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(71) Applicant *(for all designated States except US)*: **BOSTON SCIENTIFIC SCIMED, INC.** [US/US]; One Scimed Place, Maple Grove, MN 55311-1566 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BEHAN, Niall** [IE/IE]; COIS LOCHA, CARRAGHADOO, Kilcogan, County Galway (IE). **MCMORROW, David** [IE/IE]; 21 CARRAIG ARD, Fort Lorenzo, Galway City (IE). **O'CONNOR, Timothy** [IE/IE]; Kiniska Claregalway, County Galway (IE).

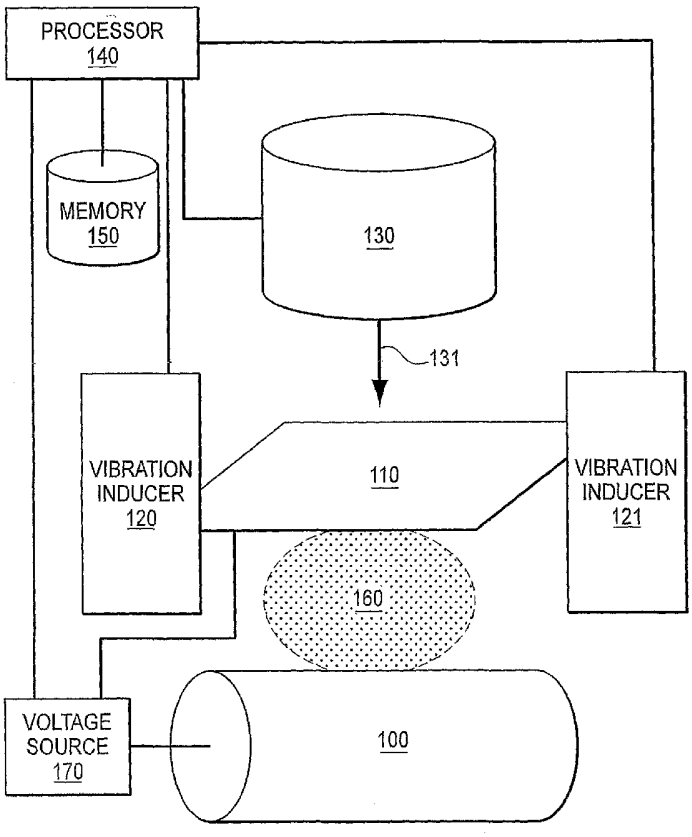
(74) Agents: **RINGEL, Douglas, E.** et al.; KENYON & KENYON LLP, 1500 K Street, N.W., Suite 700, Washington, DC 20005-1257 (US).

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(54) Title: COATING A MEDICAL APPLIANCE UTILIZING A VIBRATING MESH NEBULIZER



(57) Abstract: A method of coating a medical appliance is provided that includes contacting a coating material (131) with a first side of a mesh nebulizer (110) . The mesh nebulizer (110) includes at least one aperture. The method also includes vibrating the mesh nebulizer (110) and arranging the medical appliance (100) in a region of a second side of the mesh nebulizer (110) . The second side is opposite the first side. A system is provided for coating a medical appliance (100) that includes a coating source (130) , a mesh nebulizer (110) an arrangement (120,121) for vibrating the mesh nebulizer (110) , and an arrangement for holding the medical appliance (100) .

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COATING A MEDICAL APPLIANCE UTILIZING A VIBRATING MESH NEBULIZER

Field Of The Invention

The present invention relates to medical appliances. More particularly, the present invention relates to a method of coating a medical appliance using a vibrating mesh nebulizer to produce a mist of coating material, a system for coating a medical appliance, and a medical appliance produced by the method.

Background Information

Medical devices may be coated so that the surfaces of such devices have desired properties or effects. For example, it may be useful to coat medical devices to provide for the localized delivery of therapeutic agents to target locations within the body, such as to treat localized disease (e.g., heart disease) or occluded body lumens. Localized drug delivery may avoid some of the problems of systemic drug administration, which may be accompanied by unwanted effects on parts of the body which are not to be treated. Additionally, treatment of the afflicted part of the body may require a high concentration of therapeutic agent that may not be achievable by systemic administration. Localized drug delivery may be achieved, for example, by coating balloon catheters, stents and the like with the therapeutic agent to be locally delivered. The coating on medical devices may provide for controlled release, which may include long-term or sustained release, of a bioactive material.

Aside from facilitating localized drug delivery, medical devices may be coated with materials to provide beneficial surface properties. For example, medical devices are often coated with radiopaque materials to allow for fluoroscopic visualization while placed in the body. It is also useful to coat certain devices to achieve enhanced biocompatibility and to improve surface properties such as lubriciousness.

Metal stents may be coated with a polymeric coating that may contain a dissolved and/or suspended bioactive agent. The bioactive agent and the polymeric coating may be dissolved in a solvent mix and spray coated onto the stents. The solvent may then evaporate to leave a dry coating on the stent.

Conventional spray-coating technology may require nitrogen gas in order to produce a spray plume. This may result in a very high velocity spray plume. Because of the high velocity spray plume, long distances between a spray nozzle and a stent may be used in order to deliver a good coating finish. This may result in poor material efficiency, sometimes on the order of 1%. Furthermore the use of nitrogen gas may increase manufacturing costs.

Webbing may be a problem with two-fluid gas atomisers, particularly when coating large vessel coronary stents.

In the manufacture of a drug eluting stent, there are a number of challenges. Goals in the manufacture of coating stents include precise coating weight and complete encapsulation of stent struts, with minimal webbing between struts. Additionally, a stent may preferably be coated with a uniform coating on the inside and the outside of the stent and may be required to meet a product specification for kinetic drug release (KDR).

Medical appliances may be coated using spray technology. This may entail the use of a two-fluid atomiser, or spray nozzle. The atomiser may be supplied with coating solution and nitrogen gas. The nozzle may be configured so that the coating solution forms a thin film on the pre-filming face of the nozzle, and droplets may then be sheared off the film by the flow of atomising gas.

Spray coating may have a number of limitations. In a spray coating operation, droplet size and droplet velocity may be inextricably linked. It may not be possible to control either of these factors without impacting the other. Additionally, droplet size may only be controlled within a relatively large window due to the gas atomization process. Atomization energy is provided by the nitrogen gas stream. This may result in a very high velocity with a correspondingly high energy spray plume, which is a significant contributor to difficulty in fixturing stents during the coating process.

Droplet size may be a critical factor in controlling kinetic drug release. Precise control of droplet size may be important in order to develop a high degree of control of KDR.

