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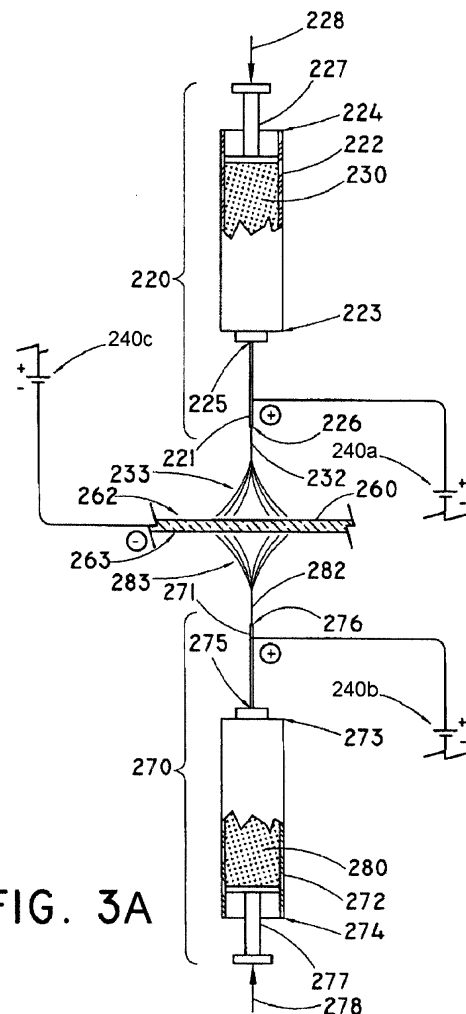
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Staple Court
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London, WC1V 7QH (GB)**(54) **Electrospinning apparatus and method**

(57) An electrospinning apparatus (10) includes a first spinneret (220) and a second spinneret (270), each including a reservoir (222, 272) and an orifice (221, 271). The first and second spinnerets (220, 270) have first and second electrical charges generated by first and second voltage sources, respectively. The first spinneret orifice (221) is located substantially opposite the second spinneret orifice (271). The first and second spinnerets (220, 270) may be used to prepare a medical device (260) defining a lumen with a proximal end, a distal end, a luminal (263) surface and an abluminal surface (262). The first spinneret orifice (221) distal end may be configured to be located outside of the medical device lumen and between about 0.1 inches (0.25 cm) and about 6.0 inches (15 cm) from the medical device abluminal surface (262). The second spinneret orifice (271) distal end may be configured to be located in the medical device (260) lumen and between about 0.1 inches (0.25 cm) and about 6.0 inches (15 cm) from the medical device luminal surface (263).

**FIG. 3A****EP 2 617 878 A1**

Description

[0001] This application relates to an electrospinning apparatus, and in particular to needle-to-needle electrospinning. This application further related to a method for preparing a medical device.

[0002] A variety of medical conditions are treated, at least in part, by inserting a medical device into the body of an afflicted patient. For example, a stent may be used to prevent vessel occlusion, in one application, or to maintain the position of a graft used to repair tissue or disease within the body. For example, a graft may be employed to span an aneurysm within a body vessel.

[0003] Medical devices may be inserted into the body temporarily or left in the body for extended periods, even indefinitely. For example, a stent and/or graft may be implanted indefinitely within a body vessel to maintain vessel integrity, e.g., blood flow. These devices can be introduced, for example, into the esophagus, trachea, colon, biliary tract, urinary tract, vascular system or other location of a human or animal patient. For example, many treatments of the vascular system entail the introduction of a device such as a stent, catheter, balloon, wire guide, cannula, or the like, including combinations of such devices. When such devices are so used, however, body vessel walls may become damaged, possibly resulting in inflammation, thrombosis and stenosis.

[0004] To mitigate any deleterious side effects, for example thrombosis formation and stenosis, medical devices may be adapted to the biological environment in which they are used. Accordingly, medical devices may be coated with biocompatible materials. Electrostatic spinning, or "electrospinning," is one process that may be used to apply a suitable biocompatible coating or covering to a medical device.

