandrel **230** having a plurality of expandable medical devices **232** attached to the mandrel **230**. The system **200** also includes a plurality of bearings **240** for supporting the rotating mandrel **230**, a means for rotating and translating the mandrel **250** along a cylindrical axis of the expandable medical device **232**, a monitor **260**, and a central processing unit (CPU) **270**.

The dispenser **210** is preferably a piezoelectric dispenser for dispensing a beneficial agent into the opening in the medical device **232**. The dispenser **210** has a fluid outlet or orifice **212**, a fluid inlet **214** and an electrical cable **216**. The piezoelectric dispenser **200** dispenses a fluid droplet through the orifice **212**.

At least one observation system **220** is used to observe the formation of the droplets and the positioning of the dispenser **210** relative to the plurality of openings in the medical device **232**. The observation system **220** may include a charge coupled device (CCD) camera. In one embodiment, at least two CCD cameras are used for the filling process. The first camera can be located above the micro-jetting dispenser **210** and observes the filling of the medical device **232**. The first camera is also used for mapping of the mandrel **230** as will be described below. A second camera is preferably located on a side of the micro-jetting dispenser **210** and observes the micro-jetting dispenser **210** from a side or orthogonal view. The second camera is preferably used to visualize the micro-jetting dispenser during the positioning of the dispenser before loading of the medical device **232** with a beneficial agent. However, it can be appreciated that the observation system **220** can include any number of visualization systems including a camera, a microscope, a laser, machine vision system, or other known device to one skilled in the art. For example, refraction of a light beam can be used to count droplets from the dispenser. The total magnification to the monitor should be in the range of 50 to 100 times.

In one embodiment, a LED synchronized light **224** with the PZT pulse provides lighting for the system **200**. The delay between the PZT pulse and the LED pulse is adjustable, allowing the capture of the droplet formation at different stages of development. The observation system **220** is also used in mapping of the mandrel **230** and medical devices **232** for loading of the openings. In one embodiment, rather than using a LED synchronized light **224**, the lighting is performed using a diffused fluorescent lighting system. It can be appreciated that other lighting systems can be used without departing from the present invention.

A plurality of expandable medical devices **232** are mounted to the mandrel **230** as described above. For example, a mandrel which is about 12 inches in length can accommodate about 11 stents having a length of about 17 mm each. Each mandrel **230** is labeled with a bar code **234** to ensure that each mandrel is properly identified, mapped, and then filled to the desired specifications.

The mandrel **230** is positioned on a plurality of bearings **240**. As shown in FIG. **6**, one example of the bearings **240** have a V-shaped notch **242**. The mandrel **230** is positioned within the V-shaped notch **242** and secured using a clip **244**. The clip **244** is preferably a coil spring, however, other means of securing the mandrel within the V-shaped notch can be used including any type of clip or securing means can be used. The bearings **240** can be constructed of a metallic material, preferably different than the mandrel wire, such as stainless steel, copper, brass, or iron.

The mandrel **230** is connected to a means for rotating and translating the mandrel **250** along the cylindrical axis of the medical device **232**. The means for rotating and translating the mandrel **250** can be any type or combination of motors or other systems known to one skilled in the art.

In one embodiment, the mandrel **250** and medical device **232** are moved from a first position to a second position to fill the openings of the medical device **232** with the beneficial agent. In an alternative embodiment, the system further includes a means for moving the dispensing system along the cylindrical axis of the medical device **232** from a first position to a second position.

A monitor **260** is preferably used to observe the loading of the medical device **232** with a beneficial agent. It can be appreciated that any type of monitor or other means of observing the mapping and loading process can be used.

A central processing unit **270** (or CPU) controls the loading of the medical device **232** with the beneficial agent. The CPU **270** provides processing of information on the medical device **232** for the dispensing of the beneficial agent. The CPU **270** is initially programmed with the manufacturing specifications as to the size, shape and arrangement of the openings in the medical device **232**. A keyboard **272** is preferably used to assist with the loading of the CPU **270** and for input of information relating to the loading process.

The medical devices **232** are preferably affixed to the mandrel **230** and mapped prior to the loading process. The mapping process allows the observation system and associated control system to determine a precise location of each of the openings which may vary slightly from device to device and mandrel to mandrel due to inaccuracies of loading the devices on the mandrels. This precise location of each of the openings is then saved as the specific map for that specific mandrel. The mapping of the mandrel **230** is performed by using the observation system to ascertain the size, shape and arrangement of the openings of each medical device **232** located on the mandrel **230**. Once the mandrel **230** including the plurality of medical devices **232** have been mapped, the mapping results are compared to the manufacturing specifications to provide adjustments for the dispenser to correctly dispense the beneficial agent into each of the holes of the medical device **232**.