Furthermore, it has been shown that the high velocity spray plume produced by two-fluid atomisers may cause stents to get blown out of alignment on the stent coating fixtures. This has led to difficulty in controlling coat weight, and has led to coating bare spots due to uncontrolled interaction between a stent and a coating fixture. One approach to counter this issue has been to significantly increase the nozzle-to-stent distance. While this reduces the

movement of the stent on the coating fixture, it may result in low coating material efficiencies, perhaps on the order of 1%. A further disadvantage of two-fluid atomisers is that many of the droplets may bounce off the object to be coated, which may further limit the material efficiency. The coating of flexible, self-expanding stents and/or longer stents may create a further difficulty whereby the stent is moved, flexed and/or bent on a fixture during coating. There is therefore a need for reducing coating defects in medical appliances.

Each of the references cited herein is incorporated by reference herein for background information.

Brief Description Of The Drawings

Figure 1 is a schematic diagram of an exemplary system according to the present invention.

Figure 2 is a zoomed-in view of an exemplary embodiment of a nebulizer.

Figure 3 illustrates an exemplary embodiment of the present invention including a coating chamber.

Figure 4 is a schematic diagram of an exemplary embodiment of a nebulizer.

Figure 5 is another schematic diagram of another exemplary embodiment of a nebulizer.

Figure 6 is a flowchart illustrating an exemplary method according to the present invention.

Detailed Description

A method of coating a medical appliance is provided that includes contacting a coating material with a first side of a mesh nebulizer. The mesh nebulizer includes at least one aperture. The method also includes vibrating the mesh nebulizer and arranging the medical appliance in a region of a second side of the mesh nebulizer. The second side is opposite the first side.

The mesh nebulizer may form droplets of the coating material.

The method may include transporting the droplets from the mesh nebulizer to the medical appliance. The transporting may be performed by a gas source. The transporting may be performed by gravity, and the mesh nebulizer may be positioned above the medical appliance.

The method may include providing an electrostatic potential between the mesh nebulizer and the medical appliance. The mesh nebulizer may impart an electrostatic charge to the droplets of the coating material.

The method may include selecting a size of the at least one aperture of the mesh nebulizer. The size of the apertures may determine the size of the droplets. The size of the at least one aperture may be between about .1 μm and about 200 μm, may be between about 3 μm and about 20 μm, and may in particular be about 10 μm.

The method may include selecting a frequency of the vibration of the mesh nebulizer. The method may include varying the frequency of the vibration of the mesh nebulizer. The method may include selecting an amplitude of the vibration of the mesh nebulizer. The method may include varying the amplitude of the vibration of the mesh nebulizer.

The coating material may include at least one of a protein and a peptide.

The method may include selecting a location of the at least one aperture on the mesh nebulizer and/or a quantity of the at least one aperture on the mesh nebulizer.

The method may include fixturing the medical appliance to allow the coating material to contact about all of a surface of the medical appliance.

A medical appliance is provided having a coating applied by a method. The method includes contacting a coating material with a first side of a mesh nebulizer. The mesh nebulizer includes at least one aperture. The method also includes vibrating the mesh nebulizer and arranging the medical appliance in a region of a second side of the mesh nebulizer. The second side is opposite the first side.

A system is provided for coating a medical appliance that includes a coating source, a mesh nebulizer, an arrangement for vibrating the mesh nebulizer, and an arrangement for holding the medical appliance.

A method is provided of coating a medical appliance that includes directing at least two small aperture tubes at a collision region and forcing a coating material out of the apertures of the tubes. The method also includes arranging the medical appliance in another region adjacent to the collision region.

An exemplary embodiment of the present invention proposes the use of nebuliser technology in the coating of medical devices, in particular drug eluting stents. Nebulisers are medical devices used to vaporise medications for inhalation, specifically to convert liquid

drugs into fine droplets for inhalation. Small, controllable droplet size, with typical size ranges in the order 1 to 5 microns, may be achievable with a nebulizer. A low energy droplet cloud may be desirable and therefore converting a solution into small droplets without imparting high velocities to the droplets may be desired. Additionally precise control of a delivered drug volume may be desirable.

A component of some nebuliser designs is a convex mesh which may have numerous, precisely-sized holes. The drug to be administered may be placed in the concave side of the mesh, and the mesh may be vibrated at high frequency using a piezoelectric drive. This may result in the drug being converted into a cloud of small droplets, which may be delivered on the lower (convex) side of the mesh.

Use of nebulisers instead of two-fluid atomisers may offer several advantages in coating drug eluting stents, or any other medical device. Extremely precise droplet size may be possible with a nebulizer. Precise droplet size control may be advantageous since it has been demonstrated that droplet size correlates directly to kinetic drug release (KDR). Precise control of KDR may be achievable with precise control of droplet size. Additionally, droplet size may be programmable. In particular, geometric changes may be made to the nebuliser to provide a specific desired droplet size. Additionally, droplet size may be controlled independently of droplet velocity. Due to the low velocity of the plume coupled with fine droplet size, very small stent features may be coated without webbing. No atomisation gas may be required.

Use of this method of atomisation may offer several advantages. The size of the droplets may be extremely precise because it may be determined by the size of the holes in the mesh (which may be tailor-made to suit the application). This may contribute to precise control of KDR and an ability to coat complex geometries with small feature dimensions. Due to the absence of atomisation gas, the droplets may fall away from the mesh under the force of gravity at low velocity. The volume of liquid atomised, and the droplet velocity, can also be precisely controlled by adjusting the frequency and amplitude of the mesh vibration. Furthermore, the number of holes in the mesh and their layout on the mesh can be tailored. This could enable greatly increased coating material efficiency, as the atomised cloud could be sized to suit the stent being coated. Furthermore, fixturing of stents during the coating process can be greatly simplified, as there is no longer a need to hold the stent securely to

prevent it getting blown away by the atomisation gas. This may be particularly important for future generation stents which may be longer and more easily damaged during handling.

In an alternative exemplary embodiment, an electrostatic system may be integrated with the nebuliser. This may enable higher material efficiency while retaining precise droplet size. No atomisation gas may be required in the exemplary method, and consequently stent fixturing may be greatly simplified. Therefore, the coating process may be well controlled. An electrostatic system may be accomplished by attaching a power source to the nebuliser mesh and providing a grounding contact to the stent. This may deliver higher material efficiency.

An alternative nebuliser design may atomise fluids using two capillary tubes, which may be oriented at an angle to each other. The fluid to be atomised may be pumped through the tubes. Small droplets may exit the ends of the tubes, and the size of these droplets may be determined by the diameter of the tube. Due to the angular arrangement, the droplets from each tube may collide, leading to further break-up of the droplets. The droplet size produced by this type of nebuliser may be approximately 5 microns. A nebuliser using two capillary tubes in angular arrangement may be configured in a number of ways. In particular, capilliary tube size, diameter, angle, fluid flow rate are key parameters.

Since nebulizers may not require a propellant gas, there may be fewer factors controlling the aerosol properties. However, the aerosol plume may require a gas current to entrain the plume so that it flows in the direction of the stent. This gas flow may be directed and accelerated towards the stent by means of a venturi type baffle arrangement.

