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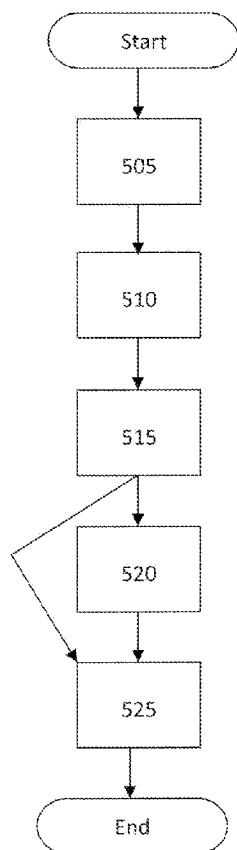
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(54) Title: SYSTEM AND PROCESS FOR FORMATION OF A TIME-RELEASED, DRUG-ELUTING TRANSFERABLE COATING

FIG. 5



(57) Abstract: A system and method are disclosed for coating surfaces of expandable medical devices with composite coatings. Coatings are composed of various materials including, e.g., polymers and drugs. Transfer of the coatings within a patient or other host forms a drug-eluting coating that delivers time-released drugs over time for treatment of a medical condition.



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**SYSTEM AND PROCESS FOR FORMATION OF A
TIME-RELEASED, DRUG-ELUTING TRANSFERABLE COATING**

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CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/491,847, filed May 31, 2011 and U.S. Provisional Application No. 61/649,585, filed May 21, 2012, each of which are incorporated herein by reference in their entirety.

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FIELD OF THE INVENTION

[0002] The present invention relates generally to preparation of composite coatings. More particularly, the invention relates to a system and process for forming transferable coatings on expandable medical devices that upon deployment within a patient or host yield
15 time-released, drug-eluting coatings for treatment of medical conditions.

BACKGROUND OF THE INVENTION

[0003] Expandable medical balloons have conventionally been used in the medical arts
20 to open up plaque-restricted vessels by compressing the plaque that has accumulated within the vessel. However, in the process of expansion, these vessels can be damaged at the point of deployment of the medical balloons. Further, to date, conventional balloon technologies have been unable to provide any delivery of drugs over time to tissues damaged by the balloon expansion or the resulting distension of vessel walls. And, while stents have been used to deliver
25 drugs within a patient over a period of time, the stents must remain in the patient for the period over which the drug delivery occurs, which can be problematic as the body responds to the presence of the stent. Accordingly, new devices and methods are needed that can deliver drugs over time in a patient that provide medical intervention without the need for the delivery device to remain in the patient.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0004] FIG. 1 shows a system for formation of transferable coatings on the surface of expandable medical devices, according to an embodiment of the invention.

35 [0005] FIG. 2 shows two expandable balloons of an “over-the-wire” catheter type used in accordance with the invention.

[0006] FIG. 3 shows a test configuration of system **100** for preparing e-RESS and e-STAT transferable coatings in accordance with the present invention

[0007] FIG. 4 presents exemplary process steps for delivering e-RESS coating layers as a component of transferable coatings formed in accordance with an embodiment of the invention.

[0008] FIG. 5 presents exemplary process steps for delivering e-STAT coating layers as a component of transferable coatings formed in accordance with an embodiment of the invention.

[0009] FIG. 6 presents exemplary process steps for delivering combined e-RESS/e-STAT coating layers as a component of transferable coatings formed in accordance with an embodiment of the invention.

[0010] FIG. 7 shows a transferable, time-released drug-eluting coating delivered in accordance with an embodiment of the process of the invention.

SUMMARY OF THE INVENTION

[0011] In its simplest form, the present invention includes a system and process for forming composite coatings on expandable medical devices that, upon deployment within a patient or host, transfer time-released, drug-eluting deposits at selected sites within the patient that deliver treatments for various medical conditions. In various embodiments, preparation of drug-eluting coatings on balloon surfaces is detailed including modifications that allow transfer of the drug-eluting coatings within target vessels where medical intervention is needed for treatment, that results in the formation of the time-released, drug-eluting coatings therein.

[0012] In various embodiments, particles that yield the coating layers include various materials including polymers, drugs, and polymer/drug combinations detailed herein.

[0013] The present invention also includes a process for modifying the surface of the composite coating that contains, e.g., time-released drugs that allows delivery of the material within the coating from the surface of the medical balloon to a target location within the patient, which forms a time-released, drug-eluting deposit of material at the target location. Formation of these drug-eluting deposits and deployment from expandable medical balloons to the actual host vessels (e.g., heart) has been demonstrated.

[0014] The purpose of the foregoing abstract is to enable the United States Patent and Trademark Office and the public generally, especially scientists, engineers, and practitioners in the art who are not familiar with patent or legal terms or phraseology, to determine quickly from a cursory inspection the nature and essence of the technical disclosure of the application. The

abstract is neither intended to define the invention of the application, which is measured by the claims, nor is it intended to be limiting as to the scope of the invention in any way.

[0015] Various advantages and novel features of the present invention are described herein and will be readily apparent to those skilled in this art from the following detailed description. In the preceding and following descriptions the preferred embodiment of the invention is shown and described by way of illustration of the best mode contemplated for carrying out the invention. As will be realized, the invention is capable of modification in various respects without departing from the invention. These and other enhancements and applications are described further herein.

[0016] The following description includes detail of the preferred best mode of one embodiment of the present invention. It will be clear from this description of the invention that the invention is not limited to these illustrated embodiments. The person of ordinary skill in the art will recognize that the invention is susceptible of various modifications and alternative constructions. Therefore the present description should be seen as illustrative and not limiting. It should further be understood that there is no intention to limit the invention to the specific form disclosed, but on the contrary, the invention is to cover all modifications, alternative constructions, and equivalents falling within scope of the invention as defined in the claims. Accordingly, the drawings and description should be seen as illustrative of the invention and not as limiting in any way.

[0017] Provided herein is a method for forming an implantable, drug-eluting coating on the surface of an expandable medical device, characterized by the steps of: mounting an expandable delivery device with an internally disposed conducting member that maximizes conduction of charge on the surface of the device; delivering preselected potentials with the conducting member to the surface of the expandable delivery device to maximize collection of coating particles on the surface thereof; and coating the expandable delivery device with coating particles delivered via an e-RESS process, and e-STAT process, or a combined e-RESS process and e-STAT process to form one or more coating layers on the surface thereof.

[0018] In some embodiments, the expandable delivery device is a medical balloon. In some embodiments, at least one coating layer of the expandable delivery device includes a drug-eluting component and at least one coating layer includes a biosorbable polymer forming the implantable drug eluting coating on the surface of the device. In some embodiments, the medical balloon comprises nylon.

[0019] In some embodiments, the coating provides transfer of at least a portion of the one or more coating layers upon contact with a host vessel.

[0020] In some embodiments, wherein the expandable delivery device is at least a portion of a medical implant device. In some embodiments, the expandable delivery device is an interventional device. In some embodiments, the expandable delivery device is a diagnostic device. In some embodiments, the expandable delivery device is mounted to a delivery device prior to insertion into a host vessel. In some embodiments, the delivery device is a catheter.

[0021] In some embodiments, the conduction of charge on the surface is via gas-phase conduction or surface conduction of charge. In some embodiments, the delivering of preselected potentials includes delivering an active potential with the conducting component. In some embodiments, the delivering of preselected potentials does not include applying an active potential to the conducting component. In some embodiments, the delivering includes applying an electrostatic field potential on the surface of the expandable delivery device of at least about 15 kV prior to the coating step with the e-STAT process.

[0022] In some embodiments, the biosorbable polymer and drug eluting component are located within the same coating layer. In some embodiments, the coating includes coating the surface simultaneously with the e-RESS process and the e-STAT process to encapsulate a drug and a biosorbable polymer in a single layer of the drug-eluting coating.

[0023] In some embodiments, the drug-eluting component includes a drug dispersed within a biosorbable polymer disposed in a single coating layer. In some embodiments, the biosorbable polymer and drug-eluting component are located in different coating layers. In some embodiments, at least one coating layer includes a binding component comprising polylactoglycolic acid (PLGA).

[0024] In some embodiments, the expandable delivery device is at least partially expanded during coating of same.

[0025] In some embodiments, at least a portion of the biosorbable polymer has a preselected molecular weight that enhances transferability of the drug-eluting coating to the receiving surface within the host vessel. In some embodiments, the drug is a time-released drug that provides time-selectivity for treatment of a host or patient. In some embodiments, the drug has a crystalline form. In some embodiments, the drug comprises sirolimus.

[0026] In some embodiments, the coating includes masking one or more preselected portions of the expandable delivery device. In some embodiments, the masking includes forming preselected shapes selected from: oval, square, rectangle, triangular, or cylindrical within the coating layers on the surface of the expandable delivery device that contain an active drug delivered in the drug-eluting coating when in contact with the receiving surface.

[0027] In some embodiments, at least one coating layer includes a releasing agent selected from the group consisting of: hydrophilic or hydrophobic chemicals or polymers that

lower the interfacial energy between the surface of the medical device and the coating layers, water soluble chemicals or polymers that dissolve to eliminate adhesion between coatings layers and the medical device surface, brittle or friable coatings that lose mechanical cohesion upon, polyethylene glycols (PEG), hydrogels, polyesters, polyacrylates, polysaccharides, silicones, silanes, tocopherol, glycerin, sucrose, cellulose, shellac, and combinations thereof providing release of the coating to the receiving surface upon contact with same. In some embodiments, the releasing agent is located within a coating layer disposed between the surface of the expandable delivery device and a first layer comprising a biosorbable polymer.

[0028] In some embodiments, at least one coating layer on the surface of the expandable delivery device comprises a low-energy releasing agent selected from the group consisting of: a releasing agent with surface energy of less than 35 dynes/cm or agents onto which a drop of water would experience a contact angle of greater than 90 degrees, polyvinyl alcohols (PVA), ethylene vinyl acetates (EVA), polyolefins, fluorosilanes, fluoroacrylates, fluorohydrocarbons, paraffin, long chain hydrocarbons, and combinations thereof. In some embodiments, the low-energy releasing agent is located within a coating layer disposed between the surface of the expandable delivery device and a first layer comprising a biosorbable polymer.

[0029] In some embodiments, at least one coating layer on the surface of the expandable delivery device comprises an adhesive agent selected from the group consisting of: agents with cationic moieties that assist in cellular adhesion/uptake, shattering agents that penetrate tissue surface and promote adhesion through mechanical entanglement, viscous polymeric agents, and cationic polyamino acids such as polyarginine, polylysine, polyhistidine, and polyethyleneimine (PEI), 3,4-dihydroxy-L-phenylalanine (dopa), (as in active component in mussel adhesive), laminins, cationic surfactant molecules such as didodecyldimethylammonium bromide (DMAB), ethylhexadecyldimethylammonium bromide, dodecyltrimethyl ammonium bromide, tetradodecylammonium bromide, dimethylditetradecylammonium bromide, detrabutylammonium iodide, DEAE-dextran hydrochloride, and hexadimethrine bromide, and combinations thereof that affixes the transferable coating material to the receiving surface upon expansion of the expandable delivery device. In some embodiments, the transferable coating material includes an adhesion layer that enhances adhesion with the receiving surface. In some embodiments, the adhesive agent is included with the biosorbable polymer in a single coating layer on the surface of the expandable delivery device.

[0030] In some embodiments, at least one coating layer includes both the biosorbable polymer and a drug or therapeutic agent to provide timed-release delivery of the drug or therapeutic agent by dissolution of the biosorbable polymer layer within the coating material transferred to the host vessel. In some embodiments, the leading layer of the transferable coating

on the surface of the expandable delivery device contains therapeutic drug particles modified with a surface charge prior.

[0031] In some embodiments, the coating particles are of a size between about 0.01 micrometers and about 10 micrometers.

5 [0032] In some embodiments, the step of sintering the transferable coating material to form a dense, thermally stable film on the surface of the expandable delivery device prior to delivery of same at a temperature in the range from about 25 °C to about 150 °C.

[0033] In some embodiments, the sintering includes sintering the transferable coating material in the presence of a solvent gas to form a dense, thermally stable film on the surface of
10 the expandable delivery device.

[0034] In some embodiments, the method further includes the step of transferring at least a portion of the coating from the expandable delivery device to a receiving surface of a host vessel to form a drug-eluting deposit therein. In some embodiments, the transferring includes expanding the expandable delivery device to transfer and implant at least a portion of the drug-
15 eluting coating to the receiving surface of the host vessel. In some embodiments, the step of expanding includes expanding the expandable delivery device using a fluid that maintains rigidity and integrity of along the external surface of same. In some embodiments, the expanding includes at least partially deflating the expandable delivery device to reduce the physical dimensions of the expandable delivery device when inserting same into the host vessel
20 prior to transferring the coating to the receiving surface of the host vessel.