In an alternative embodiment, the mapping of the mandrel **230** is performed on an opening by opening comparison. In operation, the observation system maps a first opening in the medical device and compares the mapping result to the manufacturing specifications. If the first opening is positioned as specified by the manufacturing specifications, no adjustment is needed. However, if the first opening is not positioned as specified by the manufacturing specifications, an adjustment is recorded and an adjustment is made during the dispensing process to correct for the position which is different than as specified in the manufacturing specifications. The mapping is repeated for each opening of the medical device until each medical device **232** has been mapped. In addition, in one embodiment, if an opening is mapped and the opening is positioned pursuant to the manufacturing specifications, the mapping process can be designed to proceed to map at every other opening or to skip any number of openings without departing from the present invention.

After the mandrel has been mapped, the medical device **232** is filled with the beneficial agent based on the manufacturers' specification and adjustments from the mapping results. The CPU provides the programmed data for filling of each medical device **232**. The programmed data includes the medical device design code, date created, lot number being created, number of medical devices **232** on the mandrel, volume of each opening in the medical device **232**, different beneficial agents to be loaded or dispensed into the openings in the medical device **232**, the number of layers, drying/baking time for each layer, and any other data.

In one embodiment, the medical device **232** will have at least 10 beneficial agent layers which will be filled including at least one barrier layer, at least one therapeutic layer having a beneficial agent, and at least one cap layer. The beneficial agent layers may include layers which vary in concentration and strength of each solution of drug or therapeutic agent, amount of polymer, and amount of solvent.

In operation, the operator will input or scan the bar code **234** of the mandrel into the CPU **270** before the filling process begins. The initial filling generally includes a mixture of polymer and solvent to create a barrier layer. Each of the openings are typically filled to about 80% capacity and then the mandrel is removed from the system and placed into an oven for baking. The baking process evaporates the liquid portion or solvent from the openings leaving a solid layer. The mandrel is typically baked for about 60 minutes plus or minus 5 minutes at about 55 degrees C. To assist in error prevention, the CPU software receives the bar code of the mandrel and will not begin filling the second layer until at least 60 minutes since the last filling. The second layer and subsequent layers are then filled in the same manner as the first layer until the opening has been filled to the desired capacity. The reservoir **218** can also be bar coded to identify the solution in the reservoir.

The observation system **220** also can verify that the dispenser **210** is dispensing the beneficial agent into the openings through either human observation on the monitor **270** or via data received from the observation system and conveyed to the CPU to confirm the dispensing of the beneficial agent in the openings of the medical device **232**. Alternatively, refraction of a light beam can be used to count droplets dispensed at a high speed.

The dispensers **100** run very consistently for hours at a time, but will drift from day to day. Also, any small change in the waveform will change the drop size. Therefore, the output of the dispenser **100** can be calibrated by firing a known quantity of drops into a cup and then measuring the amount of drug in the cup. Alternatively, the dispenser **100** can be fired into a cup of known volume and the number of drops required to exactly fill it can be counted.

In filling the openings of the medical device **232**, the microjetting dispenser **100** dispenses a plurality of droplets into the opening. In one preferred embodiment, the dispenser is capable of dispensing 3000 shots per second through a microjetting dispenser of about 40 microns. However, the droplets are preferably dispensed at between about 8 to 20 shots per hole depending on the amount of fill required. The microjetting dispenser fills each hole (or the holes desired) by proceeding along the horizontal axis of the medical device **232**. The CPU **270** turns the dispenser **100** on and off to fill the openings substantially without dispensing liquid between openings on the medical device. Once the dispenser has reached an end of the medical device **232**, the means for rotating the mandrel rotates the mandrel and a second passing of the medical device **232** along the horizontal axis is performed. In one embodiment, the medical devices **232** are stents having a diameter of about 3 mm and a length of about 17 mm and can be filled in about six passes. Once the medical device **232** is filled, the dispenser **210** moves to the next medical device **232** which is filled in the same manner.

The CPU **270** insures that the mandrel is filled accurately by having safety factors built into the filling process. It has also been shown that by filling the openings utilizing a microjetting dispenser, the amount of drugs or therapeutic agent

used is substantially less than coating the medical device **232** using previously known method including spraying or dipping. In addition, the micro-jetting of a beneficial agent provides an improved work environment by exposing the worker to a substantially smaller quantity of drugs than by other known methods.

The system **200** also includes an electrical power source **290** which provides electricity to the piezoelectric micro-jetting dispenser **210**.

The medical devices **232** can be removed from the mandrel by expanding the devices and sliding them off the mandrel. In one example, stents can be removed from the mandrel by injecting a volume of air between the outer diameter of the wire member **162** and the inner diameter of the outer jacket. The air pressure causes the medical device **232** to expand such that the inner diameter of the medical device **232** is greater than the outer diameter of the mandrel. In one embodiment, a die is place around the mandrel to limit the expansion of the medical device **232** as the air pressure between the outer diameter of the wire member **162** and the inner diameter of the outer jacket **164**. The die can be constructed of stainless steel or plastics such that the medical devices **232** are not damaged during removal from the mandrel. In addition, in a preferred embodiment, the medical devices **232** are removed four at a time from the mandrel. A 12-inch mandrel will accommodate about 11, 3 mm by 17 mm medical devices having approximately 597 openings.