[0005] Electrospinning is a process for creating a non-woven network of fibres using an electrically charged solution that is driven from a source to a target with an electrical field. More specifically, a solution is driven from an orifice, such as a needle. A voltage is applied to the orifice resulting in a charged solution jet or stream from the orifice to the target. The jet forms a cone shape, termed a Taylor cone, as it travels from the orifice. As the distance from the orifice increases, the cone becomes stretched until the jet splits or splays into many fibres prior to reaching the target. The fibres are extremely thin, typically in the nanometer range. The collection of fibres on the target forms a thin mesh layer of fibrous material.

[0006] Electrospinning, however, is still a manufacturing technique in need of further development and refinement.

[0007] The present disclosure relates to an apparatus and method for electrospinning. Exemplary embodiments of the disclosure will be described.

[0008] According to an aspect of the present invention, there is provided an electrospinning apparatus as specified in claim 1.

[0009] The apparatus is capable of coating a medical device with one or more of a variety of different materials in an efficient and effective manner.

[0010] Each of the first solution and the second solution may include at least one of a polymer, a protein, a bio-adhesive and/or a bioactive agent.

[0011] In an embodiment, an electrospinning apparatus may include a first spinneret and a second spinneret. The first spinneret may include a reservoir and an orifice. The first spinneret orifice may include a proximal end fluidly coupled to the reservoir and a distal end through which a first solution may be electrospun. The first spinneret may have a first electrical charge. The second spinneret may include a reservoir and an orifice. The second spinneret orifice may include a proximal end fluidly coupled to the reservoir and a distal end through which a second solution may be electrospun. The second spinneret may have a second electrical charge. The first spinneret orifice may be located substantially opposite the second spinneret orifice. The first and second spinnerets may be used to prepare a medical device defining a lumen with a proximal end, a distal end, a luminal surface and an abluminal surface. The first spinneret orifice distal end may be configured to be located outside of the medical device lumen between the medical device proximal end and the medical device distal end. The first spinneret orifice distal end may be configured to be located between about 0.1 inches (0.25 cm) and about 6.0 inches (15 cm) from the medical device abluminal surface. The first spinneret orifice distal end may be configured to directly face the medical device abluminal surface. The second spinneret orifice distal end may be configured to be located in the medical device lumen between the medical device proximal end and the medical device distal end. The second spinneret orifice distal end may be configured to be located between about 0.1 inches (0.25 cm) and about 6.0 inches (15 cm) from the medical device luminal surface. The second spinneret orifice distal end may be configured to directly face the medical device luminal surface.

[0012] In an embodiment, an electrospinning apparatus may include a first spinneret and a second spinneret. The first spinneret may include a reservoir and an orifice. The first spinneret orifice may include a proximal end fluidly coupled to the reservoir and a distal end through which a first solution may be electrospun. The first spinneret may have a first electrical charge. The second spinneret may include a reservoir and an orifice. The second spinneret orifice may include a proximal end fluidly coupled to the reservoir and a distal end through which a second solution may be electrospun. The second spinneret may have a second electrical charge. The first spinneret orifice may be located substantially opposite the second spinneret orifice. The first and second spinnerets may be used to prepare a medical device defining a lumen with a proximal end, a distal end, a luminal surface and an abluminal surface. The first spinneret orifice distal end may be configured to be located outside of the med-

ical device lumen between the medical device proximal end and the medical device distal end. The first spinneret orifice distal end may be configured to directly face the medical device abluminal surface. The second spinneret orifice distal end may be configured to be located in the medical device lumen between the medical device proximal end and the medical device distal end. The second spinneret orifice distal end may be configured to directly face the medical device luminal surface.

[0013] According to a second aspect of the present invention, there is provided a method for preparing a medical device as specified in claim 13.

[0014] The method may include moving the medical device relative to the first spinneret orifice or the second spinneret orifice and simultaneously electrospinning the first solution about a length or a width of the medical device first surface and the second solution about a length or a width of the medical device second surface.

[0015] In an embodiment, a method for preparing a medical device may include providing the medical device. The medical device may include a first surface and an opposing second surface. The method may include providing an electrospinning apparatus. The electrospinning apparatus may include a first spinneret and a second spinneret located substantially opposite the first spinneret. The first spinneret may include a reservoir and an orifice fluidly coupled to the first spinneret reservoir. The second spinneret may include a reservoir and an orifice fluidly coupled to the second spinneret reservoir. The method may include applying a first electrical charge to the first spinneret and applying a second electrical charge to the second spinneret. A sign of the second electrical charge may be the same as a sign of the first electrical charge. The method may include applying a third electrical charge to the medical device. A sign of the third electrical charge may be opposite of the sign of the first electrical charge and the sign of the second electrical charge. The method may include locating the first spinneret orifice nearby the medical device first surface and locating the second spinneret orifice nearby the medical device second surface. The method may include simultaneously electrospinning the first solution onto the medical device first surface and the second solution onto the medical device second surface.