[0035] Provided herein are devices comprising the elements noted herein, which may be produced according to methods described herein.

DETAILED DESCRIPTION

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[0036] A system and process are detailed for forming composite coatings of transferable material on the surface of expandable medical devices. While various embodiments of the invention will be described in reference to coating of expandable medical balloons, the invention is not intended to be limited thereto. For example, the invention is applicable to any of a variety
30 of expandable medical devices. Thus, no limitations are intended. The invention finds application in medical intervention technologies wherein medical catheters and stents are routinely deployed including, e.g., medical angioplasty and treatment of vascular conditions. For example, these composite coatings of transferable material are deployed at various target locations within the vascular system of a patient or host by activation (i.e., expansion) of the
35 expandable device. The term “**coating**” as used herein means at least one layer containing a

selected material or materials (e.g., preselected drugs and polymers) of a selected thickness that extends over at least a portion of the surface of the expandable medical device. Once the material from the composite coating is transferred or otherwise implanted at the site of delivery within the patient or host, the expandable medical device is removed. The transferred material then delivers, e.g., time-released drugs that provide medical intervention at the site of delivery without the device remaining in the patient or host. The present invention provides benefits for delivery of drugs not achieved with prior art devices including, but not limited to, e.g., preparation of composite coatings of transferable materials onto the surface of expandable medical delivery devices, transfer of the composite material from the surface of the medical balloon to the target location within the host vessel, implantation of the transferable material that forms the time-released drug-eluting deposit within the patient or host, and removal of the expandable medical device once the material is transferred into the patient or host. At least some portion of the drug-eluting deposit remains at the target site providing delivery of the time-released drug for the term of treatment without the medical delivery device remaining in the patient or host. Composite coatings comprising one or more layers of selected materials are formed on the surface of individual medical balloons by electrostatic collection of coating particles.

[0037] FIG. 1 is a schematic showing a coating system 100 for coating expandable medical balloon devices 4, according to one embodiment of the invention. System 100 includes a coating chamber 50 that mounts to a coating delivery stage 2. Coating delivery stage 2 is configured to deliver respective e-STAT and e-RESS coating particles generated in processes e-RESS plumes 22 and e-STAT plumes 24, described herein. e-RESS is a process by which electrostatically charged coating particles of a selected size (between about 5 μm to about 100 nm) are delivered by Rapid Expansion of Supercritical Solution (RESS) and electrostatically collected to form one or more coating layers on the surface of medical balloon 4. The e-RESS process is detailed in U.S. patents 4,582,731; 4,734,227; 4,734,451; 6,749,902; and 6,756,084 assigned to Battelle Memorial Institute (Richland, WA), which patents are incorporated herein in their entirety. e-STAT is a process by which dry coating particles of a selected size (between about 0.1 μm to about 10 μm) are delivered by abrupt entrainment of the solid particles in a carrier gas without use of an expansion fluid or delivery solvent. The particles are electrostatically collected to form one or more coating layers on the surface on the medical balloon devices 4. The e-STAT process is detailed in patent publication number WO 2007/011707 A2 (assigned to Battelle Memorial Institute, Richland, WA, USA, and MiCell Technologies, Inc., Raleigh, NC, USA), which reference is incorporated herein in its entirety. The e-RESS and e-STAT processes can be performed either sequentially (i.e., first one and then

the other), or concurrently (i.e., simultaneously) to form any number of individual coating layers or to provide unique combinations and concentrations of materials in a single coating layer. Any combination or sequence of e-RESS and e-STAT steps may be used to produce a coating. The e-RESS process for forming coating particles is preferred for delivery of materials that are soluble in a supercritical fluid or other solvent and where micrometer-scale (or smaller diameter) particles are desirable or where other particle types are generated. For example, rapid nucleation occurs during the RESS process and typically leads to formation of amorphous or non-crystalline nanoparticles. The e-STAT process is preferred when delivery of particles is desired which are insoluble in a supercritical fluid solvent, or when a solution or solvent may alter the desirable physical or chemical properties of the particles, as when, e.g., highly crystalline particles are desired or need to be collected. Both processes can be used together in cases where combinations of particles with different properties or solubilities are desired or when different particles must be co-collected to form a single coating layer. Thus, no limitations are intended to exemplary embodiments. Coating layers composed of these various e-RESS and/or e-STAT coating particles are generated and deposited on the surface of the medical balloons forming coating layers, as detailed hereafter.

[0038] In the instant embodiment, an e-STAT delivery nozzle **20** is positioned adjacent to, and apart from, the e-RESS delivery nozzle **18**, but positioning of delivery nozzles **18** and **20** nozzles is not limited. In a preferred embodiment, chamber **50** includes a balloon mounting assembly **16** of a dual ring type that circumvolves the e-RESS delivery nozzle **18**. Balloon mounting assembly **16** includes an upper staging ring **12** and a lower (base) staging ring **14** that provide an equal separation distance between delivery nozzle **18** and balloons **4** mounted in upper staging ring **12** of stage **16**. Ring **12** also provides a suitable separation distance between adjacent medical balloons **4** for coating. Separation distance between balloons **4** is variable and need only be sufficient to prevent interference with electric fields that effect the electrostatic collection of e-RESS and e-STAT particles. Medical balloons **4** are preferably of an “over-the-wire” catheter type that include an inner guide wire (not shown) covered by a sleeve (not shown) internal to balloon **4**, forming a tube-within-a-balloon or a sleeve-within-a-balloon arrangement, described further herein. e-RESS nozzle **18** couples to a cylinder **36** filled with a preselected solvent (e.g., R236ea). e-RESS nozzle **18** sprays a coating material in a supercritical solvent that expands as a plume **24** of electrostatically charged coating particles that collect on the surface of the medical balloons **4** mounted in mounting assembly **16**. In the instant embodiment, solvent is delivered via syringe pump **32** and mixed in a high pressure cell **34** (e.g., 50 cm³ cell volume) with a 2nd material (e.g. PLGA polymer) and the resulting mixed coating solution is delivered via syringe pump **30** through a heated block **28** configured with temperature control feedback at

a high pressure (e.g., 5500 psi), forming the supercritical solution containing the mixed materials. Pressure is maintained within the delivery system by passing solution through the small diameter (e.g., 50 μm to 200 μm) e-RESS nozzle **18**.

[0039] In the figure, the e-RESS nozzle **18** consists of a length of capillary tubing (exemplary dimensions: 100 μm I.D. X 1/16th inch O.D. X 10 cm) constructed of, e.g., a thermoplastic polymer [e.g., polyether ether ketone also known as PEEK® (Victrex USA, Inc., West Conshohocken, PA, USA)], but is not limited thereto. For example, other capillary materials may be used including, but not limited to, e.g., stainless steel. The nozzle materials may also be preformed, e.g., of sapphire. Thus, no limitations are intended. In the exemplary embodiment, RESS nozzle **18** (comprising, e.g., PEEK® tubing) is encased in stainless steel (e.g., 1/4" OD stainless steel tubing) that is grounded to establish a uniform electric field over each balloon **4** mounted to mounting assembly **16**. Pressure drops continuously over the length of the nozzle (capillary) **18**. The supercritical coating solution is delivered through e-RESS nozzle **18** as a plume **22** of coating particles in conjunction with a timed pneumatic valve **40** at a preselected pressure (e.g., 5500 psi) and a preselected temperature (e.g., 150 °C). The expanded e-RESS solution produces dry coating particles (e.g., of a solute polymer) of a preselected size in a plume **22** of solvent gas. The solute particles then are electrostatically collected on the surface of the medical balloons, forming a coating layer. In exemplary tests, coating particles were generated by expansion of a near-critical or a supercritical solution prepared using a hydrofluorocarbon solvent, (e.g., fluoropropane R-236ea, Dyneon, Oakdale, MN, USA) that further contained a dissolved biosorbable polymer [e.g., a 50:50 poly(DL-lactide-co-glycolide) (PLGA)] available commercially (Catalog No. B6010-2P, LACTEL® Absorbable Polymers, a division of Durect, Corp., Pelham, AL, USA). In the instant tests, the supercritical solution delivered at 5500 psi and 150 °C through the expansion nozzle **18** was expanded into ambient (i.e., STP) conditions, but is not limited thereto. For example, delivery of RESS coating particles may be made at various pressures and temperatures.

[0040] In the e-STAT process, e-STAT orifice **20** delivers dry coating particles in a plume **24** in the absence of a supercritical solvent to the surfaces of medical balloons **4** in mounting assembly **16**. In the instant embodiment, e-STAT orifice **20** is constructed from a modified bulkhead union (e.g., 1/2-inch SWAGELOK®) composed of a plastic material (e.g., nylon), but is not limited thereto. e-STAT orifice **20** is not charged. e-STAT orifice **20** couples to a reservoir **46** filled with a preselected drug (e.g., Sirolimus) or other coating material in a crystalline or dry powder form with particles preferably of a size in the range from about 10 μm to about 10 nm, but is not limited thereto. The drug or coating material in dry form is provided to e-STAT nozzle **20** through tubing **44** (e.g., 1/2 inch polypropylene or another polymeric

tubing). Drug reservoir **46** containing the dry coating powder couples to a pneumatic valve **42** that delivers the dry coating particles as a plume **24** through the connecting tubing **44** and the e-STAT orifice **20** into the containment vessel **50** at a preselected pressure (e.g., 500 psi nitrogen) and temperature where particles are electrostatically collected on the surface of the medical balloons **4** mounted in mounting assembly **16**. Pressures at which dry coating particles are delivered are not limited. Pneumatic valve **42** further couples to a gas reservoir **48** containing an inert gas (e.g., N₂) via tubing **49** that provides a discharging gas to pneumatic valve **42**. In e-STAT processing of coatings for biomedical balloon applications, metal-containing guide wires **8** encased within the inner sleeve of the balloon **4** are charged with voltages that range preferably from about 5 kV to about 25 kV. More particularly, voltages range from about 10 kV to about 20 kV.

[0041] For combined e-RESS and e-STAT coating processes, delivery conditions are those described previously herein for the individual RESS and STAT processes, but the processes are performed simultaneously. Thus, the disclosure is not intended to be limited by the descriptions to the individual e-RESS and e-STAT processes.

[0042] FIG. 2 shows two medical balloons **4** of an “over-the-wire” catheter type coated in conjunction with one embodiment of the invention. In the figure, medical balloons **4** each include a catheter guide **6** through which a metal guide (conducting) wire **8** passes. Guide wire **8** passes through the center of each balloon **4** in a sleeve **10** that runs the length of balloon **4**. The sleeve-within-the balloon configuration separates sleeve **10** from the expansion volume of each balloon **4**. Sleeve **10** and balloon **4** are fused at either end of the balloon **4**, forming a seal that allows for inflation of balloon **4** by introducing expansion gas through catheter guide **6**. In the test configuration, balloons **4** were expanded by means of, e.g., a syringe coupled to a luer connection described hereafter positioned at the end of each catheter guide **6** distal to the expandable balloon **4**, but the mechanism for expansion of balloons is not limited thereto. For example, a pneumatic pressure system may also be used, e.g., for production scale processing. Thus, no limitations are intended. In one balloon (on the right) of FIG. 2, metal guide wire **8** in balloon **4** was inserted to the tip of balloon **4** without protruding from the upper end (i.e., the normal coating condition). In the other balloon (on the left) of FIG. 2, balloon **4**, guide wire **8** was retracted to below the mid section of balloon **4** prior to coating. Results in each image demonstrate that the coating on balloon **4** covers an area equal to the terminal position of guide wire **8** in sleeve **10**, illustrating the effect the guide wire **8** has on collection efficiency of the coating materials.