EXAMPLE 1

In the example below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

DMSO=Dimethyl Sulfoxide

IV=Inherent Viscosity

PLGA=poly(lactide-co-glycolide)

TABLE I

Solutions	Drug	Polymer	Solvent
A	None	4% PLGA 50/50 IV = 0.82	DMSO
DA	0.64% paclitaxel	8% PLGA 50/50 IV = 0.59	DMSO
DD	0.14% paclitaxel	8% PLGA 50/50 IV = 0.59	DMSO
L	None	8% PLGA 50/50 IV = 0.59	DMSO

TABLE II

Layer No.	Solution	Layer No., this Solution
1	A	1
2	A	2
3	A	3
4	A	4
5	A	5
6	A	6
7	A	7
8	A	8
9	A	9
10	DA	1
11	DA	2
12	DD	1
13	L	1

A plurality of medical devices, preferably 11 medical devices per mandrel are placed onto a series of mandrels. Each mandrel is bar coded with a unique indicia which identifies at least the type of medical device, the layers of beneficial agents to be loaded into the opening of the medical devices, and a specific identity for each mandrel. The bar code information and the mapping results are stored in the CPU for loading of the stent.

A first mixture of poly(lactide-co-glycolide) (PLGA) (Birmingham Polymers, Inc.), and a suitable solvent, such as DMSO is prepared. The mixture is loaded by droplets into holes in the stent. The stent is then preferably baked at a temperature of 55 degrees C. for about 60 minutes to evaporate the solvent to form a barrier layer. A second layer is laid over the first by the same method of filling polymer solution into the opening followed by solvent evaporation. The process is continued until 9 individual layers have been loaded into the openings of the medical device to form the barrier layer.

A second mixture of paclitaxel, PLGA, and a suitable solvent such as DMSO forming a therapeutic layer is then introduced into the openings of the medical device over the barrier layer. The solvent is evaporated to form a drug filled protective layer and the filling and evaporation procedure repeated until the hole is filled until the desired amount of paclitaxel has been added to the openings of the medical device.

A third mixture of PLGA and DMSO is then introduced into the openings over the therapeutic agent to form a cap layer. The solvent is evaporated and the filling and evaporation procedure repeated until the cap layer has been added to the medical device, in this embodiment, a single cap layer has been added.

In order to provide a plurality of layers of beneficial agents having a desired solution, the reservoir is replaced and the piezoelectric micro-jetting dispenser is cleaned. The replacement of the reservoir and cleaning of the dispenser insures that the different beneficial layers have a desired solution including the correct amount of drugs, solvent, and polymer.

Following implantation of the filled medical device in vivo, the PLGA polymer degrades via hydrolysis and the paclitaxel is released.

While the invention has been described in detail with reference to the preferred embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made and equivalents employed, without departing from the present invention.

What is claimed is:

1. A method of obtaining a quantity of a dry, solid form of an agent of interest comprising:

(a) providing a liquid which comprises an agent of interest dissolved or dispersed in a volatile liquid medium;

(b) depositing a microquantity of the liquid onto a preselected site of a substrate; and

(c) drying the microquantity by volatizing the volatile liquid medium to produce a dry, solid form of the agent of interest;

wherein the solution is delivered into the opening having a depth of about 125 to about 140 microns and an area of at least 5×10^{-6} square inches.

2. The method of claim **1**, wherein step (b) comprises loading the beneficial agent into the openings.

3. The method of claim **1**, wherein the volatile liquid medium comprises a solvent for the agent of interest and the liquid of step (a) comprises a solution of the active agent dissolved in the solvent.

4. The method of claim **1**, wherein the agent of interest comprises a pharmaceutical agent.

5. The method of claim **4**, wherein the pharmaceutical agent comprises a peptide or a protein.

6. The method of claim **1**, wherein the volatile liquid medium is non-aqueous.

7. The method of claim **1**, wherein the microquantity has a volume between 1 nl and 1 μL.

8. The method of claim **1**, wherein the microquantity has a volume between 10 nl and 500 nl.

9. The method of claim **8**, wherein the microscale reservoir has a volume between 1 nl and 100 μL.

10. The method of claim **1**, wherein step (b) comprises depositing two or more discrete microquantities onto two or more discrete preselected sites, respectively.

11. The method of claim **10**, wherein the discrete preselected sites are provided on a single substrate.

12. The method of claim **10**, wherein the single substrate comprises 100 or more discrete preselected sites.

13. The method of claim **10**, wherein each of the two or more preselected sites is a microscale reservoir.

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