[0016] Other systems, methods, features and advantages will be, or will become, apparent to one with skill in the art upon examination of the following figures and detailed description. It is intended that all such additional systems, methods, features and advantages be included within this description, be within the scope of the disclosure, and be protected by the following claims.

[0017] Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings, in which:

FIG. 1 is a schematic representation of an exemplary electrospinning apparatus.

FIG. 2 is a schematic representation of an exemplary

electrospinning apparatus.

FIG. 3 is a schematic representation of an exemplary electrospinning apparatus.

FIG. 3A is a schematic representation of an exemplary electrospinning apparatus.

FIG. 4 is a schematic representation of an exemplary electrospinning apparatus.

FIGS. 5A and 5B are schematic representations of exemplary spinneret configurations.

[0018] The components in the Figures are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the disclosure.

[0019] The present disclosure provides a method and apparatus for coating a medical device.

[0020] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

Definitions

[0021] The term "body vessel" means any tube-shaped body passage lumen that conducts fluid, including but not limited to blood vessels such as those of the human vasculature system, esophageal, intestinal, biliary, urethral and ureteral passages.

[0022] The term "biocompatible" refers to a material that is substantially non-toxic in the *in vivo* environment of its intended use, and that is not substantially rejected by the patient's physiological system (i.e., is non-antigenic). This can be gauged by the ability of a material to pass the biocompatibility tests set forth in International Standards Organization (ISO) Standard No. 10993 and/or the U.S. Pharmacopeia (USP) 23 and/or the U.S. Food and Drug Administration (FDA) blue book memorandum No. G95-1, entitled "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." Typically, these tests measure a material's toxicity, infectivity, pyrogenicity, irritation potential, reactivity, hemolytic activity, carcinogenicity and/or immunogenicity. A biocompatible structure or material, when introduced into a majority of patients, will not cause a significantly adverse, long-lived or escalating biological reaction or response, and is distinguished from a mild, transient inflammation which typically accompanies surgery or implantation of foreign objects into a living organism.

[0023] The term "hydrophobic" refers to material that

tends not to combine with water. One way of observing hydrophobicity is to observe the contact angle formed between a water droplet or solvent and a substrate; the higher the contact angle the more hydrophobic the surface. Generally, if the contact angle of a liquid on a substrate is greater than 90°. then the material is said to be hydrophobic.

[0024] The term "implantable" refers to an ability of a medical device to be positioned, for any duration of time, at a location within a body, such as within a body vessel. Furthermore, the terms "implantation" and "implanted" refer to the positioning, for any duration of time, of a medical device at a location within a body, such as within a body vessel.

[0025] The phrase "controlled release" refers to an adjustment in the rate of release of a bioactive agent from a medical device in a given environment. The rate of a controlled release of a bioactive agent may be constant or vary with time. A controlled release may be characterized by a drug elution profile, which shows the measured rate at which the bioactive agent is removed from a drug-coated device in a given solvent environment as a function of time.

[0026] The phrase "bioactive agent" refers to any pharmaceutically active agent that results in an intended therapeutic effect on the body to treat or prevent conditions or diseases. Bioactive agents include any suitable biologically active chemical compounds, biologically derived components such as cells, peptides, antibodies, and polynucleotides, and radiochemical bioactive agents, such as radioisotopes. An "anti-proliferative" agent/factor/drug includes any protein, peptide, chemical or other molecule that acts to inhibit cell proliferative events. Examples of anti-proliferative agents include microtubule inhibitors such as vinblastine, vincristine, colchicine and paclitaxel, or other agents such as cisplatin.

[0027] The term "pharmaceutically acceptable" refers to those compounds of the present disclosure which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower mammals without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the disclosure.

[0028] The term "coating," unless otherwise indicated, refers generally to material attached to an implantable medical device prior to implantation. A coating can include material covering any portion of a medical device, and can include one or more coating layers. A coating can have a substantially constant or a varied thickness and composition. Coatings can be adhered to any portion of a medical device surface, including the luminal surface, the abluminal surface, or any portions or combinations thereof.