A nebuliser may be configured in a number of ways to facilitate stent coating. In particular, mesh hole size, location and quantity may be altered. Vibration frequency and amplitude may also be tailored. Materials may be changed to facilitate use with solvent-based coatings.

The stent may be rotated and/or moved axially, or alternatively may remain fixed, depending on the size of the atomised cloud. Stent fixturing may be accomplished by supporting the stent on a pair of wires, possibly without the need to pass a wire through the center of the stent. This may accelerate the stent fixturing process, and substantially improve the quality of the stent coating, particlarly on the stent internal surface. Furthermore, this

method may enable the coating of more delicate stents with increasingly complex feature details.

The design of the nebuliser may facilitate the delivery of more than one fluid to the rear surface of the mesh, thus enabling coat mixing at the point of application. This may offer benefits where short shelf-life materials are used in coating, or in the use of coating materials which are not suitable for long-term storage when pre-mixed. This approach may also be used to alter coat composition during the application of coating, thus enabling creation of products where KDR or coat composition can be altered for different areas of the product being coated. Arrays of pores may be designed in various shapes, including rectangles and lines. Pores may be of different sizes to accommodate different materials and may be separated on the concave side of the nebulizer by walls or other barriers. Different materials may mix in the plume after being nebulized through different sized pores.

Figure 1 is a schematic diagram of an exemplary system according to the present invention. Stent 100 is shown positioned below nebulizer mesh 110. Nebulizer mesh 110 is positioned between vibration inducers 120, 121. Alternatively, there may be more or fewer vibration inducers 120, 121. Vibration inducers 120, 121 may induce vibration in a direction parallel and/or perpendicular to nebulizer mesh 110, and may induce a complex vibration. Nebulizer mesh 110 includes one or more pores that may be between about .1 μm and about 200 μm, may be between about 3 μm and about 20 μm, and may be about 10 μm. The pores in nebulizer mesh 110 may be of uniform size or may be variably sized. Additionally, the pores in nebulizer mesh 110 may be frustoconical, vortex-shaped, and/or any other appropriate shape. Coating source 130 provides a coating material in the direction of arrow 131 to nebulizer mesh 110. After passing through the pores of nebulizer mesh 110, the coating material may form plume 160, which may consist of droplets. Droplets having a diameter of about 5 microns may be produced by a pore size of 3 microns in nebulizer mesh 110. The droplets in plume 160 may have a very narrow size distribution, and therefore may produce a uniform coating on stent 100. Processor 140 coupled to memory 150 may contain and/or execute instructions for operating coating source 130, vibration inducers 120, 121, and/or voltage source 170. Voltage source 170 may be connected to stent 100 and/or nebulizer mesh 110 and may impart an electric potential that provides a charge to the droplets

in plume 160 that is opposite to the charge on stent 100. Plume 160 may be directed to coat stent 100 by gravity, by an additional gas source, and/or by an electrostatic potential.

Figure 2 is a zoomed-in view of an exemplary embodiment of nebulizer mesh 110. Nebulizer mesh 110 includes pores 200, 201, 202, 203, 204, which in this exemplary embodiment are vortex-shaped. Alternatively, pores 200, 201, 202, 203, 204 of nebulizer mesh 110 may be frusto-conical or any other appropriate shape.

Figure 3 illustrates an exemplary embodiment of the present invention including coating chamber 310. Nebulizer mesh 110 is situated at an upper portion of coating chamber 310. Coating chamber 310 encloses stent 100. Coating chamber 310 includes gas intakes 320, which may allow a gas to enter coating chamber 310. Gas intakes 320 may also provide a flow of gas under pressure to coating chamber 320. Gas exhaust 330 may remove gas and or excess material (for instance, coating material that has not adhered to stent 100) from coating chamber 320. Alternatively, coating chamber 310 may be airtight and/or evacuated, or may enclose an inert gas. When a coating material is arranged on mesh nebulizer 110, and mesh nebulizer 110 is vibrated, cone plume 300 of coating material in coating chamber 310 may be formed. Cone plume 300 may settle on stent 100 arranged in cone plume 300 by gravity, or may be assisted in moving toward stent 100 by a gas flowing from gas intakes 320 to gas exhaust 330.

Figure 4 is a schematic diagram of an exemplary embodiment of mesh nebulizer 110. Mesh nebulizer 110 includes pores 200, 201 and lateral barriers 400, 401. Alternatively, there may be more or fewer pores 200, 201, and/or more or fewer lateral barriers 400, 401. Coating material 410 is situated on a top side of mesh nebulizer 110, and is situated in a vicinity of pores 200, 201. Lateral barriers 400, 401 and/or another element may impart a vibration to mesh nebulizer. The vibration may correspond to sinusoid 420, and may consist of a vibration in a direction of double arrow 421. Alternatively or additionally, a lateral vibration in a plane of nebulizer mesh 110 may be induced. The vibration of nebulizer mesh 110 may induce coating material 410 to pass through pores 200, 201 to create plume 160.

Figure 5 is another schematic diagram of another exemplary embodiment of nebulizer mesh 110 showing a zoomed in view of pore 200. Pore 200 is frustoconical, though alternative shapes may be possible. Coating material 410 flows through pore 200 when nebulizer mesh 110 is vibrated to form plume 160, which may be composed of droplets of a

small diameter. The droplets of plume 160 may have a narrow size distribution, and may be between about .1 μm and about 200 μm, or may be between about 3 μm and about 20 μm. In one exemplary embodiment, pore 200 may be about 3 microns in diameter and the droplets in plume 160 may be about 5 microns in diameter.

Figure 6 is a flowchart illustrating an exemplary method according to the present invention. The flow in figure 6 starts in start circle 600 and proceeds to action 610, which indicates to select a size, a location, and/or a quantity of pores of a mesh nebulizer. From action 610, the flow proceeds to decision 620, which asks whether a source of electrostatic potential is available. If the response to decision 620 is affirmative, the flow proceeds to action 630, which indicates to provide an electrostatic potential between the mesh nebulizer and the medical appliance so that the mesh nebulizer imparts an electrostatic charge to the droplets of the coating material opposite the charge of the medical appliance. From action 630, the flow proceeds to action 640, which indicates to contact a coating material with a first side of the mesh nebulizer. From action 640, the flow proceeds to action 650, which indicates to select a frequency and an amplitude of the vibration of the mesh nebulizer. From action 650, the flow proceeds to action 660, which indicates to vibrate the mesh nebulizer to form droplets of the coating material. From action 660, the flow proceeds to action 670, which indicates tofixture the medical appliance in a deposition region to allow the coating material to contact a surface of the medical appliance. From action 670, the flow proceeds to end circle 680. If the response to decision 620 is negative, the flow proceeds to action 640.

As used herein, the term "therapeutic agent" includes one or more "therapeutic agents" or "drugs". The terms "therapeutic agents", "active substance" and "drugs" are used interchangeably herein and include pharmaceutically active compounds, nucleic acids with and without carrier vectors such as lipids, compacting agents (such as histones), virus (such as adenovirus, andenoassociated virus, retrovirus, lentivirus and α-virus), polymers, hyaluronic acid, proteins, cells and the like, with or without targeting sequences.