[0043] FIG. 3 shows a test configuration of system **100** for preparing e-RESS and e-STAT transferable coatings in accordance with the present invention. System **100** includes a

balloon mounting assembly **16** for mounting and coating expandable medical devices including medical balloons **4**. In the e-RESS coating process used in conjunction with the present invention, lower (base) staging ring **14**, metal sheath (post) **19** surrounding e-RESS nozzle **18**, and guide wires **8** are grounded. In the figure, medical balloons **4** are shown vertically mounted on upper staging ring **12** of mounting assembly **16**. The upper ends of balloon catheters **6** are inserted in slots machined in the upper stage ring **12**, providing vertical staging of balloons **4** for coating. Guide wires **8** (not shown) are enclosed within the balloons **4** within the internal catheter guide sleeves **6** (e.g., in a tube-within-a-balloon arrangement). At the top end of balloons **4**, one end of guide wires **8** extends through sleeve **10** from inside the inner balloon **4**, with the tip of the metal guide wire **8** retracted immediately (~ 1 mm) below the tip of balloon **4**. Metal guide wires **8** extend a non-limiting distance of ~ 12 inches from the end of balloon **4** within catheter guide **6**. Guide wires **8** protrude from the catheter guide **6**, e.g., below base staging ring **14**, which are then coupled to an electrical source **22** (e.g., a high voltage power supply). This arrangement allows preselected potentials or electrical grounding to be applied to each guide wire **8** that delivers an electric field through surfaces of each balloon **4** individually or collectively during deposition of coating particles. Retraction of the guide wire **8** into the balloon **4** prevents disruptive fields (i.e. coronal discharge) from forming at the exposed tip of wire **8** that can lead to poor quality depositions on the balloon **4** surface. Guide wires **8** in the instant embodiment, provide a convenient way to electrically connect the interior of the balloons **4** to the surface of the balloons **4**, but the process is not intended to be limited to the use of catheter guide wires **8** as active electrodes. In one embodiment, base staging ring **14** is composed of a molded or machined engineering plastic (e.g., DELRIN®) to which a conductive metal (e.g., copper) grounding wire or ring (not shown) is positioned along the perimeter of lower staging ring **14**, providing a common potential to each metal guide wire **8** during e-RESS coating of medical balloons **4** with e-RESS coating particles. In the instant embodiment, base ring **14** includes a loop for attaching guide wires **8** to grounding screws mounted next, or adjacent, to the conductive ring on base staging ring **14**. The grounding ring further couples to a power source **22**, e.g., using a clip mechanism or other attaching means, which permits guide wires **8** to be charged or grounded (when not charged) as required for preparation of specific coatings on the surface of medical balloons **4** described further herein. When charged, guide wires **8** provide a uniform field over the surface of balloon **4**. In the test configuration, balloons **4** were inflated by connecting a 1 cm^3 (cc) syringe to a luer coupling (shown at left) located at the catheter **6** end of balloons **4** and fully depressing the syringe plunger, allowing the plunger to come back to an equilibrium position determined by the plunger friction in the syringe body, thereby providing a source of air that inflated each balloon **4**. For commercial processing, a

manifold of luer connections may be attached at the terminal ends of the catheters 6 and pumped to a pre-determined pressure such that each balloon 4 is pressurized equally for purposes of coating. A separate gas supply and pneumatics can be coupled for inflation of individual balloons 4 or simultaneous inflation of multiple balloons 4 during production. No limitations are intended.

Drug-Eluting Coatings

[0044] Composite coatings deposited to surfaces of expandable medical devices in conjunction with the invention using modified e-RESS and e-STAT processes can include various combinations of polymers and drugs in one or more coating layers that define the composite coating. Transferable deposits of the present invention prepared on the surfaces of expandable medical devices are preferably, but not exclusively, drug-eluting materials. The components of these composite coatings are subsequently transferred from the medical device to a specific location in a vessel (e.g., an artery) or other vascular location within a patient or host by activation or inflation of the balloons. Drugs and other therapeutic agents present in the various layers of the composite coating transferred are needed, thereby effecting treatment. Inclusion of a time-released drug or drugs in the transferred coating provides medical intervention or treatment at the delivery site over time (e.g., in a time-released fashion). The present invention further provides target delivery of a drug or drugs without need for long-term retention of the delivery device (i.e., the medical balloon or a stent) within the patient or host.

[0045] In one embodiment, the drug-eluting coating of transferrable material includes a drug that is dispersed in a matrix consisting of a biosorbable polymer that allows the drug to be deployed in a time-released fashion to a target location within the vascular system of the patient or host. In a preferred embodiment, the coating on the balloon that is completely or partially transferred to the vessel wall when deployed in the host vessel includes at least one layer that includes at least one drug. The coating may also include at least one biosorbable polymer (e.g., PLGA) in a single layer or in different layers. Tests conducted using medical-grade tubing as vessel surrogates and on test animals at conditions similar to those found in a human body have demonstrated that coating components collected on the surface of medical balloons using the above-described methods are successfully transferred to the inner vessel walls, forming a drug-eluting deposit within these specimens as detailed hereafter.

Polymer Coating Materials

[0046] In some embodiments, coating particles can include various materials selected from, e.g., polymers, drugs, biosorbable materials, bioactive proteins and peptides, as well as combinations of these materials. These materials find use in coatings that are applied to, e.g., medical devices (e.g., medical balloons) and medical implant devices (e.g., drug-eluting stents), but are not limited thereto. Choice for near-critical or supercritical fluid is based on the solubility of the selected solute(s) of interest, which is not limited.

[0047] Polymers used in conjunction with various embodiments include, but are not limited to, e.g., polylactoglycolic acid (PLGA); polyethylene vinyl acetate (PEVA); poly(butyl methacrylate) (PBMA); perfluorooctanoic acid (PFOA); tetrafluoroethylene (TFE); hexafluoropropylene (HFP); polylactic acid (PLA); polyglycolic acid (PGA); including combinations of these polymers. Other polymers include various mixtures of tetrafluoroethylene; hexafluoropropylene; and vinylidene fluoride (e.g., THV) at varying molecular ratios (e.g., 1:1:1).

[0048] Biosorbable polymers used in conjunction in some embodiments include, but are not limited to, e.g., polylactic acid (PLA); poly(DL-lactide-co-glycolide) (PLGA); poly(lactic-co-glycolic acid); polycaprolactone (poly(ϵ -caprolactone)) (PCL); polyglycolide (PG) or (PGA); poly-3-hydroxybutyrate; LPLA poly(L-lactide); DLPLA poly(DL-lactide); PDO poly(dioxolane); PGA-TMC; 85/15 DLPLG poly(DL-lactide-co-glycolide); 75/25 DLPL; 65/35 DLPLG; 50/50 DLPLG; TMC poly(trimethylcarbonate); poly(CPP:SA); poly(1,3-bis-p-(carboxyphenoxy)propane-co-sebacic acid); and blends; combinations; homopolymers; condensation polymers; alternating; block; dendritic; crosslinked; and copolymers thereof.

[0049] Durable (biostable) polymers used in some embodiments include, but are not limited to, e.g., polyester; aliphatic polyester; polyanhydride; polyethylene; polyorthoester; polyphosphazene; polyurethane; polycarbonate urethane; aliphatic polycarbonate; silicone; a silicone-containing polymer; polyolefin; polyamide; polycaprolactam; polyamide; polyvinyl alcohol; acrylic polymer; acrylate; polystyrene; epoxy; polyethers; cellulotics; expanded polytetrafluoroethylene; phosphorylcholine; polyethylene-terephthalate; polymethylmethacrylate; poly(ethylmethacrylate/n-butylmethacrylate); parylene C; polyethylene-co-vinyl acetate; polyalkyl methacrylates; polyalkylene-co-vinyl acetate; polyalkylene; polyalkyl siloxanes; polyhydroxyalkanoate; polyfluoroalkoxyphosphazene; poly(styrene-b-isobutylene-b-styrene); poly-butyl methacrylate; poly-buta-diene; and blends; combinations; homopolymers; condensation polymers; alternating; block; dendritic; crosslinked; and copolymers thereof. Other polymers selected for use can include polymers to which drugs

are chemically (e.g., ionically and/or covalently) attached or otherwise mixed, including, but not limited to, e.g., heparin-containing polymers (HCP).

Drugs/Drug Delivery

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[0050] In various embodiments, time-released drugs are delivered to a wall of a vascular vessel (e.g., an artery) within a host or patient using a coating comprised of one or more coating layers. Coating layers can include various therapeutic agents in various combinations including, e.g., biosorbable polymers and drugs that are deposited onto the surface of, e.g., expandable
10 polymer devices (e.g., a medical balloon). The expandable polymer device is subsequently transferred to, and deployed within the vascular system of a host or patient as detailed herein.

[0051] Drugs used in conjunction with various embodiments include, but are not limited to, e.g., antibiotics (e.g., Rapamycin [CAS No. 53123-88-9], LC Laboratories, Woburn, MA, USA, anticoagulants (e.g., Heparin [CAS No. 9005-49-6]; antithrombotic agents (e.g.,
15 clopidogrel); antiplatelet drugs (e.g., aspirin); immunosuppressive drugs; antiproliferative drugs; chemotherapeutic agents (e.g., paclitaxel also known by the tradename TAXOL® [CAS No. 33069-62-4], Bristol-Myers Squibb Co., New York, NY, USA) and/or a pro-drug, a derivative, an analog, a hydrate, an ester, and/or a salt thereof). Examples of antibiotics include, but are not limited to, e.g., amikacin, amoxicillin, gentamicin, kanamycin, neomycin, netilmicin,
20 paromomycin, tobramycin, geldanamycin, herbimycin, carbacephem (loracarbef), ertapenem, doripenem, imipenem, cefadroxil, cefazolin, cefalotin, cephalixin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftobiprole, clarithromycin, clavulanic acid, clindamycin, teicoplanin, azithromycin, dirithromycin,
25 erythromycin, troleandomycin, telithromycin, aztreonam, ampicillin, azlocillin, bacampicillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, meticillin, nafcillin, norfloxacin, oxacillin, penicillin-G, penicillin-V, piperacillin, pivampicillin, pivmecillinam, ticarcillin, bacitracin, colistin, polymyxin-B, ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, afenide,
30 prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfamethoxazole, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole, demeclocycline, doxycycline, oxytetracycline, tetracycline, arspenamine, chloramphenicol, lincomycin, ethambutol, fosfomycin, furazolidone, isoniazid, linezolid, mupirocin, nitrofurantoin, platensimycin, pyrazinamide, quinupristin/dalfopristin, rifampin, thiamphenicol, rifampicin, minocycline, sultamicillin,
35 sulbactam, sulphonamides, mitomycin, spectinomycin, spiramycin, roxithromycin, and

meropenem. Antibiotics can also be grouped into classes of related drugs, for example, aminoglycosides (e.g., amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin), ansamycins (e.g., geldanamycin, herbimycin), carbacephem (loracarbef) carbapenems (e.g., ertapenem, doripenem, imipenem, meropenem), first generation
 5 cephalosporins (e.g., cefadroxil, cefazolin, cefalotin, cefalexin), second generation cephalosporins (e.g., cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime), third generation cephalosporins (e.g., cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone), fourth generation cephalosporins (e.g., cefepime), fifth generation cephalosporins (e.g., ceftobiprole), glycopeptides (e.g., teicoplanin,
 10 vancomycin), macrolides (e.g., azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spectinomycin), monobactams (e.g., aztreonam), penicillins (e.g., amoxicillin, ampicillin, azlocillin, bacampicillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, meticillin, nafcillin, oxacillin, penicillins-G and -V, piperacillin, pivampicillin, pivmecillinam, ticarcillin), polypeptides (e.g., bacitracin, colistin,
 15 polymyxin-B), quinolones (e.g., ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, trovafloxacin), sulfonamides (e.g., afenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfamethoxazole, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole), tetracyclines (e.g., demeclocycline, doxycycline, minocycline,
 20 oxytetracycline, tetracycline).

[0052] Drugs used in some embodiments described herein include, but are not limited to, e.g., immunosuppressive drugs such as a macrolide immunosuppressive drug, which may comprise one or more of: rapamycin; biolimus (biolimus A9); 40-O-(2-Hydroxyethyl)rapamycin (everolimus); 40-O-Benzyl-rapamycin; 40-O-(4'-Hydroxymethyl)benzyl-rapamycin; 40-O-[4'-
 25 (1,2-Dihydroxyethyl)]benzyl-rapamycin; 40-O-Allyl-rapamycin; 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin; (2'E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin; 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin; 40-O-(3-Hydroxy)propyl-rapamycin; 40-O-(6-Hydroxy)hexyl-rapamycin; 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin; 40-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin; 40-O-[(2S)-2,3-Dihydroxyprop-1-
 30 yl]-rapamycin; 40-O-(2-Acetoxy)ethyl-rapamycin; 40-O-(2-Nicotinoyloxy)ethyl-rapamycin; 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin; 40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin; 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin; 39-O-Desmethyl-39_40-O,O-ethylene-rapamycin; (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin; 28-O-Methyl-rapamycin; 40-O-(2-Aminoethyl)-rapamycin; 40-O-(2-Acetaminoethyl)-rapamycin; 40-O-(2-Nicotinamidoethyl)-rapamycin; 40-O-(2-(N-Methyl-imidazo-2'-yl)carbethoxamido)ethyl)-

rapamycin; 40-O-(2-Ethoxycarbonylaminoethyl)-rapamycin; 40-O-(2-Tolylsulfonamidoethyl)-rapamycin; 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin; 42-Epi-(tetrazolyl)rapamycin (tacrolimus); 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus); (42S)-42-Deoxy-42-(1H-tetrazol-1-yl)-rapamycin (zotarolimus); and salts, derivatives, isomers, racemates, diastereoisomers, pro-drugs, hydrates, esters, or analogs thereof.