[0029] "Pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of

humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in J. Pharm Sciences, 66: 1-19 (1977), which is hereby incorporated by reference.

[0030] The term "pharmaceutically acceptable ester" refers to esters which hydrolyse *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than six carbon atoms. Examples of particular esters include formates, acetates, propionates, butyates, acrylates and ethylsuccinates.

[0031] The term "pharmaceutically acceptable prodrug" refers to those prodrugs of the compounds of the present disclosure which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the disclosure. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to provide the parent compound having the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

Electrospinning

[0032] FIG. 1 shows an electrospinning apparatus 10 for coating an object, such as a substrate or medical device. A solution 30 is loaded into a reservoir 22, such as a syringe-like container. The reservoir 22 is fluidly coupled to an orifice 24, such as a needle, to form a spinneret 20.

[0033] The orifice 24 has a distal opening 25 through which the solution 30 is driven by a displacement system 26. The displacement system 26 may comprise any suitable controllable variable rate fluid displacement system, but is desirably an automated system to ensure consistent and accurate flow rates. For example, in FIG. 1, the displacement system 26 is represented in a simplified manner as being provided by a plunger. In one example, the fluid displacement system may deliver solution 30 at a delivery rate of about 0 mL/hr to about 25 mL/hr, of about 1 mL/hr to about 10 mL/hr, or about 3 mL/hr to about 7 mL/hr.

[0034] An electric potential 40 is established across

the spinneret 20 and a target 50. In one example, the electric potential is between about 10 kV and about 35 kV, between about 15 kV and about 30 kV, or between about 20 kV and about 25 kV. The electric potential 40 aids the displacement system 26 and motivates the solution 30 from the orifice distal opening 25. The solution forms a charged jet or stream 32 from the distal opening 25 to the target 50. The solution stream 32 forms a cone shape 33, called a Taylor cone, between the spinneret 20 and the target 50. As the solution stream 32 travels from the opening 25, the cone 33 splays or stretches at a position 34 between the spinneret 20 and the target 50. In one example, the distance between the distal opening 25 and the target 50 is between about 0.1 inches to about 6 inches, between about 0.5 inches to about 4 inches, or between about 1 inch to about 2 inches. Position 34 need not be substantially intermediate the orifice distal opening 25 and the target 50, and may be located at any desired distance between the orifice distal opening 25 and the target 50. The splaying or stretching action creates a plurality of fibres that may or may not dry upon reaching the target, depending on the volatility of the chosen solvent.

[0035] In one example, an electrospinning apparatus may apply a coating or covering on a medical device surface. For example, in FIG. 2, a portion of a medical device 160 is placed in between a spinneret 120 and a target, such as a mandrel 150. In one example, the distance between the spinneret 120 and the medical device 160 is between about 0.1 inches (0.25 cm) to about 6 inches (15 cm), between about 0.5 inches (1.3 cm) to about 4 inches (10 cm), or between about 1 inch (2.5 cm) to about 2 inches (5 cm). The medical device includes a first surface 162, and an opposing second surface 163. For example, the first surface may be an outer surface, an exterior surface or an abluminal surface, and the opposing second surface may be an inner surface, an interior surface or a luminal surface. The mandrel 150 is located adjacent the medical device second surface 163. The spinneret 120 includes a reservoir 122 having a distal end 123 and a proximal end 124. The reservoir is loaded with solution 130 and is fluidly coupled at the reservoir distal end 123 to an orifice 125 at the orifice proximal end 126. The reservoir proximal end 124 is fluidly coupled to a displacement system 128, such as a plunger. The orifice distal end 127 is oriented in the direction of the medical device 160. For example, the orifice distal end 127 may be oriented towards the mandrel 150 such that any solution 130 exiting the orifice distal end 127 is directed towards the mandrel 150. A voltage source 140 is electrically coupled to the spinneret 120 and mandrel 150.