The therapeutic agent may be any pharmaceutically acceptable agent such as a non-genetic therapeutic agent, a biomolecule, a small molecule, or cells.

Exemplary non-genetic therapeutic agents include anti-thrombogenic agents such heparin, heparin derivatives, prostaglandin (including micellar prostaglandin E1), urokinase,

and PPack (dextrophenylalanine proline arginine chloromethylketone); anti-proliferative agents such as enoxaprin, angiopeptin, sirolimus (rapamycin), tacrolimus, everolimus, monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, rosiglitazone, prednisolone, corticosterone, budesonide, estrogen, estrodiol, sulfasalazine, acetylsalicylic acid, mycophenolic acid, and mesalamine; anti-neoplastic/anti-proliferative/anti-mitotic agents such as paclitaxel, epothilone, cladribine, 5-fluorouracil, methotrexate, doxorubicin, daunorubicin, cyclosporine, cisplatin, vinblastine, vincristine, epothilones, endostatin, trapidil, halofuginone, and angiostatin; anti-cancer agents such as antisense inhibitors of c-myc oncogene; anti-microbial agents such as triclosan, cephalosporins, aminoglycosides, nitrofurantoin, silver ions, compounds, or salts; biofilm synthesis inhibitors such as non-steroidal anti-inflammatory agents and chelating agents such as ethylenediaminetetraacetic acid, O,O'-bis (2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid and mixtures thereof; antibiotics such as gentamycin, rifampin, minocyclin, and ciprofolxacin; antibodies including chimeric antibodies and antibody fragments; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; nitric oxide; nitric oxide (NO) donors such as lisidomine, molsidomine, L-arginine, NO-carbohydrate adducts, polymeric or oligomeric NO adducts; anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, enoxaparin, hirudin, warfarin sodium, Dicumarol, aspirin, prostaglandin inhibitors, platelet aggregation inhibitors such as cilostazol and tick antiplatelet factors; vascular cell growth promotors such as growth factors, transcriptional activators, and translational promotors; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; agents which interfere with endogeneus vascoactive mechanisms; inhibitors of heat shock proteins such as geldanamycin; angiotensin converting enzyme (ACE) inhibitors; beta-blockers; bAR kinase (bARKct) inhibitors; phospholamban inhibitors; and any combinations and prodrugs of the above.

Exemplary biomolecules include peptides, polypeptides and proteins; oligonucleotides; nucleic acids such as double or single stranded DNA (including naked and cDNA), RNA, antisense nucleic acids such as antisense DNA and RNA, small interfering RNA (siRNA), and ribozymes; genes; carbohydrates; angiogenic factors including growth factors; cell cycle inhibitors; and anti-restenosis agents. Nucleic acids may be incorporated into delivery systems such as, for example, vectors (including viral vectors), plasmids or liposomes.

Non-limiting examples of proteins include serca-2 protein, monocyte chemoattractant proteins ("MCP-1) and bone morphogenic proteins ("BMP's"), such as, for example, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15. Preferred BMPS are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, and BMP-7. These BMPs can be provided as homdimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively, or in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedghog" proteins, or the DNA's encoding them. Non-limiting examples of genes include survival genes that protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; serca 2 gene; and combinations thereof. Non-limiting examples of angiogenic factors include acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor, and insulin like growth factor. A non-limiting example of a cell cycle inhibitor is a cathespin D (CD) inhibitor. Non-limiting examples of anti-restenosis agents include p15, p16, p18, p19, p21, p27, p53, p57, Rb, nFkB and E2F decoys, thymidine kinase ("TK") and combinations thereof and other agents useful for interfering with cell proliferation.

Exemplary small molecules include hormones, nucleotides, amino acids, sugars, and lipids and compounds have a molecular weight of less than 100kD.

Exemplary cells include stem cells, progenitor cells, endothelial cells, adult cardiomyocytes, and smooth muscle cells. Cells can be of human origin (autologous or allogenic) or from an animal source (xenogenic), or genetically engineered. Non-limiting examples of cells include side population (SP) cells, lineage negative (Lin-) cells including

Lin-CD34-, Lin-CD34+, Lin-cKit+, mesenchymal stem cells including mesenchymal stem cells with 5-aza, cord blood cells, cardiac or other tissue derived stem cells, whole bone marrow, bone marrow mononuclear cells, endothelial progenitor cells, skeletal myoblasts or satellite cells, muscle derived cells, go cells, endothelial cells, adult cardiomyocytes, fibroblasts, smooth muscle cells, adult cardiac fibroblasts + 5-aza, genetically modified cells, tissue engineered grafts, MyoD scar fibroblasts, pacing cells, embryonic stem cell clones, embryonic stem cells, fetal or neonatal cells, immunologically masked cells, and teratoma derived cells.

Any of the therapeutic agents may be combined to the extent such combination is biologically compatible.

Any of the above mentioned therapeutic agents may be incorporated into a polymeric coating on the medical device or applied onto a polymeric coating on a medical device. The polymers of the polymeric coatings may be biodegradable or non-biodegradable. Non-limiting examples of suitable non-biodegradable polymers include polystrene; polyisobutylene copolymers and styrene-isobutylene-styrene block copolymers such as styrene-isobutylene-styrene tert-block copolymers (SIBS); polyvinylpyrrolidone including cross-linked polyvinylpyrrolidone; polyvinyl alcohols, copolymers of vinyl monomers such as EVA; polyvinyl ethers; polyvinyl aromatics; polyethylene oxides; polyesters including polyethylene terephthalate; polyamides; polyacrylamides; polyethers including polyether sulfone; polyalkylenes including polypropylene, polyethylene and high molecular weight polyethylene; polyurethanes; polycarbonates, silicones; siloxane polymers; cellulosic polymers such as cellulose acetate; polymer dispersions such as polyurethane dispersions (BAYHDROL®); squalene emulsions; and mixtures and copolymers of any of the foregoing.

Non-limiting examples of suitable biodegradable polymers include polycarboxylic acid, polyanhydrides including maleic anhydride polymers; polyorthoesters; poly-amino acids; polyethylene oxide; polyphosphazenes; polylactic acid, polyglycolic acid and copolymers and mixtures thereof such as poly(L-lactic acid) (PLLA), poly(D,L,-lactide), poly(lactic acid-co-glycolic acid), 50/50 (DL-lactide-co-glycolide); polydioxanone; polypropylene fumarate; polydepsipeptides; polycaprolactone and co-polymers and mixtures thereof such as poly(D,L-lactide-co-caprolactone) and polycaprolactone co-butylacrylate; polyhydroxybutyrate valerate and blends; polycarbonates such as tyrosine-derived

polycarbonates and arylates, polyiminocarbonates, and polydimethyltrimethylcarbonates; cyanoacrylate; calcium phosphates; polyglycosaminoglycans; macromolecules such as polysaccharides (including hyaluronic acid; cellulose, and hydroxypropylmethyl cellulose; gelatin; starches; dextrans; alginates and derivatives thereof), proteins and polypeptides; and mixtures and copolymers of any of the foregoing. The biodegradable polymer may also be a surface erodable polymer such as polyhydroxybutyrate and its copolymers, polycaprolactone, polyanhydrides (both crystalline and amorphous), maleic anhydride copolymers, and zinc-calcium phosphate.