[0053] Drugs used in various embodiments described further herein include, but are not limited to, e.g., Acarbose; acetylsalicylic acid; acyclovir; allopurinol; alprostadil; prostaglandins; amantadine; ambroxol; amlodipine; S-aminosalicylic acid; amitriptyline; atenolol; azathioprine; balsalazide; beclomethasone; betahistine; bezafibrate; diazepam and diazepam derivatives; budesonide; bufexamac; buprenorphine; butizine; methadone; calcium salts; potassium salts; magnesium salts; candesartan; carbamazepine; captopril; cetirizine; chenodeoxycholic acid; theophylline and theophylline derivatives; trypsin; cimetidine; clobutinol; clonidine; cotrimoxazole; codeine; caffeine; vitamin D and derivatives of vitamin D; colestyramine; cromoglicic acid; coumarin and coumarin derivatives; cysteine; ciclosporin; cyproterone; cytabarine; dapiprazole; desogestrel; desonide; dihydralazine; diltiazem; ergot alkaloids; dimenhydrinate; dimethyl sulphoxide; dimeticone; domperidone and domperidan derivatives; dopamine; doxazosin; doxylamine; benzodiazepines; diclofenac; desipramine; econazole; ACE inhibitors; enalapril; ephedrine; epinephrine; epoetin and epoetin derivatives; morphinans; calcium antagonists; modafinil; orlistat; peptide antibiotics; phenytoin; riluzoles; risedronate; sildenafil; topiramate; estrogen; progestogen and progestogen derivatives; testosterone derivatives; androgen and androgen derivatives; ethebamide; etofenamate; etofibrate; fenofibrate; etofylline; famciclovir; famotidine; felodipine; fentanyl; fenticonazole; gyrase inhibitors; fluconazole; fluarizine; fluoxetine; flurbiprofen; ibuprofen; fluvastatin; follitropin; formoterol; fosfomicin; furosemide; fusidic acid; gallopamil; ganciclovir; gemfibrozil; ginkgo; Saint John's wort; glibenclamide; urea derivatives as oral antidiabetics; glucagon; glucosamine and glucosamine derivatives; glutathione; glycerol and glycerol derivatives; hypothalamus hormones; guanethidine; halofantrine; haloperidol; heparin (and derivatives); hyaluronic acid; hydralazine; hydrochlorothiazide (and derivatives); salicylates; hydroxyzine; imipramine; indometacin; indoramine; insulin; iodine and iodine derivatives; isoconazole; isoprenaline; glucitol and glucitol derivatives; itraconazole; ketoprofen; ketotifen; lacidipine; lansoprazole; levodopa; levomethadone; thyroid hormones; lipoic acid (and derivatives); lisinopril; lisuride; lofepramine; loperamide; loratadine; maprotiline; mebendazole; mebeverine; meclozine; mefenamic acid; mefloquine; meloxicam; mepindolol; meprobamate; mesalazine; mesuximide; metamazole; metformin; methylphenidate; metixene; metoprolol; metronidazole; mianserin;

miconazole; minoxidil; misoprostol; mizolastine; moexipril; morphine and morphine derivatives; evening primrose; nalbuphine; naloxone; tilidine; naproxen; narcotine; natamycin; neostigmine; nicergoline; nicethamide; nifedipine; niflumic acid; nimodipine; nimorazole; nimustine; nisoldipine; adrenaline and adrenaline derivatives; novamine sulfone; noscapine;

5 nystatin; olanzapine; olsalazine; omeprazole; omoconazole; oxaceprol; oxiconazole; oxymetazoline; pantoprazole; paracetamol (acetaminophen); paroxetine; penciclovir; pentazocine; pentifylline; pentoxifylline; perphenazine; pethidine; plant extracts; phenazone; pheniramine; barbituric acid derivatives; phenylbutazone; pimozone; pindolol; piperazine; piracetam; pirenzepine; piribedil; piroxicam; pramipexole; pravastatin; prazosin; procaine;

10 promazine; propiverine; propranolol; propyphenazone; protionamide; proxyphylline; quetiapine; quinapril; quinaprilat; ramipril; ranitidine; reproterol; reserpine; ribavirin; risperidone; ritonavir; ropinirole; roxatidine; ruscogenin; rutoside (and derivatives); sabadilla; salbutamol; salmeterol; scopolamine; selegiline; sertaconazole; sertindole; sertraline; silicates; simvastatin; sitosterol; sotalol; spaglumic acid; spirapril; spironolactone; stavudine; streptomycin; sucralfate; sufentanil;

15 sulfasalazine; sulpiride; sultiam; sumatriptan; suxamethonium chloride; tacrine; tacrolimus; talinolol; taurolidine; temazepam; tenoxicam; terazosin; terbinafine; terbutaline; terfenadine; terlipressin; tertatolol; teryzoline; theobromine; thiamazole; phenothiazines; tiagabine; tiapride; propionic acid derivatives; ticlopidine; timolol; tinidazole; tioconazole; tioguanine; tioxolone; tiopramide; tizanidine; tolazoline; tolbutamide; tolcapone; tolnaftate; tolperisone; topotecan;

20 torasemide; tramadol; tramazoline; trandolapril; tranlycypromine; trapidil; trazodone; triamcinolone derivatives; triamterene; trifluoperidol; trifluridine; trimipramine; tripelennamine; triprolidine; trifosfamide; tromantadine; trometamol; tropalpin; troxerutine; tulobuterol; tyramine; tyrothricin; urapidil; valaciclovir; valproic acid; vancomycin; vecuronium chloride; Viagra; venlafaxine; verapamil; vidarabine; vigabatrin; viloazine; vincamine; vinpocetine;

25 viquidil; warfarin; xantinol nicotinate; xipamide; zafirlukast; zalcitabine; zidovudine; zolmitriptan; zolpidem; zopiclone; zotipine; amphotericin B; caspofungin; voriconazole; resveratrol; PARP-1 inhibitors (including imidazoquinolinone; imidazopyridine; and isoquinolindione); tissue plasminogen activator (tPA); melagatran; lanoteplase; reteplase; staphylokinase; streptokinase; tenecteplase; urokinase; abciximab (ReoPro); eptifibatide;

30 tirofiban; prasugrel; clopidogrel; dipyridamole; cilostazol; VEGF; heparan sulfate; chondroitin sulfate; elongated "RGD" peptide binding domain; CD34 antibodies; cerivastatin; etorvastatin; losartan; valartan; erythropoietin; rosiglitazone; pioglitazone; mutant protein Apo A1 Milano; adiponectin; (NOS) gene therapy; glucagon-like peptide 1; atorvastatin; and atrial natriuretic peptide (ANP); lidocaine; tetracaine; dibucaine; hyssop; ginger; turmeric; Arnica montana;

helenalin; cannabichromene; rofecoxib; hyaluronidase; and salts, derivatives, isomers, racemates, diastereoisomers, prodrugs, hydrates, esters, or analogs thereof.

Anti-thrombotic agents

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[0054] Anti-thrombotic agents (e.g., clopidogrel) are also contemplated for use in the methods and devices described herein. Use of anti-platelet drugs (e.g., aspirin), for example, to prevent platelet binding to exposed collagen, is contemplated for anti-restenotic or anti-thrombotic therapy. Anti-platelet agents include “GpIIb/IIIa inhibitors” (e.g., abciximab, eptifibatide, tirofiban, RheoPro) and “ADP receptor blockers” (prasugrel, clopidogrel, ticlopidine). Particularly useful for local therapy are dipyridamole, which has local vascular effects that improve endothelial function (e.g., by causing local release of t-PA, that will break up clots or prevent clot formation) and reduce the likelihood of platelets and inflammatory cells binding to damaged endothelium, and cAMP phosphodiesterase inhibitors, e.g., cilostazol, that could bind to receptors on either injured endothelial cells or bound and injured platelets to prevent further platelet binding.

Chemotherapeutic agents

[0055] Chemotherapeutic agents may also be used. Examples of chemotherapeutic agents include, but are not limited to, e.g., angiostatin; DNA topoisomerase; endostatin; genistein; ornithine decarboxylase inhibitors; chlormethine; melphalan; pipobroman; triethylene-melamine; triethylenethiophosphoramine; busulfan; carmustine (BCNU); streptozocin; 6-mercaptopurine; 6-thioguanine; deoxyco-formycin; IFN- α ; 17 α -ethinylestradiol; diethylstilbestrol; testosterone; prednisone; fluoxymesterone; dromostanolone propionate; testolactone; megestrolacetate; methylprednisolone; methyl-testosterone; prednisolone; triamcinolone; chlorotrianisene; hydroxyprogesterone; estramustine; medroxyprogesteroneacetate; flutamide; zoladex; mitotane; hexamethylmelamine; indolyl-3-glyoxylic acid derivatives; (e.g., indibulin); doxorubicin and idarubicin; plicamycin (mithramycin) and mitomycin; mechlorethamine; cyclophosphamide analogs; trazenes-dacarbazine (DTIC); pentostatin and 2-chlorodeoxyadenosine; letrozole; camptothecin (and derivatives); navelbine; erlotinib; capecitabine; acivicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; ambomycin; ametantrone acetate; anthramycin; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bisnafide; bisnafide dimesylate; bizelesin; bropiramine; cactinomycin; calusterone; carbetimer; carubicin

hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); cirolemycin; crisnatol mesylate; decitabine; dexormaplatin; dezaguanine mesylate; diaziquone; duazomycin; edatrexate; eflomithine; elsamitrucin; enloplatin; enpromate; epipropidine; erbulozole; etanidazole; etoprine; flurocitabine; fosquidone; lometrexol; losoxantrone hydrochloride;

5 masoprocol; maytansine; megestrol acetate; melengestrol acetate; metoprine; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitosper; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; perfosfamide; piposulfan; plomestane; porfimer sodium; porfiromycin; puromycin; pyrazofurin; riboprine; safingol; simtrazene; sparfosate sodium; spiromustine; spiroplatin; streptonigrin;

10 sulofenur; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; thiamiprine; tirapazamine; trestolone acetate; triciribine phosphate; trimetrexate glucuronate; tubulozole hydrochloride; uracil mustard; uredepa; verteporfin; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; zeniplatin; zinostatin; 20-epi-1,25 dihydroxyvitamin-D3; 5-ethynyluracil; acylfulvene; adecypenol; ALL-TK antagonists;

15 ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; anagrelide; andrographolide; antagonist-D; antagonist-G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen; antiestrogen; estrogen agonist; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin-1; axinastatin-2; axinastatin-3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; BCR/ABL antagonists; benzochlorins;

20 benzoylstauosporine; beta lactam derivatives; beta-alethine; betaclamycin-B; betulinic acid; bFGF inhibitor; bisaziridinylspermine; bistratene-A; breflate; buthionine sulfoximine; calcipotriol; calphostin-C; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; clomifene

25 analogues; clotrimazole; collismycin-A; collismycin-B; combretastatin-A4; combretastatin analogue; conagenin; crambescidin-816; cryptophycin-8; cryptophycin-A derivatives; curacin-A; cyclopentantraquinones; cycloplatam; cypemycin; cytolytic factor; cytostatin; dacliximab; dehydrodidemnin B; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; didemnin-B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol; docosanol;

30 dolasetron; dronabinol; duocarmycin-SA; ebselen; ecomustine; edelfosine; edrecolomab; elemene; emitefur; estramustine analogue; filgrastim; flavopiridol; flezelastine; fluasterone; fluorodaunorubicin hydrochloride; forfenimex; gadolinium texaphyrin; galocitabine; gelatinase inhibitors; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idramantone; ilomastat; imatinib (e.g., Gleevec); imiquimod; immunostimulant