[0036] Still referring to FIG. 2, the voltage source 140 generates an electric potential between the spinneret 120 and mandrel 150. In one example, the electric potential applied by the voltage source is between about 10 kV and about 35 kV, between about 15 kV and about 30 kV, or between about 20 kV and about 25 kV. The plunger 128 may be advanced in a distal direction 129, and may

urge the solution 130 from the spinneret 120. The electric potential and plunger movement 129 may motivate the solution 130 from the spinneret 120. The solution 130 exits the orifice distal end 127 as a charged solution stream or jet 132. The solution stream 132 is directed towards the medical device first surface 162. For example, the solution stream 132 may be directed at the focused mandrel 150 located adjacent the medical device second surface 163. As the solution stream 132 travels away from the orifice distal end 127 towards the medical device 160, the solution stream 132 splays 133 before contacting the medical device first surface 162. The splaying 133 may form a plurality of fibres, such as nanofibres. The fibres contact the medical device first surface 162 to form a coating of non-woven fibres thereon. In one example, the solution 130 may have a delivery rate of about 0 mL/hr to about 25 mL/hr, of about 1 mL/hr to about 10 mL/hr, or about 3 mL/hr to about 7 mL/hr.

[0037] In an embodiment, the medical device 160 may be moved relative to the spinneret 120 and/or target 150. Movement of the medical device 160 relative to the spinneret 120 and/or target 150 may permit the coating of any portion of the medical device first surface 162. For example, the first surface 162 may be coated almost entirely, partially, or at discrete locations. For example, the medical device 160 may be moved laterally 165 to direct the fibres about the horizontal length of the medical device first surface 162. The medical device 160 also may be moved vertically to direct the fibres about the vertical length (e.g., top to bottom) of the medical device 160. Alternatively, the medical device 160 may remain stationary while the spinneret 120 and/or target 150 move relative to the medical device 160.

[0038] The relative motion of the spinneret 120 and medical device 160 may influence several properties of the resulting coating of fibres. For example, if the medical device 160 is moved laterally 165, as the relative speed between the spinneret 120 and medical device 160 is increased, the thickness of the coating will be reduced, and the fibres may tend to be increasingly aligned with each other. This may affect the strength, resiliency, and porosity of the coating. If the spinneret 120 is moved relative to the target 150, for example increasing the distance between the target 150 and spinneret 120, the solution stream 132 will travel a greater distance and may affect the splaying and drying of the solution stream 132.

[0039] In another example, the spinneret orifice may be located about the medical device second surface and the focused mandrel may be located adjacent the medical device first surface. For example, the apparatus configuration of FIG. 2 may be reversed, with the orifice distal end located about the medical device second surface and the focused mandrel adjacent the medical device first surface. This configuration may permit coating or covering the medical device second surface with electrospun fibres.

[0040] In an embodiment, an electrospinning apparatus may simultaneously apply a coating on a medical

device first surface and second surface. For example, in FIG. 3, a portion of a medical device 260 is placed in between a first spinneret orifice 221 and a second spinneret orifice 271. The medical device 260 includes a first surface 262 and an opposing second surface 263. For example, the first surface may be an outer surface, an exterior surface or an abluminal surface, and the opposing second surface may be an inner surface, an interior surface or a luminal surface. The first spinneret 220 includes a reservoir 222 having a distal end 223 and a proximal end 224. The reservoir 222 is loaded with a first solution 230 and is fluidly coupled at the reservoir distal end 223 to the orifice 221, such as a needle, at the orifice proximal end 225. The reservoir proximal end 224 is fluidly coupled to a displacement system 227, such as a plunger. The first spinneret orifice distal end 226 is oriented in the direction of the medical device first surface 262. For example, the first spinneret orifice distal end 226 may be substantially oriented towards the second spinneret orifice 271 such that any solution exiting the first spinneret orifice distal end 226 is directed towards the second spinneret orifice 271. It should be noted that the first spinneret orifice distal end 226 need not be directly opposite the second spinneret orifice 271.

[0041] The second spinneret 270 includes a reservoir 272 having a distal end 273 and a proximal end 274, and is loaded with a second solution 280. The second spinneret 270 is fluidly coupled at the reservoir distal end 273 to the second spinneret orifice 271, such as a needle, at the orifice proximal end 275. The reservoir proximal end 274 is fluidly coupled to a displacement system 277, such as a plunger. The second spinneret orifice distal end 276 is oriented in the direction of the medical device second surface 263. For example, the second spinneret orifice distal end 276 may be oriented towards the first spinneret orifice 221 such that any solution 280 exiting the second spinneret orifice distal end 276 is directed towards the first spinneret orifice 221. A voltage source 240 is electrically coupled to the first spinneret 220 and second spinneret 270.