Such coatings used with the present invention may be formed by any method known to one in the art. For example, an initial polymer/solvent mixture can be formed and then the therapeutic agent added to the polymer/solvent mixture. Alternatively, the polymer, solvent, and therapeutic agent can be added simultaneously to form the mixture. The polymer/solvent/therapeutic agent mixture may be a dispersion, suspension or a solution. The therapeutic agent may also be mixed with the polymer in the absence of a solvent. The therapeutic agent may be dissolved in the polymer/solvent mixture or in the polymer to be in a true solution with the mixture or polymer, dispersed into fine or micronized particles in the mixture or polymer, suspended in the mixture or polymer based on its solubility profile, or combined with micelle-forming compounds such as surfactants or adsorbed onto small carrier particles to create a suspension in the mixture or polymer. The coating may comprise multiple polymers and/or multiple therapeutic agents.

The coating can be applied to the medical device by any known method in the art including dipping, spraying, rolling, brushing, electrostatic plating or spinning, vapor deposition, air spraying including atomized spray coating, and spray coating using an ultrasonic nozzle.

The coating is typically from about 1 to about 50 microns thick. In the case of balloon catheters, the thickness is preferably from about 1 to about 10 microns, and more preferably from about 2 to about 5 microns. Very thin polymer coatings, such as about 0.2-0.3 microns and much thicker coatings, such as more than 10 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of polymer coatings onto the medical device. Such multiple layers may contain the same or different therapeutic agents and/or the same or different polymers. Methods of choosing the type, thickness and

other properties of the polymer and/or therapeutic agent to create different release kinetics are well known to one in the art.

The medical device may also contain a radio-opacifying agent within its structure to facilitate viewing the medical device during insertion and at any point while the device is implanted. Non-limiting examples of radio-opacifying agents are bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, barium sulfate, tungsten, and mixtures thereof.

Non-limiting examples of medical devices according to the present invention include catheters, guide wires, balloons, filters (e.g., vena cava filters), stents, stent grafts, vascular grafts, intraluminal paving systems, implants and other devices used in connection with drug-loaded polymer coatings. Such medical devices may be implanted or otherwise utilized in body lumina and organs such as the coronary vasculature, esophagus, trachea, colon, biliary tract, urinary tract, prostate, brain, lung, liver, heart, skeletal muscle, kidney, bladder, intestines, stomach, pancreas, ovary, cartilage, eye, bone, and the like.

While the present invention has been described in connection with the foregoing representative embodiment, it should be readily apparent to those of ordinary skill in the art that the representative embodiment is exemplary in nature and is not to be construed as limiting the scope of protection for the invention as set forth in the appended claims.

WHAT IS CLAIMED IS:

1. A method of coating a medical appliance, comprising:

contacting a coating material with a first side of a mesh nebulizer, the mesh nebulizer comprising at least one aperture;

vibrating the mesh nebulizer; and

arranging the medical appliance in a region of a second side of the mesh nebulizer, the second side opposite the first side.

2. The method of claim 1, wherein the mesh nebulizer forms droplets of the coating material.

3. The method of claim 2, further comprising transporting the droplets from the mesh nebulizer to the medical appliance.

4. The method of claim 3, wherein the transporting is performed by a gas source.

5. The method of claim 3, wherein the transporting is performed by gravity, the mesh nebulizer being positioned above the medical appliance.

6. The method of claim 2, further comprising providing an electrostatic potential between the mesh nebulizer and the medical appliance, the mesh nebulizer imparting an electrostatic charge to the droplets of the coating material.

7. The method of claim 2, further comprising selecting a size of the at least one aperture of the mesh nebulizer, the size of the apertures determining the size of the droplets.

8. The method of claim 7, wherein the size of the apertures is between about .1 μm and about 200 μm.

9. The method of claim 8, wherein the size of the apertures is between about 3 μm and about 20 μm.

10. The method of claim 9, wherein the size of the apertures is about 10 μm.

11. The method of claim 7, further comprising:

selecting a further size of at least one further aperture of the mesh nebulizer;

wherein the size of the at least one aperture is adapted to atomize the coating material; and

wherein the further size of the at least one further aperture is adapted to atomize a further coating material.

12. The method of claim 11, further comprising:

arranging the at least one aperture in a first area of the mesh nebulizer;

arranging the at least one further aperture in a second area of the mesh nebulizer; and

contacting the further coating material with the first side of the mesh nebulizer in the second area;

wherein the contacting of the coating material with the first side of the mesh nebulizer is in the first area.

13. The method of claim 12, wherein the coating material and the further coating material mix on the second side of the mesh nebulizer.

14. The method of claim 2, further comprising selecting a frequency of the vibration of the mesh nebulizer.

15. The method of claim 14, further comprising varying the frequency of the vibration of the mesh nebulizer.

16. The method of claim 2, further comprising selecting an amplitude of the vibration of the mesh nebulizer.

17. The method of claim 16, further comprising varying the amplitude of the vibration of the mesh nebulizer.

18. The method of claim 1, wherein the coating material includes at least one of a protein and a peptide.

19. The method of claim 1, further comprising selecting at least one of:

a location of the at least one aperture on the mesh nebulizer; and

a quantity of the at least one aperture on the mesh nebulizer.

20. The method of claim 19, wherein:

the location of the at least one aperture on the mesh nebulizer is selected;

the at least one aperture is a plurality of apertures; and

the apertures are arranged in one of a line and a rectangular array.

21. The method of claim 1, wherein the coating material includes at least one of a protein and a peptide.

22. The method of claim 1, further comprising fixturing the medical appliance to allow the coating material to contact about all of a surface of the medical appliance.

23. A medical appliance having a coating applied by a method, the method comprising:

contacting a coating material with a first side of a mesh nebulizer, the mesh nebulizer comprising at least one aperture;

vibrating the mesh nebulizer; and

arranging the medical appliance in a region of a second side of the mesh nebulizer, the second side opposite the first side.

24. A system for coating a medical appliance, comprising:

a coating source;

a mesh nebulizer;

an arrangement for vibrating the mesh nebulizer; and

an arrangement for holding the medical appliance.

25. A method of coating a medical appliance, comprising:

directing at least two small aperture tubes at a collision region;

forcing a coating material out of the apertures of the tubes; and

arranging the medical appliance in another region adjacent to the collision region.