35 peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons;

interleukins; iobenguane; iododoxorubicin; ipomeanol; iroplact; irsogladine; isobengazole; isohomohalicondrin-B; itasetron; jasplakinolide; kahalalide-F; lamellarin-N triacetate; leinamycin; lenograstim; lentinan sulfate; leptolstatin; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide-7; lobaplatin; lombricine; 5 loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin-A; marimastat; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitotoxin fibroblast growth factor-saporin; mofarotene; molgramostim; Erbitux; 10 human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mustard anticancer agent; mycaperoxide-B, mycobacterial cell wall extract, myriaporone, N-acetyldinaline, N-substituted benzamides, nagrestip, naloxone+pentazocine, napavin, naphterpin, nartograstim, nedaplatin, nemorubicin, neridronic acid, nisamycin, nitric oxide modulators, nitroxide antioxidant, nitrullyn, oblimersen (Genasense), O6-benzylguanine, 15 okicenone, onapristone, ondansetron, oracin, oral cytokine inducer, paclitaxel analogues and derivatives, palauamine, palmitoylrhizoxin, pamidronic acid, panaxytriol, panomifene, parabactin, peldesine, pentosan polysulfate sodium, pentrozole, perflubron, perillyl alcohol, phenazinomycin, phenylacetate, phosphatase inhibitors, picibanil, pilocarpine hydrochloride, placetin-A, placetin-B, plasminogen activator inhibitor, platinum complex, platinum compounds, platinum-triamine complex, propyl bis-acridone, prostaglandin-J2, proteasome 20 inhibitors, protein A-based immune modulator, protein kinase-C inhibitors, microalgal, pyrazoloacridine, pyridoxylated hemoglobin polyoxyethylene conjugate, raf antagonists, raltitrexed, ramosetron, ras farnesyl protein transferase inhibitors, ras-GAP inhibitor, retelliptine demethylated, rhenium Re-186 etidronate, ribozymes, RII retinamide, rohitukine, romurtide, 25 roquinimex, rubiginone-B1, ruboxyl, saintopin, SarCNU, sarcophytol A, sargramostim, Sdi-1 mimetics, senescence derived inhibitor-1, signal transduction inhibitors, sizofiran, sobuzoxane, sodium borocaptate, solverol, somatomedin binding protein, sonermin, sparfosic acid, spicamycin-D, splenopentin, spongistatin-1, squalamine, stipiamide, stromelysin inhibitors, sulfinosine, superactive vasoactive intestinal peptide antagonist, suradista, suramin, 30 swainsonine, tallimustine, tazarotene, tellurapyrylium, telomerase inhibitors, tetrachlorodecaoxide, tetrazomine, thiocoraline, thrombopoietin, thrombopoietin mimetic, thymalfasin, thymopoietin receptor agonist, thymotrigan, thyroid stimulating hormone, tin ethyl etiopurpurin, titanocene bichloride, topsentin, translation inhibitors, tretinoin, triacetyluridine, tropisetron, turosteride, ubenimex, urogenital sinus-derived growth inhibitory factor, variolin-B, 35 velaresol, veramine, verdins, vinxaltine, vitaxin, zanoterone, zilascorb, zinostatin stimalamer,

acanthifolic acid, aminothiadiazone, anastrozole, bicalutamide, brequinar sodium, capecitabine, carmofur, Ciba-Geigy CGP-30694, cladribine, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, cytarabine ocfosphate, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine,

5 Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine, fludarabine phosphate, N-(2'-furanidyl)-5--fluorouracil, Daiichi Seiyaku FO-152, 5-FU-fibrinogen, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, nolvadex, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi

10 Chemical PL-AC, stearate, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT, uricytin, Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine (BiCNU), Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid

15 CL-286558, Sanofi CY-233, cyplatate, dacarbazine, Degussa D-19-384, Sumimoto DACHP(Myrr)2, diphenylspiromustine, diplatinum cytostatic, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, etoposide phosphate, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, mycophenolate, Nippon Kayaku NK-121, NCI NSC-

20 264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, thiotepa, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol, Taiho 4181-A, aclarubicin, actinomycin-D, actinoplanone, Erbamont ADR-456, aerophysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins,

25 anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, caliche mycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B,

30 Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American

35 Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitomycin analogues,

mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomycin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, 5 sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thiazine, 10 tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024, zorubicin, 5-fluorouracil (5-FU), the peroxidate oxidation product of inosine, adenosine, or cytidine with methanol or ethanol, cytosine arabinoside (also referred to as 10 Cytarabin, araC, and Cytosar), 5-Azacytidine, 2-Fluoroadenosine-5'-phosphate (Fludara, also referred to as FaraA), 2-Chlorodeoxyadenosine, Abarelix, Abbott A-84861, Abiraterone acetate, Aminoglutethimide, Asta Medica AN-207, Antide, Chugai AG-041R, Avorelin, aseranox, Sensus B2036-PEG, buserelin, BTG CB-7598, BTG CB-7630, Casodex, cetrolis, clastroban, clodronate disodium, Cosudex, Rotta Research CR-1505, cytadren, crinone, deslorelin, 15 droloxifene, dutasteride, Elimina, Laval University EM-800, Laval University EM-652, epitiostanol, epristeride, Mediolanum EP-23904, EntreMed 2-ME, exemestane, fadrozole, finasteride, formestane, Pharmacia & Upjohn FCE-24304, ganirelix, goserelin, Shire gonadorelin agonist, Glaxo Wellcome GW-5638, Hoechst Marion Roussel Hoe-766, NCI hCG, idoxifene, isocordoin, Zeneca ICI-182780, Zeneca ICI-118630, Tulane University J015X, 20 Schering Ag J96, ketanserin, lanreotide, Milkhaus LDI-200, letrozol, leuprolide, leuprorelin, liarozole, lisuride hydrogen maleate, loxiglumide, mepitiostane, Ligand Pharmaceuticals LG-1127, LG-1447, LG-2293, LG-2527, LG-2716, Bone Care International LR-103, Lilly LY-326315, Lilly LY-353381-HCl, Lilly LY-326391, Lilly LY-353381, Lilly LY-357489, miproxifene phosphate, Orion Pharma MPV-2213ad, Tulane University MZ-4-71, nafarelin, 25 nilutamide, Snow Brand NKS01, Azko Nobel ORG-31710, Azko Nobel ORG-31806, orimeten, orimetene, orimetine, ormeloxifene, osaterone, Smithkline Beecham SKB-105657, Tokyo University OSW-1, Peptech PTL-03001, Pharmacia & Upjohn PNU-156765, quinagolide, ramorelix, Raloxifene, statin, sandostatin LAR, Shionogi S-10364, Novartis SMT-487, somavert, somatostatin, tamoxifen, tamoxifen methiodide, teverelix, toremifene, triptorelin, TT- 30 232, vapreotide, vorozole, Yamanouchi YM-116, Yamanouchi YM-511, Yamanouchi YM-55208, Yamanouchi YM-53789, Schering AG ZK-1911703, Schering AG ZK-230211, and Zeneca ZD-182780, alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphetinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston-A10, antineoplaston-A2, antineoplaston-A3, antineoplaston-A5, 35 antineoplaston-AS2-1, Henkel-APD, aphidicolin glycinate, asparaginase, Avarol, baccharin,

batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, calcium carbonate, Calcet, Calci-Chew, Calci-Mix, Roxane calcium carbonate tablets, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, 5 Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Cell Pathways CP-461, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytosytin, Merz D-609, DABIS maleate, datelliptinium, DFMO, didemnin-B, dihaematoporphyrin ether, dihydrolenperone dinaline, distamycin, Toyo Pharmar DM-341, 10 Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel, Encore Pharmaceuticals E7869, elliprabine, elliptinium acetate, Tsumura EPMTc, ergotamine, etoposide, etretinate, Eulexin, Cell Pathways Exisulind (sulindac sulphone or CP-246), fenretinide, Florical, Fujisawa FR-57704, gallium nitrate, gemcitabine, genkwadaphnin, Gerimed, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, 15 hydroxyurea, BTG ICRF-187, ilmofofosine, irinotecan, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, ketoconazole, Otsuka K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leucovorin, levamisole, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, Materna, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, megestrol, merbarone, merocyanine derivatives, methylanilinoacridine, 20 Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, Monocal, mopidamol, motretinide, Zenyaku Kogyo MST-16, Mylanta, N-(retinoyl)amino acids, Nilandron, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, Nephro-Calci tablets, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, 25 paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide-D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, retinoids, R-flurbiprofen (Encore Pharmaceuticals), Sandostatin, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, 30 Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, Scherring-Plough SC-57050, Scherring-Plough SC-57068, selenium (selenite and selenomethionine), SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, Sugan SU-101, Sugan SU-35 5416, Sugan SU-6668, sulindac, sulindac sulfone, superoxide dismutase, Toyama T-506,

Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine, vinblastine sulfate, vincristine, vincristine sulfate, vindesine, vindesine sulfate, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides, Yamanouchi YM-534, Zileuton, ursodeoxycholic acid, Zanosar. Drug choices are not intended to be limited. For example, coatings on medical devices can include drugs used in time-release drug applications. Proteins may be coated according to these methods and coatings described herein may comprise proteins. Peptides may be coated according to these methods and coatings described herein may comprise peptides.

Releasing Agents

[0056] In some embodiments, coating particles can include releasing agents, which may include low-energy releasing agents (also called low-energy release agents). Releasing agents may also be called a “release agent.” These materials find use in coatings that are applied to, e.g., medical devices (e.g., medical balloons) and medical implant devices (e.g., drug-eluting stents), but are not limited thereto. Choice for near-critical or supercritical fluid is based on the solubility of the selected solute(s) of interest, which is not limited.

[0057] A release agent may comprise: hydrophilic or hydrophobic chemicals or polymers that lower the interfacial energy between the surface of the medical device and the coating layers, water soluble chemicals or polymers that dissolve to eliminate adhesion between coatings layers and the medical device surface, brittle or friable coatings that lose mechanical cohesion upon, Polyethylene glycols (PEG), Hydrogels, Polyesters, Polyacrylates, Polysaccharides, Silicones, Silanes, Tocopherol, Glycerin, Sucrose, Cellulose, and Shellac.

[0058] A low-energy releasing agents may be a subset of the larger set of releasing agents. A releasing agent that is “low-energy” may be defined as a releasing agent with surface energy of less than 35 dynes/cm or agents onto which a drop of water would experience a contact angle of greater than 90 degrees. Examples of low-energy releasing agents include (but are not limited to): Polyvinyl alcohols (PVA), Ethylene vinyl acetates (EVA), Polyolefins, Fluorosilanes, Fluoroacrylates, Fluorohydrocarbons, Paraffin, and Long chain hydrocarbons.

Adhesive Agents

[0059] In some embodiments, coating particles can include adhesive agents that serve to affix the balloon coating to a receiving surface when the surface is contacted. Adhesive agents

may comprise any one or more of the following: agents with cationic moieties that assist in cellular adhesion/uptake, shattering agents that penetrate tissue surface and promote adhesion through mechanical entanglement, viscous polymeric agents, and cationic polyamino acids. Cationic polyamino acids include, but are not limited to: polyarginine, polylysine, polyhistidine, and polyethyleneimine (PEI). Adhesive agents may comprise any one or more of the following: 3,4-dihydroxy-L-phenylalanine (dopa), (as in active component in mussel adhesive), laminins, and cationic surfactant molecules. Cationic surfactant molecules include, but are not limited to: didodecyldimethylammonium bromide (DMAB), ethylhexadecyldimethylammonium bromide, dodecyltrimethyl ammonium bromide, tetradodecylammonium bromide, dimethylditetradecylammonium bromide, tetrabutylammonium iodide, DEAE-dextran hydrochloride, and hexadimethrine bromide.

e-RESS Generated Coating Layers

[0060] FIG. 4 presents exemplary process steps for generating e-RESS coating layers on expandable medical balloons that deliver transferable, drug-eluting deposits at target locations within a host or patient, according to an embodiment of the invention. In a first step (405), a preselected solvent is intermixed with at least one coating material at a preselected pressure or temperature to form a supercritical solution. Next (410), the selected coating material is discharged from the supercritical solution through a restrictor nozzle (FIG. 1) as a RESS plume to form e-RESS charged coating particles at a preselected pressure and temperature. Next (415), the e-RESS generated charged coating particles are delivered to the surface of the balloon to form a coating layer containing the charged coating particles. In some embodiments, the particles are electrostatically attracted to the surface of the balloon either with or without the addition of an actively induced electrostatic field. In an optional step (420), the coating layer containing the charged coating particles is sintered to form a stable RESS film layer, e.g., on the surface of the balloon. Next (425), form one or more coating layers on the surface of the balloon using the e-RESS process.

e-STAT Generated coating Layers

[0061] FIG. 5 presents exemplary process steps for generating e-STAT coating layers as a component of drug-eluting coatings formed in accordance with an embodiment of the

invention. First **(505)**, a potential is applied to the conductive element located within the expandable medical balloon to generate a selected potential on the surface of the balloon as described herein. A potential of -15 kV is typical. However, potentials are not intended to be limited thereto. Next **(510)**, a preselected coating material is discharged as a plume of dry charged (e-STAT) coating particles in an inert discharge gas absent a solvent at a preselected pressure and temperature. Next **(515)**, the dry charged coating particles containing the preselected coating material are electrostatically attracted to the surface of the balloon to form a dry coating layer on the surface of the balloon. In some embodiments, the electrostatic attraction between the particles and the balloon surface is performed with or without the addition of an actively induced electrostatic field. In an optional step **(520)**, the coating layer containing the charged coating particles is sintered to form a stable e-STAT film layer on the surface of the balloon or to stabilize the e-STAT particles by fusing them to a previously deposited polymer layer. Next **(525)**, the e-STAT process is repeated as necessary to form one or more coating layers on the surface of the balloon.