[0042] Still referring to FIG. 3, the voltage source 240 generates an electric potential between the first spinneret orifice 221 and second spinneret orifice 271. In one example, the electric potential applied by the voltage source is between about 10 kV and about 35 kV, between about 15 kV and about 30 kV, or between about 20 kV and about 25 kV. The plungers 227, 277 of the first spinneret 220 and second spinneret 270 may be advanced 228, 278 within their respective reservoirs 222, 272, and may urge the first solution 230 and second solution 280 from the first spinneret orifice 221 and second spinneret orifice 271, respectively. The electric potential and plunger movement may motivate the first solution 230 and second solution 280 from the first spinneret orifice 221 and second spinneret orifice 271, respectively. The first solution 230 exits the first spinneret orifice distal end 226 as a first charged solution stream or jet 232. The first solution stream 232 is directed towards the medical de-

vice first surface 262. For example, the first solution stream 232 may be directed at the second spinneret orifice 271 located about the medical device second surface 263. The second solution 280 exits the second spinneret orifice distal end 276 as a second charged solution stream or jet 282. The second solution stream 282 is directed towards the medical device second surface 263. For example, the solution stream 282 may be directed at the first spinneret orifice 221 located about the medical device first surface 263. The first solution stream 232 need not be directly opposite the second solution stream 282. For example, the first solution stream 232 may be located at any distance from the second solution stream 282 so long as a sufficient electrical attraction is maintained between the first solution stream 232 and second solution stream 282. In one example, the solutions 230, 280 may have a delivery rate of about 0 mL/hr to about 25 mL/hr, of about 1 mL/hr to about 10 mL/hr, or about 3 mL/hr to about 7 mL/hr.

[0043] As the solution streams 232, 282 travel away from their respective spinneret orifices 221, 271 in the direction of the medical device 260, the first solution stream 232 and second solution stream 282 splay 233, 283 before contacting the medical device first surface 262 and second surface 263, respectively. The splaying 233, 283 may form a plurality of fibres, such as nanofibres. The fibres contact the medical device exterior surface 263 and interior surface 262 to form a non-woven network of fibres.

[0044] As shown in FIG. 3A, a first voltage source 240a may be electrically coupled to the first spinneret 220, a second voltage source 240b may be electrically coupled to the second spinneret 270, and/or a third voltage source 240c may be electrically coupled to the medical device 260. In this example, the first voltage source 240a generates an electric charge on the first spinneret orifice 221. In other words, the first voltage source 240a generates an electric potential between the first spinneret orifice 221 and ground. Similarly, the second voltage source 240b generates an electric charge on the second spinneret orifice 271, and/or the third voltage source 240c generates an electric charge on the medical device 260. In one example, the electric potential applied by the first, second, and/or third voltage sources is between about 10 kV and about 35 kV, between about 15 kV and about 30 kV, or between about 20 kV and about 25 kV.

[0045] The electric charge on the first spinneret orifice 221 may have the same sign as the electric charge on the second spinneret orifice 271 as shown in FIG. 3A. The electric charge on the medical device 260 may have an opposite sign relative to the electric charge on the first spinneret orifice 221 and/or the second spinneret orifice 271. In one example, the first spinneret orifice 221 and the second spinneret orifice 271 are positively charged (i.e., the signs of the electric charges are positive), and the medical device 260 is negatively charged (i.e., the sign of the electric charge is negative). In another example, the first spinneret orifice 221 and the second spin-

neret orifice 271 are negatively charged (i.e., the signs of the electric charges are negative), and the medical device 260 is positively charged (i.e., the sign of the electric charge is positive). Alternatively, the electric charge on the first spinneret orifice 221 may have an opposite sign relative to the electric charge on the second spinneret orifice 271. The medical device 260 may be neutral or substantially uncharged. Alternatively, the electric charge on the medical device 260 may have the same sign as the electric charge on the first spinneret orifice 221 or the second spinneret orifice 271.