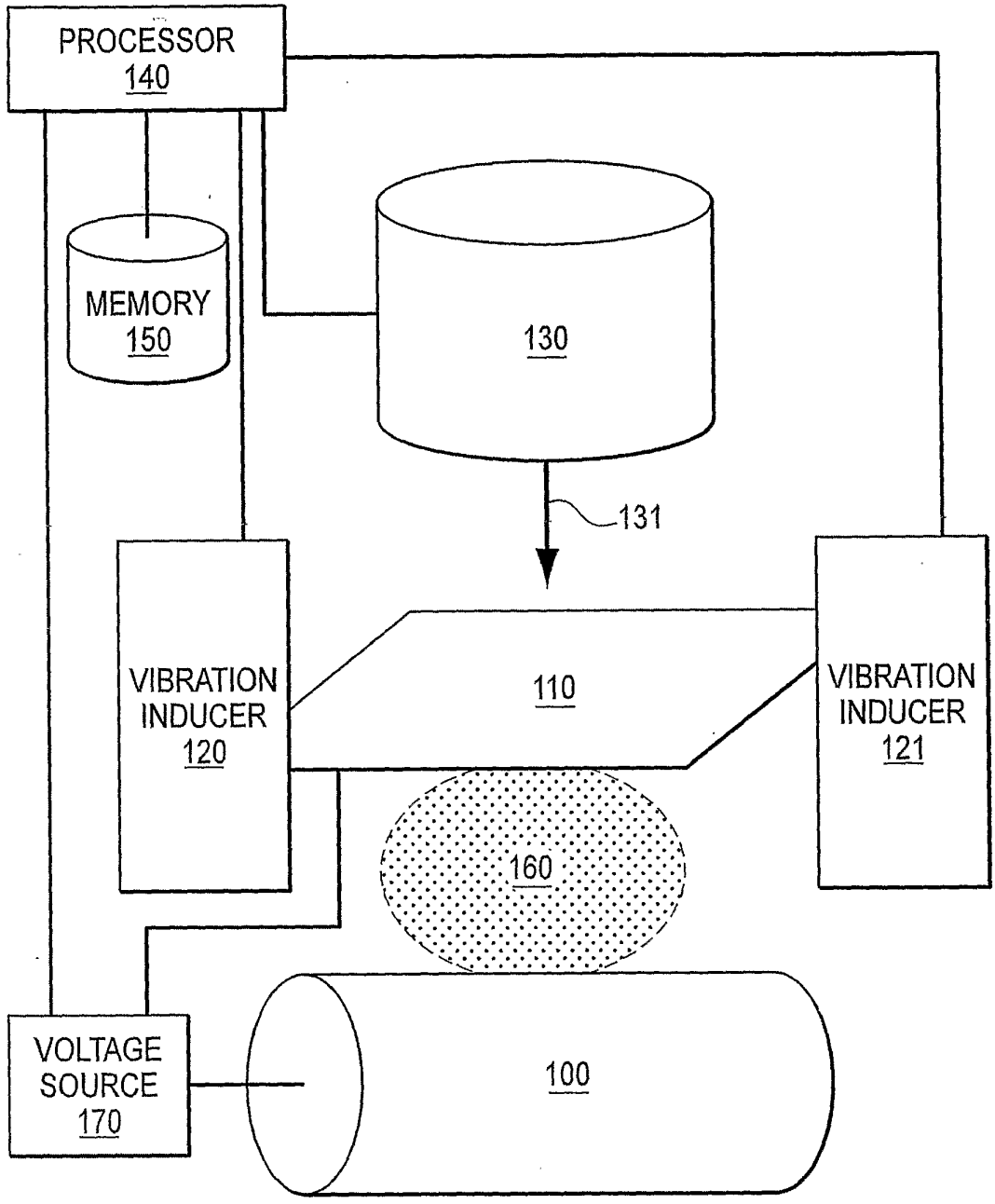

PROCESSOR
140
MEMORY
150
130
131
VIBRATION
INDUCER
120
110
VIBRATION
INDUCER
121
160
VOLTAGE
SOURCE
170
100

FIGURE 1

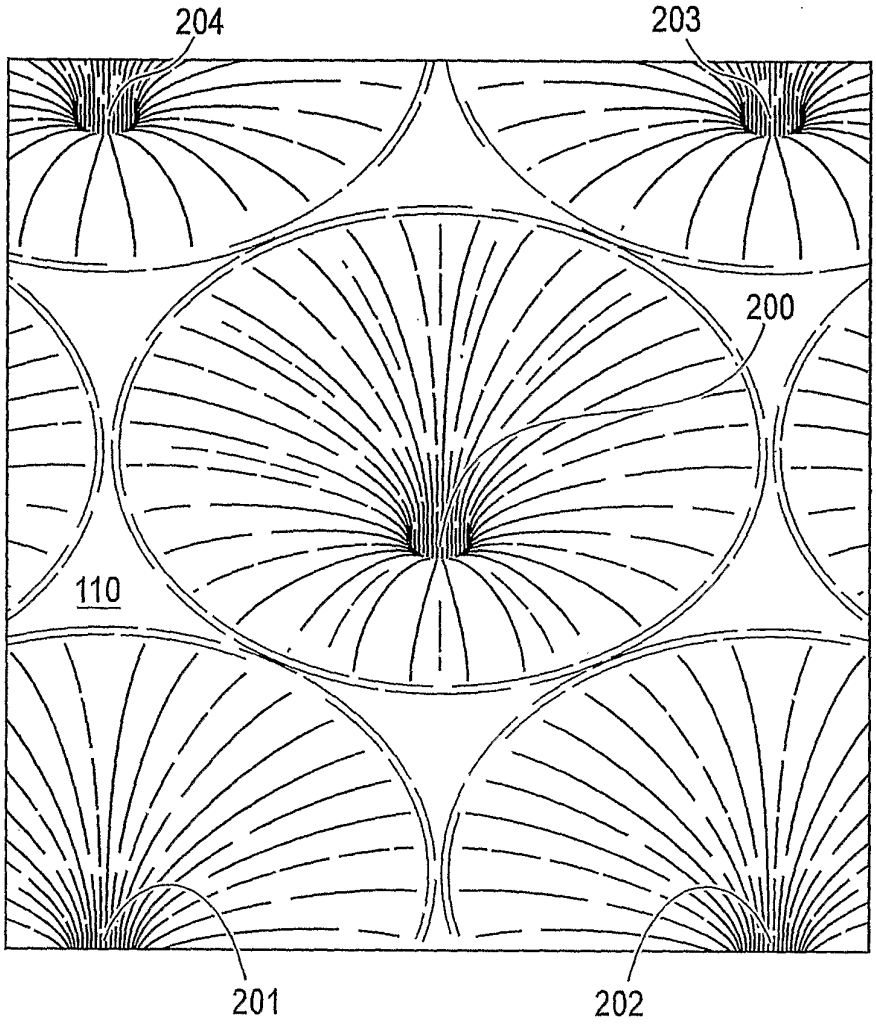


FIGURE 2

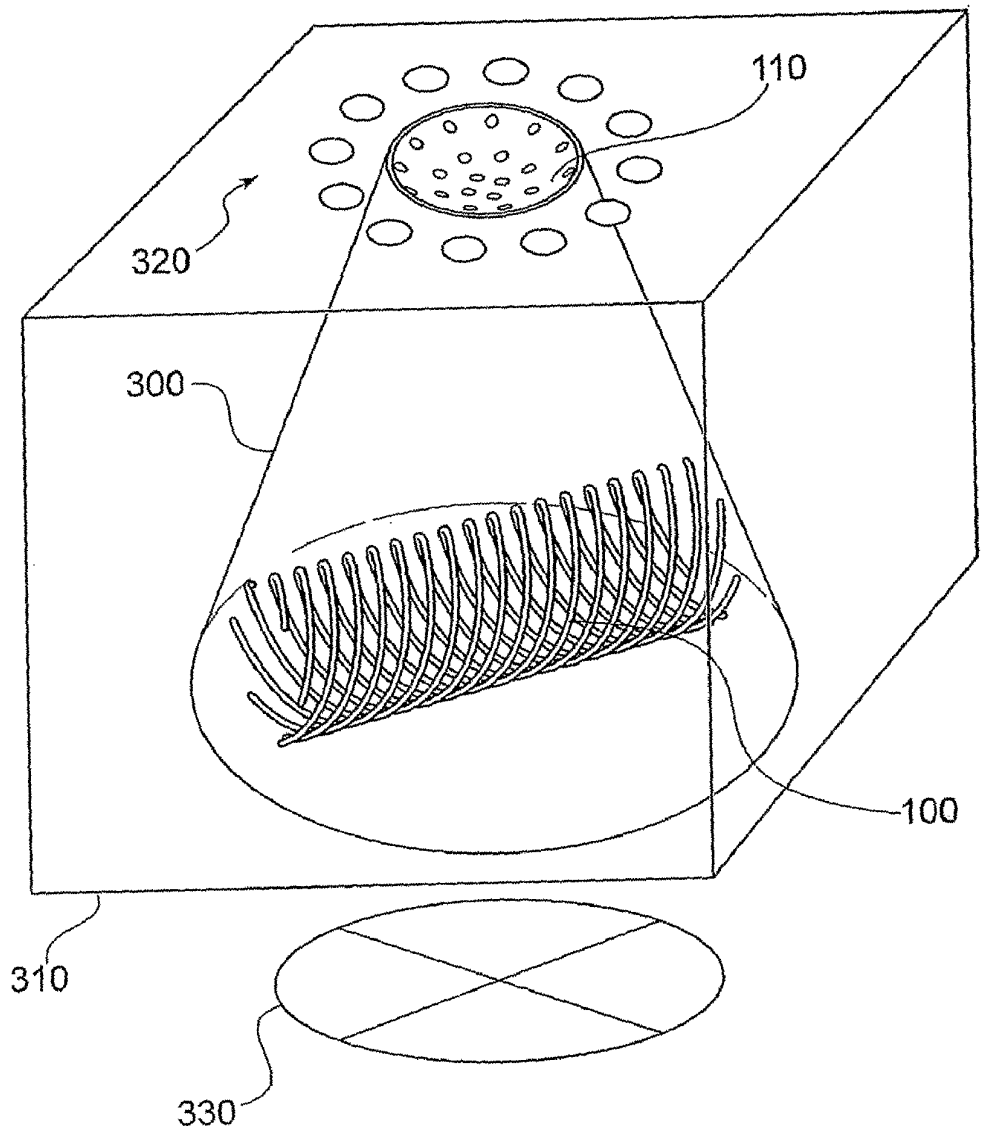


FIGURE 3

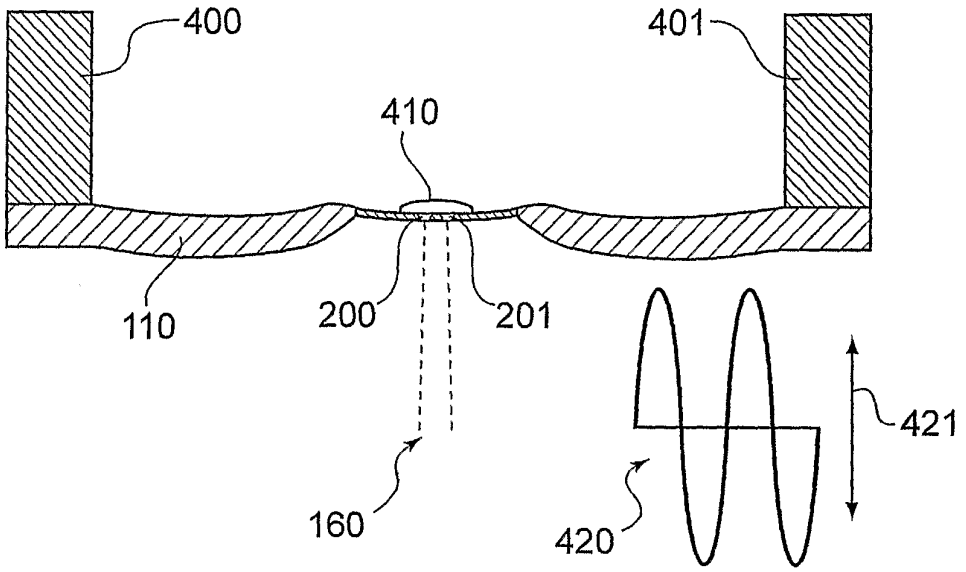


FIGURE 4

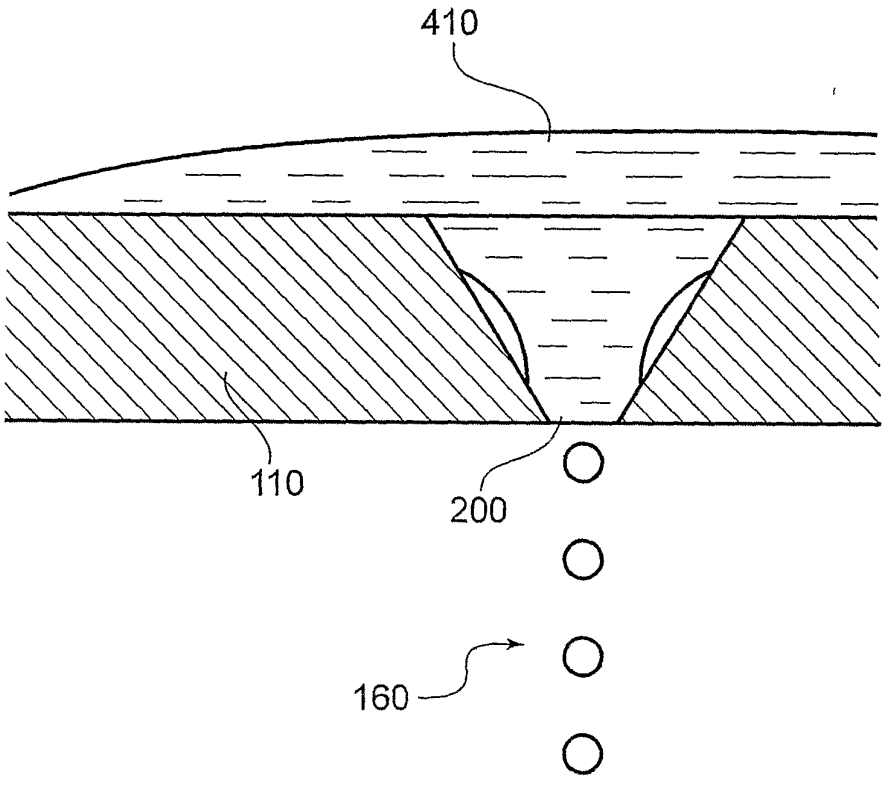


FIGURE 5

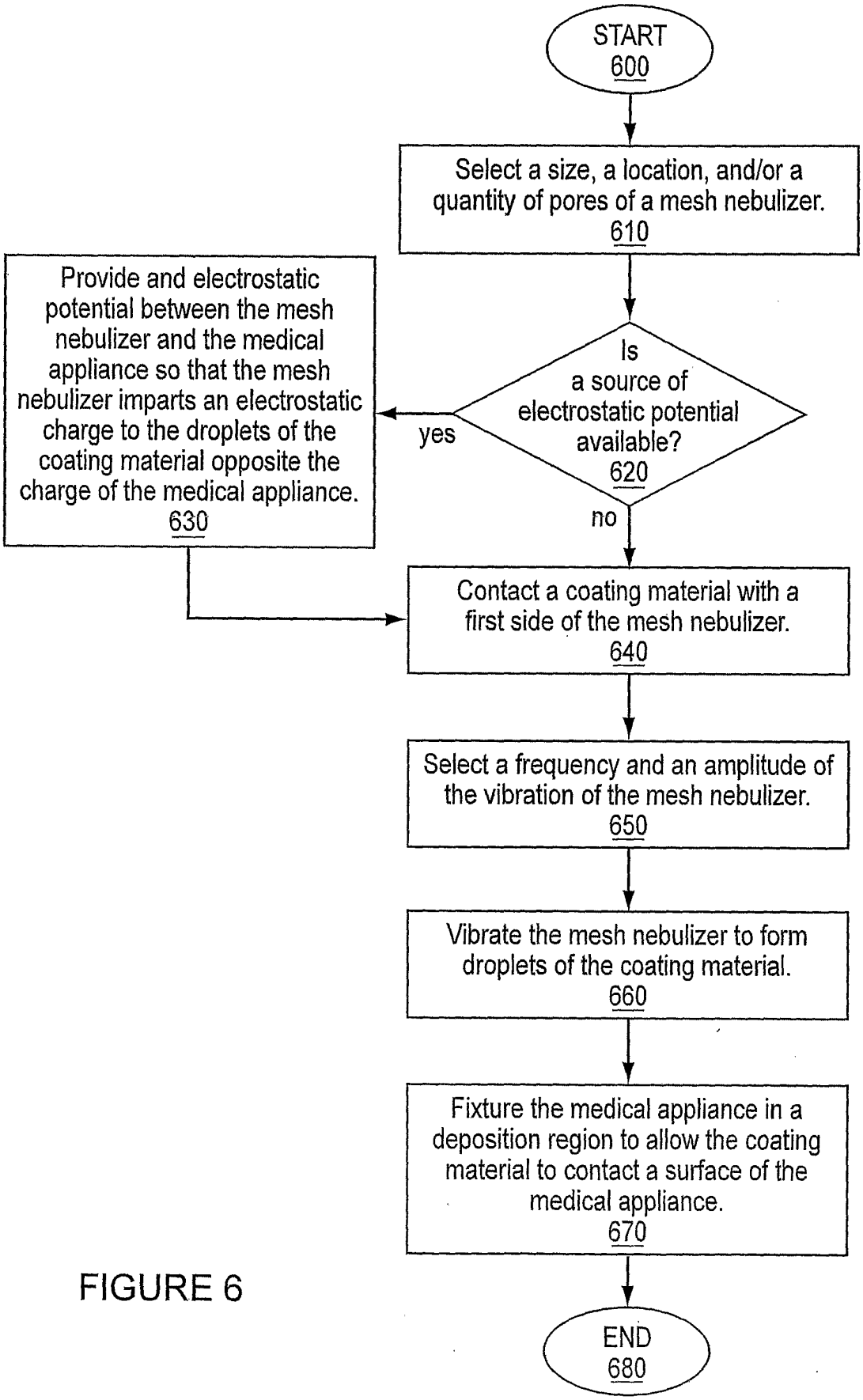

START
600
Select a size, a location, and/or a quantity of pores of a mesh nebulizer.
610
Is a source of electrostatic potential available?
620
yes
Provide and electrostatic potential between the mesh nebulizer and the medical appliance so that the mesh nebulizer imparts an electrostatic charge to the droplets of the coating material opposite the charge of the medical appliance.
630
no
Contact a coating material with a first side of the mesh nebulizer.
640