Combined e-RESS/e-STAT Generated coating Layers

[0062] FIG. 6 presents exemplary process steps for generating combined e-RESS/e-STAT coating layers as a component of drug-eluting coatings formed in accordance with an embodiment of the invention. First **(605)**, e-RESS generated charged coating particles and/or e-STAT generated charged coating particles containing a preselected coating material are discharged in respective plumes at a preselected pressure and temperature. In some embodiments, the plumes containing the e-RESS and/or e-STAT generated charged coating particles can be discharged as separately in respective plumes or simultaneously in combined plumes in any order. No limitations are intended. Next **(610)**, the e-RESS and/or e-STAT charged coating particles containing the preselected coating material are delivered to the surface of the balloon to form one or more coating layers containing the charged coating particles on the surface of the balloon. In some embodiments, the particles are electrostatically attracted to the surface of the balloon either with or without the addition of an actively induced electrostatic field. In an optional step **(615)**, the e-RESS and/or e-STAT coating layers containing the charged coating particles are sintered to form stable coating layers on the surface of the balloon. Next **(620)**, one or more e-RESS and/or e-STAT coating layers are formed on the surface of the balloon using e-RESS and/or e-STAT processes performed individually, serially, or simultaneously.

Delivery of Coatings that Form Drug-Eluting Deposits

[0063] The transferable material or “portion of the coating” is delivered from the surface of the medical balloon to the target site within the vascular system of the patient or host by expanding the medical balloon within the receiving vessel (e.g., an artery or other vessel) at the location where the therapeutic drug or other therapeutic agent is needed. This process transfers the drug-eluting composite (or “material”) to the host vessel (e.g., artery or vein) providing treatment or medical intervention in the host or patient. In exemplary tests, coatings comprised of one or more layers including a biosorbable polymer and drug were successfully deployed within the vascular system of a host or patient. Delivery and placement of all or portions of a cylindrical coating consisting of a therapeutic drug (e.g., rapamycin) encapsulated in a biosorbable polymer matrix (e.g., PLGA) into a blood vessel can provide long-term treatment of, e.g., arterial disease in patients. The drug-eluting composite/material remains deployed within the host vessel after deflation and removal of the medical balloon. Drug is continuously provided in a time-released manner by the drug-eluting composite/material without need for a permanent medical device to be present in the body. The drug-eluting coating can continue to deliver a needed drug benefit over time.

[0064] FIG. 7 is a photomicrograph showing a polymer coating transferred from medical balloon onto the inner surface of medical-grade tubing (e.g., TYGON® medical tubing) that simulates transfer in an environment like those expected for delivery in mammalian hosts and human patients. The coating material was successfully transferred from the balloon surface to the inner wall (surface) of the medical tubing. The coating material on the surface of the medical balloon attaches to the host vessel upon expansion of the balloon. Removal and transfer of coating material from the balloon surface was effected in concert with a release layer composed of a low surface energy PTFE polymer (commercial-grade) that was deposited between the surface of the balloon and a first polymer layer prior to application of a subsequent PLGA polymer layer. So-called “release layers” are preferably, but not exclusively used. In the instant test, release was accomplished by inserting the coated balloon into TYGON® tubing, expanding the balloon at a temperature of 37 °C, and pressing the expanded balloon on the inner wall of the tubing for about 2 minutes at equilibrium, or for 1 minute at a pressure of about 250 psi while immersing in an aqueous bath. Pressure used in this test is comparable to pressures used to deploy medical balloons in typical medical procedures. Results showed the entire polymer coating deposited on the balloon surface was transferred to the inner wall of the tube, forming the polymer coating. The outermost layer of the transferable coating material that becomes the innermost layer of the transferred composite deposited in the vessel lumen is

preferably, but not exclusively, a coherent layer. The transferred material may further consist of partial or incomplete layers.

Effecting Net Charge of Transferred Material Surface

5

[0065] In other embodiments, release and transfer of the transferable coating material from the surface of the medical device to the vessel wall of the host or patient may be further enhanced by adding a net positive or net negative charge to the outermost surface of the transferable coating. This enhanced charge can also enhance attraction or otherwise promote
10 adhesion of the coating particles to the surface of the vessel wall to which the coating is delivered. Such charge can also promote uptake of the therapeutic agent present within the transferred coating material into various cells of the patient or host where tissue damage induced by balloon expansion can be treated. The outermost coating layer on the surface of the medical balloon is preferably, but not exclusively, charged with a net positive charge. In some
15 embodiments, a net positive charge enhances the attraction of the coating material on the surface of the expandable delivery device to the receiving surface of the host vessel. Although a positive net charge is described here, choice of charge is not limited. Tests on host vessel surrogates have demonstrated the ability to transfer polymer and drug coating materials at conditions similar to those found in a human body.

20 [0066] Provided herein is a method for forming an implantable, drug-eluting coating on the surface of an expandable medical device, characterized by the steps of: mounting an expandable delivery device with an internally disposed conducting member that maximizes conduction of charge on the surface of the device; delivering preselected potentials with the conducting member to the surface of the expandable delivery device to maximize collection of
25 coating particles on the surface thereof; and coating the expandable delivery device with coating particles delivered via an e-RESS process, and e-STAT process, or a combined e-RESS process and e-STAT process to form one or more coating layers on the surface thereof.

[0067] In some embodiments, the expandable delivery device is a medical balloon. In some embodiments, at least one coating layer of the expandable delivery device includes a
30 drug-eluting component and at least one coating layer includes a biosorbable polymer forming the implantable drug eluting coating on the surface of the device. In some embodiments, the medical balloon comprises nylon.

[0068] In some embodiments, the coating provides transfer of at least a portion of the one or more coating layers upon contact with a host vessel.

[0069] In some embodiments, wherein the expandable delivery device is at least a portion of a medical implant device. In some embodiments, the expandable delivery device is an interventional device. In some embodiments, the expandable delivery device is a diagnostic device. In some embodiments, the expandable delivery device is mounted to a delivery device prior to insertion into a host vessel. In some embodiments, the delivery device is a catheter.

[0070] In some embodiments, the conduction of charge on the surface is via gas-phase conduction or surface conduction of charge. In some embodiments, the delivering of preselected potentials includes delivering an active potential with the conducting component. In some embodiments, the delivering of preselected potentials does not include applying an active potential to the conducting component. In some embodiments, the delivering includes applying an electrostatic field potential on the surface of the expandable delivery device of at least about 15 kV prior to the coating step with the e-STAT process.

[0071] In some embodiments, the biosorbable polymer and drug eluting component are located within the same coating layer. In some embodiments, the coating includes coating the surface simultaneously with the e-RESS process and the e-STAT process to encapsulate a drug and a biosorbable polymer in a single layer of the drug-eluting coating.

[0072] In some embodiments, the drug-eluting component includes a drug dispersed within a biosorbable polymer disposed in a single coating layer. In some embodiments, the biosorbable polymer and drug-eluting component are located in different coating layers. In some embodiments, at least one coating layer includes a binding component comprising polylactoglycolic acid (PLGA).

[0073] In some embodiments, the expandable delivery device is at least partially expanded during coating of same.

[0074] In some embodiments, at least a portion of the biosorbable polymer has a preselected molecular weight that enhances transferability of the drug-eluting coating to the receiving surface within the host vessel. In some embodiments, the drug is a time-released drug that provides time-selectivity for treatment of a host or patient. In some embodiments, the drug has a crystalline form. In some embodiments, the drug comprises sirolimus.

[0075] In some embodiments, the coating includes masking one or more preselected portions of the expandable delivery device. In some embodiments, the masking includes forming preselected shapes selected from: oval, square, rectangle, triangular, or cylindrical within the coating layers on the surface of the expandable delivery device that contain an active drug delivered in the drug-eluting coating when in contact with the receiving surface.

[0076] In some embodiments, at least one coating layer includes a releasing agent selected from the group consisting of: hydrophilic or hydrophobic chemicals or polymers that

lower the interfacial energy between the surface of the medical device and the coating layers, water soluble chemicals or polymers that dissolve to eliminate adhesion between coatings layers and the medical device surface, brittle or friable coatings that lose mechanical cohesion upon, polyethylene glycols (PEG), hydrogels, polyesters, polyacrylates, polysaccharides, silicones, silanes, tocopherol, glycerin, sucrose, cellulose, shellac, and combinations thereof providing release of the coating to the receiving surface upon contact with same. In some embodiments, the releasing agent is located within a coating layer disposed between the surface of the expandable delivery device and a first layer comprising a biosorbable polymer.

[0077] In some embodiments, at least one coating layer on the surface of the expandable delivery device comprises a low-energy releasing agent selected from the group consisting of: a releasing agent with surface energy of less than 35 dynes/cm or agents onto which a drop of water would experience a contact angle of greater than 90 degrees, polyvinyl alcohols (PVA), ethylene vinyl acetates (EVA), polyolefins, fluorosilanes, fluoroacrylates, fluorohydrocarbons, paraffin, long chain hydrocarbons, and combinations thereof. In some embodiments, the low-energy releasing agent is located within a coating layer disposed between the surface of the expandable delivery device and a first layer comprising a biosorbable polymer.

[0078] In some embodiments, at least one coating layer on the surface of the expandable delivery device comprises an adhesive agent selected from the group consisting of: agents with cationic moieties that assist in cellular adhesion/uptake, shattering agents that penetrate tissue surface and promote adhesion through mechanical entanglement, viscous polymeric agents, and cationic polyamino acids such as polyarginine, polylysine, polyhistidine, and polyethyleneimine (PEI), 3,4-dihydroxy-L-phenylalanine (dopa), (as in active component in mussel adhesive), laminins, cationic surfactant molecules such as didodecyldimethylammonium bromide (DMAB), ethylhexadecyldimethylammonium bromide, dodecyltrimethyl ammonium bromide, tetradodecylammonium bromide, dimethylditetradecylammonium bromide, detrabutylammonium iodide, DEAE-dextran hydrochloride, and hexadimethrine bromide, and combinations thereof that affixes the transferable coating material to the receiving surface upon expansion of the expandable delivery device. In some embodiments, the transferable coating material includes an adhesion layer that enhances adhesion with the receiving surface. In some embodiments, the adhesive agent is included with the biosorbable polymer in a single coating layer on the surface of the expandable delivery device.

[0079] In some embodiments, at least one coating layer includes both the biosorbable polymer and a drug or therapeutic agent to provide timed-release delivery of the drug or therapeutic agent by dissolution of the biosorbable polymer layer within the coating material transferred to the host vessel. In some embodiments, the leading layer of the transferable coating

on the surface of the expandable delivery device contains therapeutic drug particles modified with a surface charge prior.

[0080] In some embodiments, the coating particles are of a size between about 0.01 micrometers and about 10 micrometers.

5 [0081] In some embodiments, the step of sintering the transferable coating material to form a dense, thermally stable film on the surface of the expandable delivery device prior to delivery of same at a temperature in the range from about 25 °C to about 150 °C.

[0082] In some embodiments, the sintering includes sintering the transferable coating material in the presence of a solvent gas to form a dense, thermally stable film on the surface of
10 the expandable delivery device.

[0083] In some embodiments, the method further includes the step of transferring at least a portion of the coating from the expandable delivery device to a receiving surface of a host vessel to form a drug-eluting deposit therein. In some embodiments, the transferring includes expanding the expandable delivery device to transfer and implant at least a portion of the drug-
15 eluting coating to the receiving surface of the host vessel. In some embodiments, the step of expanding includes expanding the expandable delivery device using a fluid that maintains rigidity and integrity of along the external surface of same. In some embodiments, the expanding includes at least partially deflating the expandable delivery device to reduce the physical dimensions of the expandable delivery device when inserting same into the host vessel
20 prior to transferring the coating to the receiving surface of the host vessel.