[0046] The magnitude of the electric charge on the first spinneret orifice 221 may be the same as or different than the magnitude of the electric charge on the second spinneret orifice 271 and/or the magnitude of the electric charge on the medical device 260. In one example, the magnitude of the electric charge on the first spinneret orifice 221 is substantially the same as the magnitude of the electric charge on the second spinneret orifice 271. Additionally, or alternatively, the magnitude of the electric charge on the medical device 260 may be greater than the magnitudes of the electric charges on the first and/or second spinneret orifices. The magnitudes of the electric charges on the first spinneret orifice 221, the second spinneret orifice 271, and the medical device 260 may be greater than, less than, or substantially the same as one another. The relative magnitudes of the electric charges on the first spinneret orifice 221, the second spinneret orifice 271, and/or the medical device 260 may be adjusted according to the electrical conductivity of the first and/or second solutions. In one example, the first solution is different than the second solution, and the electrical conductivity of the first solution is different from the electrical conductivity of the second solution. In this example, the relative magnitudes of the electric charges on the first spinneret orifice 221 and the second spinneret orifice 271 may be adjusted to correspond to the electrical conductivity of the first and second solutions, respectively. Additionally, or alternatively, the relative magnitudes of the electric charges on the first spinneret orifice 221, the second spinneret orifice 271, and/or the medical device 260 may be adjusted to adjust the properties of the electrospun fibres and/or the properties of the coating applied to the medical device. For example, the relative magnitudes of the electric charges may be adjusted to adjust the relative thicknesses of the inner and outer layers of electrospun fibres deposited on the medical device. Additionally, or alternatively, the relative magnitudes of the electric charges may be adjusted according to the distances between the spinnerets and the medical device.

[0047] An electrospinning apparatus including multiple voltage sources (e.g., the first voltage source 240a, the second voltage source 240b, and/or the third voltage source 240c shown in FIG. 3A) may enable the electric charges of the first spinneret orifice 221, the second spinneret orifice 271, and/or the medical device 260 to be independently adjustable. For example, the sign and/or the magnitude of each of the first spinneret orifice 221,

the second spinneret orifice 271, and/or the medical device 260 may be adjustable independently of the others of the first spinneret orifice 221, the second spinneret orifice 271, and/or the medical device 260. This may enable a single electrospinning apparatus to be configured to coat the first surface 262 and the second surface 263 of the medical device 260 with the same material (e.g., by loading the same solution into each of the first spinneret 220 and the second spinneret 270) or to coat the first surface 262 and the second surface 263 of the medical device 260 with different materials (e.g., by loading different solutions into each of the first spinneret 220 and the second spinneret 270). To that end, the first solution and the second solution may be the same as or different than one another. Additionally, or alternatively, the electrospinning apparatus may be used with various solutions regardless of whether the solutions tend to be more responsive to positive electric charges, negative electric charges, relatively high electric potentials, and/or relatively low electric potentials.

[0048] In another example, an electrospinning apparatus may simultaneously apply a coating on a medical device abluminal surface and luminal surface. For example, in FIG. 4, a portion of a medical device 360 is placed intermediate a first spinneret orifice 321 and a second spinneret orifice 371. The medical device 360 includes a lumen 361 having a luminal surface 362 and abluminal surface 363. The first spinneret 320 is located nearby the medical device exterior 364 and includes a reservoir 322 having a distal end 323 and a proximal end 324. The reservoir 322 is loaded with a first solution 330 and is fluidly coupled at the reservoir distal end 323 to the orifice 321 at the orifice proximal end 325. The reservoir proximal end 324 is fluidly coupled to a displacement system 327, such as a plunger. The first spinneret orifice distal end 326 is oriented in the direction of the medical device abluminal surface 363. For example, the first spinneret orifice distal end 326 may be substantially oriented towards the second spinneret orifice 371 such that any solution exiting the first spinneret orifice distal end 326 is directed towards the second spinneret orifice 371.

[0049] The second spinneret 370 may be located nearby the medical device exterior 364 and/or in the medical device lumen 361. The second spinneret 370 includes a reservoir 372 having a distal end 373 and a proximal end 374, and is loaded with a second solution 380. The second spinneret 370 is fluidly coupled at the reservoir distal end 373 to the second spinneret orifice 371 at the orifice proximal end 375. The reservoir proximal end 374 is fluidly coupled to a displacement system 377, such as a plunger. The second spinneret orifice distal end 376 is oriented in the direction of the medical device luminal surface 362. For example, the second spinneret orifice distal end 376 may be substantially oriented towards the first spinneret orifice 321 such that any solution 380 exiting the second spinneret orifice distal end 376 is directed towards the first spinneret orifice 321. A voltage source 340 is electrically coupled to the first spinneret 320 and

second spinneret 370.