Select a frequency and an amplitude of the vibration of the mesh nebulizer.
650
Vibrate the mesh nebulizer to form droplets of the coating material.
660
Fixture the medical appliance in a deposition region to allow the coating material to contact a surface of the medical appliance.
670
END
680

FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/004994

A. CLASSIFICATION OF SUBJECT MATTER
INV. B05B17/06

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)
B05B

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 11 52 920 B (LICENTIA PATENT-VERWALTUNGS-G.M.B.H) 14 August 1963 (1963-08-14) column 3, line 66 - column 4, line 41; figure 4	1-10, 14-24
X,P	WO 2005/065843 A (BLUE MEMBRANES GMBH) 21 July 2005 (2005-07-21) page 26, line 10 - page 35, line 19; figures	1-10, 14-22,24
X	SONO-TEK: "ACCU MIST-FOR SINGLE STENT COATING APPLICATIONS"[Online] 29 April 2003 (2003-04-29), XP002312401 Retrieved from the Internet: URL:http://www.sono-tek.com/biomedical/accumist> the whole document	24

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

[X] See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2006	12/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Innecken, A

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/004994

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 553 006 A (SAMES SA) 12 April 1985 (1985-04-12) page 3, line 28 - page 4, line 4; figure	25
X	FR 1 345 548 A (IWATA TOSOKI KOGYO KK) 6 December 1963 (1963-12-06) page 2, left-hand column, line 28 - page 3, left-hand column, line 5; figures	25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/004994

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 2005065843 A	21-07-2005	DE 102004001095 A1	28-07-2005
FR 2553006 A	12-04-1985	NONE	
FR 1345548 A	06-12-1963	NONE	