[0084] Provided herein are devices comprising the elements noted herein, which may be produced according to methods described herein.

[0085] While exemplary embodiments of the present invention have been shown and described herein, it will be apparent to those skilled in the art that many changes and
25 modifications may be made without departing from the invention in its true scope and broader aspects. The appended claims are therefore intended to cover all such changes and modifications as fall within the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A method for forming an implantable, drug-eluting coating on the surface of an expandable
5 medical device, characterized by the steps of:
 mounting an expandable delivery device with an internally disposed conducting member
 that maximizes conduction of charge on the surface of the device;
 delivering preselected potentials with the conducting member to the surface of the
 expandable delivery device to maximize collection of coating particles on the surface thereof;
10 and
2. coating the expandable delivery device with coating particles delivered via an e-RESS
process, and e-STAT process, or a combined e-RESS process and e-STAT process to form one
or more coating layers on the surface thereof.
3. The method of Claim 1, wherein the expandable delivery device is a medical balloon.
15 4. The method of Claim 2, wherein at least one coating layer of the expandable delivery device
includes a drug-eluting component and at least one coating layer includes a biosorbable polymer
forming the implantable drug eluting coating on the surface of the device.
5. The method of Claim 1, wherein the coating provides transfer of at least a portion of the one
or more coating layers upon contact with a host vessel
20 6. The method of Claim 2, where the medical balloon comprises nylon.
7. The method of Claim 1, wherein the expandable delivery device is at least a portion of a
medical implant device.
8. The method of Claim 1, wherein the expandable delivery device is an interventional device.
9. The method of Claim 1, wherein the expandable delivery device is a diagnostic device.
25 10. The method of Claim 1, wherein the expandable delivery device is mounted to a delivery
device prior to insertion into a host vessel.
11. The method of Claim 9, wherein the delivery device is a catheter.
12. The method of Claim 1, wherein the conduction of charge on the surface is via gas-phase
conduction or surface conduction of charge.
30 13. The method of Claim 1, wherein the delivering of preselected potentials includes delivering
an active potential with the conducting component.
14. The method of Claim 1, wherein the delivering of preselected potentials does not include
applying an active potential to the conducting component.

15. The method of Claim 1, wherein the delivering includes applying an electrostatic field potential on the surface of the expandable delivery device of at least about 15 kV prior to the coating step with the e-STAT process.
16. The method of Claim 1, wherein the biosorbable polymer and drug eluting component are
5 located within the same coating layer.
17. The method of Claim 1, wherein the coating includes coating the surface simultaneously with the e-RESS process and the e-STAT process to encapsulate a drug and a biosorbable polymer in a single layer of the drug-eluting coating.
18. The method of Claim 1, wherein the drug-eluting component includes a drug dispersed
10 within a biosorbable polymer disposed in a single coating layer.
19. The method of Claim 1, wherein the biosorbable polymer and drug-eluting component are located in different coating layers.
20. The method of Claim 1, wherein at least one coating layer includes a binding component comprising polylactoglycolic acid (PLGA).
- 15 21. The method of Claim 1, wherein the expandable delivery device is at least partially expanded during coating of same.
22. The method of Claim 1, wherein at least a portion of the biosorbable polymer has a preselected molecular weight that enhances transferability of the drug-eluting coating to the receiving surface within the host vessel.
- 20 23. The method of Claim 21, wherein the drug is a time-released drug that provides time-selectivity for treatment of a host or patient.
24. The method of Claim 21, wherein the drug has a crystalline form.
25. The method of Claim 21, wherein the drug comprises sirolimus.
26. The method of Claim 1, wherein the coating includes masking one or more preselected
25 portions of the expandable delivery device.
27. The method of Claim 25, wherein the masking includes forming preselected shapes selected from: oval, square, rectangle, triangular, or cylindrical within the coating layers on the surface of the expandable delivery device that contain an active drug delivered in the drug-eluting coating when in contact with the receiving surface.
- 30 28. The method of Claim 1, wherein at least one coating layer includes a releasing agent selected from the group consisting of: hydrophilic or hydrophobic chemicals or polymers that lower the interfacial energy between the surface of the medical device and the coating layers, water soluble chemicals or polymers that dissolve to eliminate adhesion between coatings layers and the medical device surface, brittle or friable coatings that lose mechanical cohesion upon,
35 polyethylene glycols (PEG), hydrogels, polyesters, polyacrylates, polysaccharides, silicones,

silanes, tocopherol, glycerin, sucrose, cellulose, shellac, and combinations thereof providing release of the coating to the receiving surface upon contact with same.

29. The method of Claim 27, wherein the releasing agent is located within a coating layer disposed between the surface of the expandable delivery device and a first layer comprising a

5 biosorbable polymer.

30. The method of Claim 1, wherein at least one coating layer on the surface of the expandable delivery device comprises a low-energy releasing agent selected from the group consisting of: a releasing agent with surface energy of less than 35 dynes/cm or agents onto which a drop of water would experience a contact angle of greater than 90 degrees, polyvinyl alcohols (PVA),

10 ethylene vinyl acetates (EVA), polyolefins, fluorosilanes, fluoroacrylates, fluorohydrocarbons, paraffin, long chain hydrocarbons, and combinations thereof.

31. The method of Claim 29, wherein the low-energy releasing agent is located within a coating layer disposed between the surface of the expandable delivery device and a first layer comprising a biosorbable polymer.

15 32. The method of Claim 1, wherein at least one coating layer on the surface of the expandable delivery device comprises an adhesive agent selected from the group consisting of: agents with cationic moieties that assist in cellular adhesion/uptake, shattering agents that penetrate tissue surface and promote adhesion through mechanical entanglement, viscous polymeric agents, and cationic polyamino acids such as polyarginine, polylysine, polyhistidine, and polyethyleneimine
20 (PEI), 3,4-dihydroxy-L-phenylalanine (dopa), (as in active component in mussel adhesive), laminins, cationic surfactant molecules such as didodecyldimethylammonium bromide (DMAB), ethylhexadecyldimethylammonium bromide, dodecyltrimethyl ammonium bromide, tetradodecylammonium bromide, dimethylditetradecylammonium bromide, detrabutylammonium iodide, DEAE-dextran hydrochloride, and hexadimethrine bromide, and
25 combinations thereof that affixes the transferable coating material to the receiving surface upon expansion of the expandable delivery device.

33. The method of Claim 31, wherein the transferable coating material includes an adhesion layer that enhances adhesion with the receiving surface.

30 34. The method of Claim 31, wherein the adhesive agent is included with the biosorbable polymer in a single coating layer on the surface of the expandable delivery device.

35. The method of Claim 1, wherein at least one coating layer includes both the biosorbable polymer and a drug or therapeutic agent to provide timed-release delivery of the drug or therapeutic agent by dissolution of the biosorbable polymer layer within the coating material transferred to the host vessel.

36. The method of Claim 1, wherein the leading layer of the transferable coating on the surface of the expandable delivery device contains therapeutic drug particles modified with a surface charge prior.

37. The method of Claim 1, wherein the coating particles are of a size between about 0.01

5 micrometers and about 10 micrometers.

38. The method of Claim 1, further including the step of sintering the transferable coating material to form a dense, thermally stable film on the surface of the expandable delivery device prior to delivery of same at a temperature in the range from about 25 °C to about 150 °C.

39. The method of Claim 1, wherein the sintering includes sintering the transferable coating material in the presence of a solvent gas to form a dense, thermally stable film on the surface of the expandable delivery device.

40. The method of Claim 1, further including the step of transferring at least a portion of the coating from the expandable delivery device to a receiving surface of a host vessel to form a drug-eluting deposit therein.

15 41. The method of Claim 39, wherein the transferring includes expanding the expandable delivery device to transfer and implant at least a portion of the drug-eluting coating to the receiving surface of the host vessel.

42. The method of Claim 40, wherein the step of expanding includes expanding the expandable delivery device using a fluid that maintains rigidity and integrity of along the external surface of same.

20 43. The method of Claim 40, wherein the expanding includes at least partially deflating the expandable delivery device to reduce the physical dimensions of the expandable delivery device when inserting same into the host vessel prior to transferring the coating to the receiving surface of the host vessel.

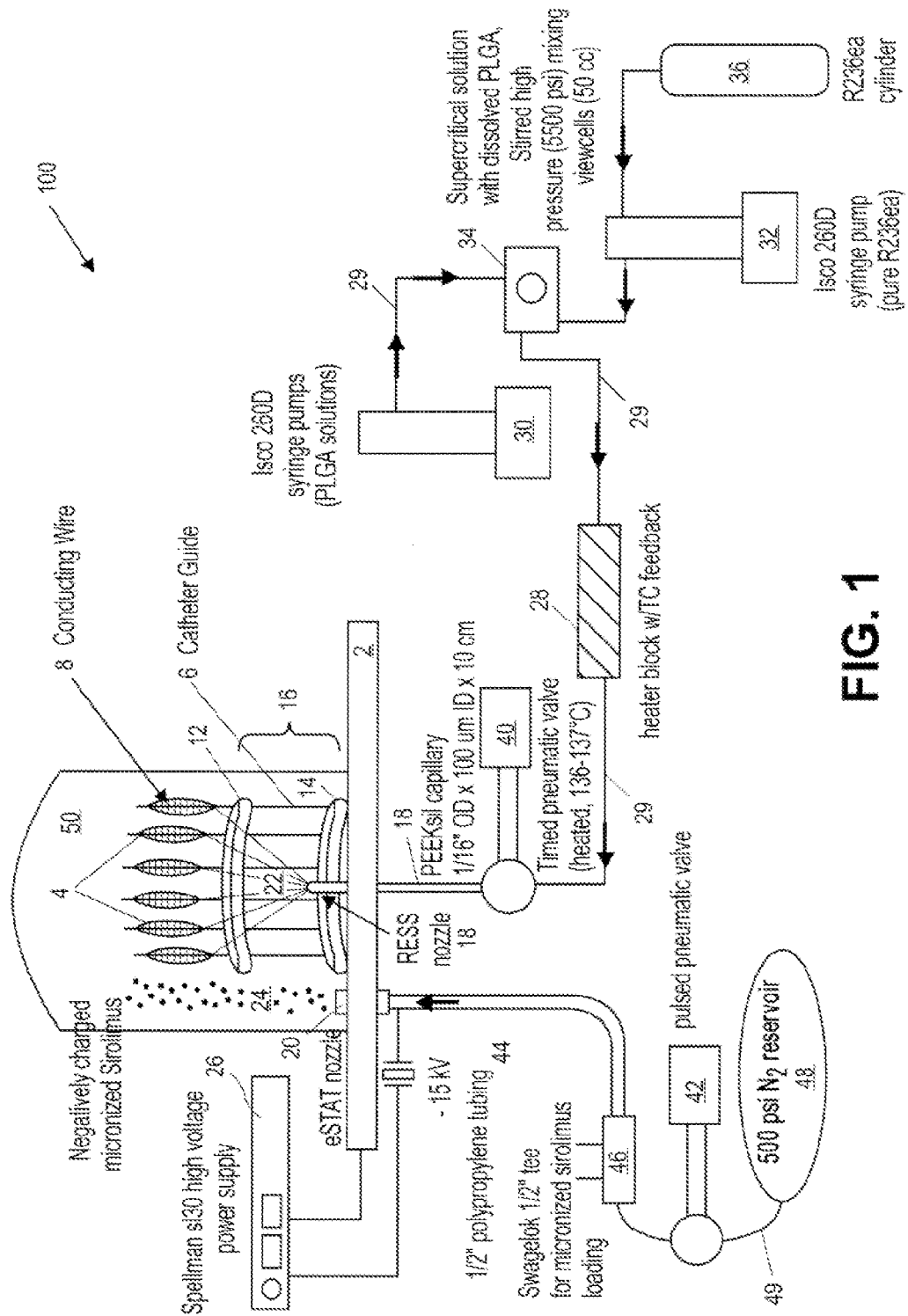


FIG. 1

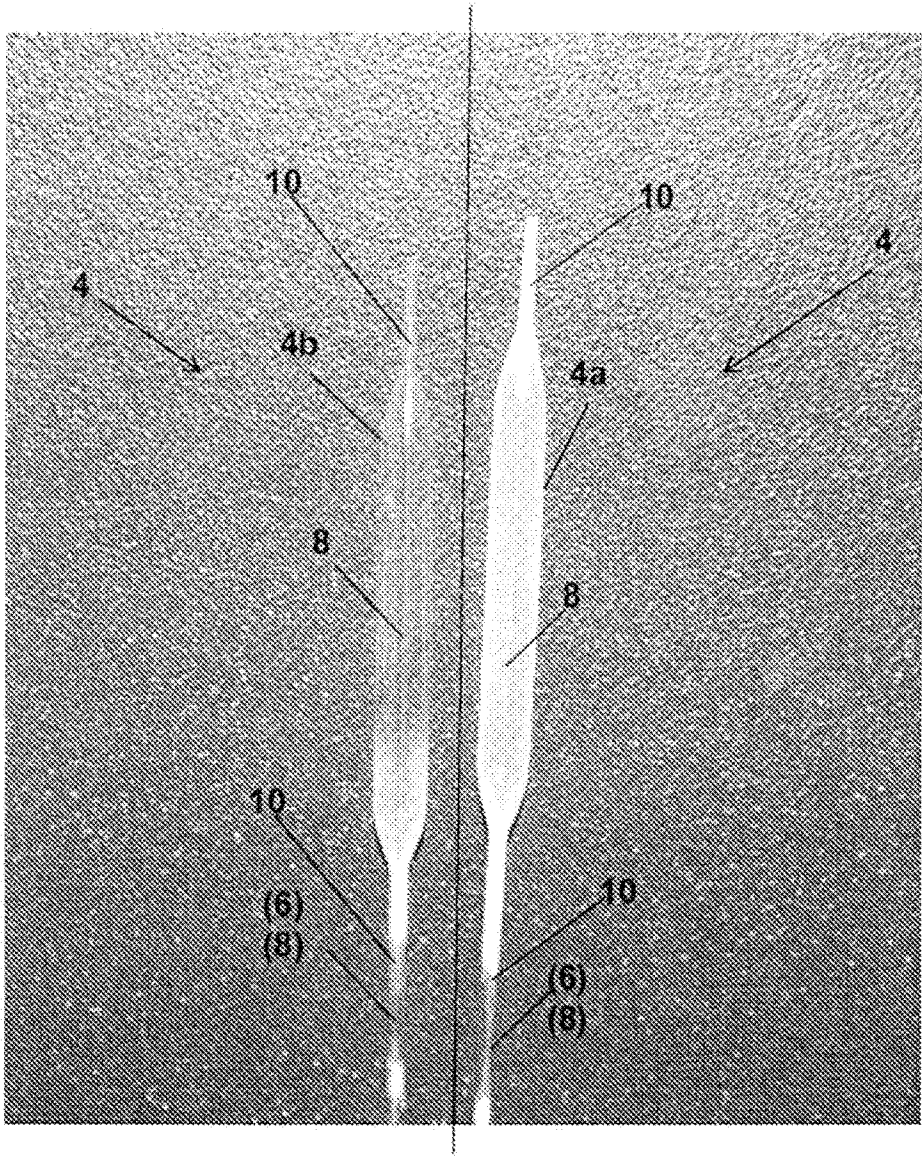


FIG. 2

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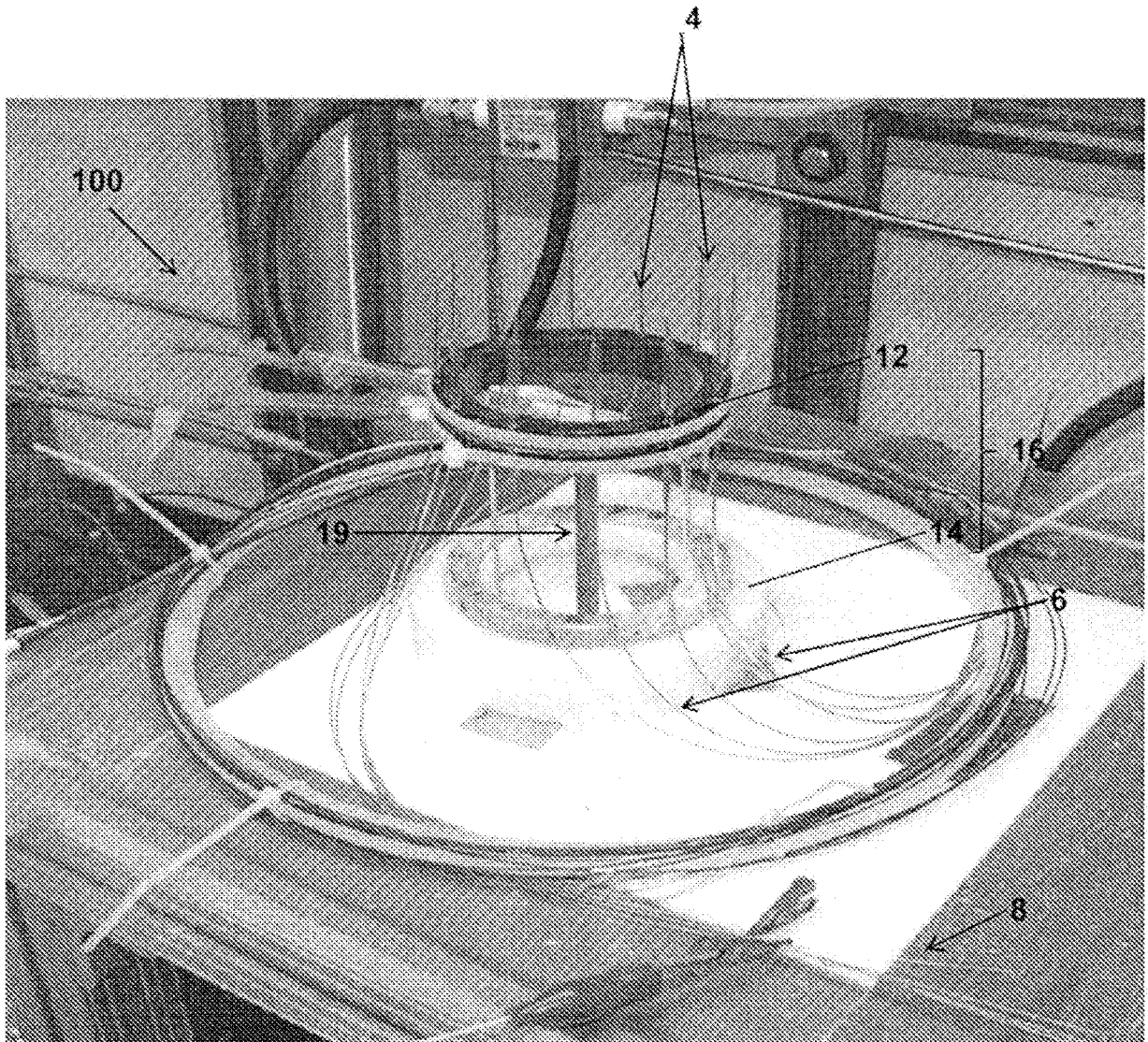


FIG. 3

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FIG. 4

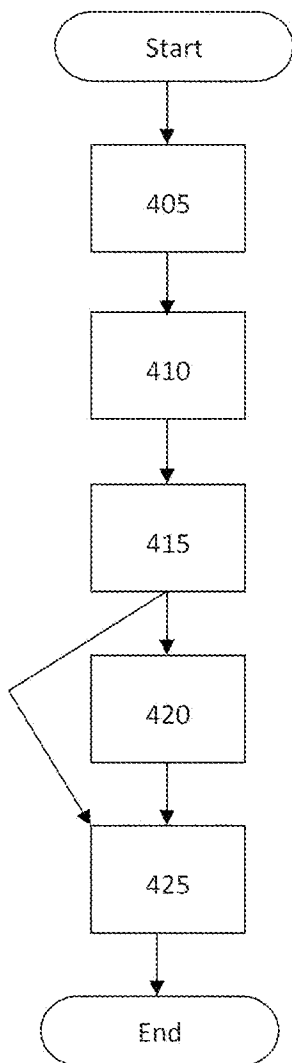
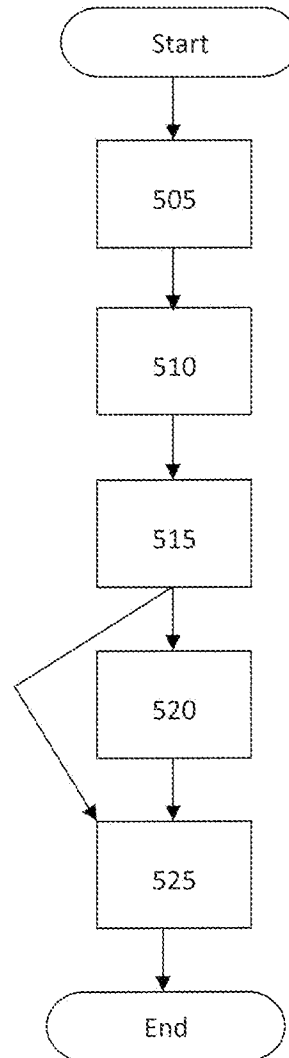


FIG. 5



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FIG. 6

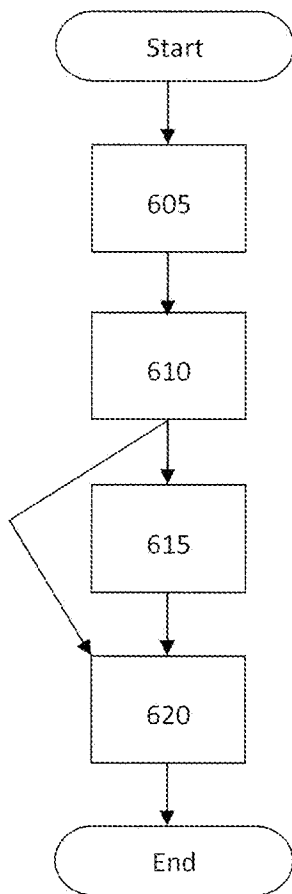
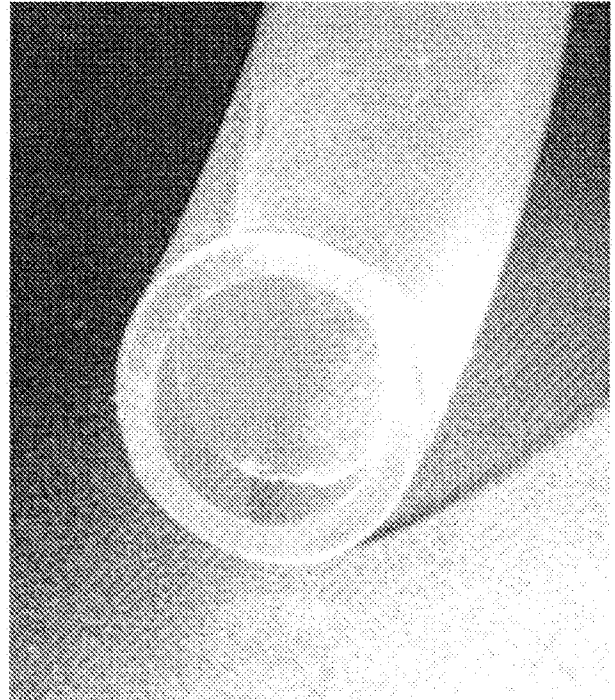


FIG. 7



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/040040

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61F 2/02 (2012.01) USPC - 623/1.46 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) - A61F 2/00, 2/02; A61K 31/00, 38/00; B05D 3/14, 7/02, 7/24 (2012.01) USPC - 210/634, 748.01; 239/3, 8, 690; 424/422, 423; 427/180; 514/1, 12.2, 54; 623/1.11, 1.46 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) MicroPatent, Google Patent and WIPO		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0222017 A1 (FULTON et al) 04 December 2003 (04.12.2003) entire document	1, 4, 7-9, 12-14, 16, 18, 19, 26, 36-38
-		
Y		3, 5, 6, 10, 11, 15, 17, 20-25, 27-35, 39-43
Y	US 2005/0131513 A1 (MYERS) 16 June 2005 (16.06.2005) entire document	3, 5, 6, 10, 11
Y	US 2009/0123515 A1 (TAYLOR et al) 14 May 2009 (14.05.2009) entire document	15, 17, 20
Y	US 2010/0015200 A1 (MCCLAIN et al) 21 January 2010 (21.01.2010) entire document	21-25, 27-35, 39-43
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* 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 16 August 2012		Date of mailing of the international search report 07 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774