[0050] Still referring to FIG. 4, the voltage source 340 generates an electric potential between the first spinneret orifice 321 and second spinneret orifice 371. In one example, the electric potential applied by the voltage source is between about 10 kV and about 35 kV, between about 15 kV and about 30 kV, or between about 20 kV and about 25 kV. Additionally, or alternatively, an electrical charge may be applied to the first spinneret orifice 321, the second spinneret orifice 371, and/or the medical device 360 as described above with reference to FIG. 3A. In this example, the electrical charge on the first spinneret orifice 321 may have the same sign as the electrical charge on the second spinneret orifice 371, which may be opposite of the electrical charge on the medical device 360. Additionally, or alternatively, the electric charges on the first spinneret orifice 321, the second spinneret orifice 371, and/or the medical device 360 may be independently adjustable as described above with reference to FIG. 3A. Returning to FIG. 4, the plungers 327, 377 of the first spinneret 320 and second spinneret 370 may be advanced 328, 378 within their respective reservoirs 322, 372, and may urge the first solution 330 and second solution 380 from the first spinneret orifice 321 and second spinneret orifice 371, respectively. In one example, the solutions 330, 380 may have a delivery rate of about 0 mL/hr to about 25 mL/hr, of about 1 mL/hr to about 10 mL/hr, or about 3 mL/hr to about 7 mL/hr. The electric potential and plunger movement may motivate the first solution 330 and second solution 380 from the first spinneret orifice 321 and second spinneret orifice 371, respectively. The first solution 330 exits the first spinneret orifice distal end 326 as a first charged solution stream or jet 332. The first solution stream 332 is directed towards the medical device abluminal surface 363. For example, the first solution stream 332 may be directed at the second spinneret orifice 371 located in the medical device lumen 361. The second solution 380 exits the second spinneret orifice distal end 376 as a second charged solution stream or jet 382. The second solution stream 382 is directed towards the medical device luminal surface 362. For example, the solution stream 382 may be directed at the first spinneret orifice 321 located about the medical device exterior 364. The first solution stream 332 need not be directly opposite the second solution stream 382. For example, the first solution stream 332 may be located at any distance from the second solution stream 382 so long as a sufficient electrical attraction is maintained between the first solution stream 332 and second solution stream 382 and/or between the first solution stream 332 and the medical device 260 and the second solution stream 382 and the medical device 360.

[0051] As the solution streams 332, 382 travel away from their respective spinneret orifices 321, 371 in the direction of the medical device 360, the first solution stream 332 and second solution stream 382 splay 333, 383 before contacting the medical device abluminal surface 363 and luminal surface 362, respectively. The

splaying 333, 383 may form a plurality of fibres, such as nanofibres. The fibres contact the medical device abluminal surface 363 and luminal surface 362 to form a non-woven network of fibres.

[0052] Referring further to FIGS. 1-4, the spinnerets may have any suitable configuration. For example, a spinneret may comprise a conical or hemispherical configuration. FIG. 5A depicts a spinneret 510 having a conical outer profile 511. FIG. 5B depicts a spinneret 520 having a hemispherical outer profile 521. Modification of the spinneret configuration may alter the electrical field and optimize the attractive forces upon the electrospun fibres.

15 Solutions

[0053] Solutions for use in the present disclosure may include any liquids containing materials to be electrospun. For example, solutions may include, but are not limited to, suspensions, emulsions, melts, and hydrated gels containing the materials, substances, or compounds to be electrospun. Solutions may further include solvents or other liquids or carrier molecules.

[0054] Materials appropriate for electrospinning may include any compound, molecule, substance, or group or combination thereof that forms any type of structure or group of structures during or after electrospinning. For example, materials may include natural materials, synthetic materials, or combinations thereof. Naturally occurring organic materials include any substances naturally found in the body of plants or other organisms, regardless of whether those materials have or can be produced or altered synthetically. Synthetic materials include any materials prepared through any method of artificial synthesis, processing, or manufacture. In one example the materials are biologically compatible materials.

[0055] One class of materials for electrospinning comprises proteins, such as extracellular matrix (ECM) proteins. ECM proteins include, but are not limited to, collagen, fibrin, elastin, laminin, and fibronectin. In one example, the protein is collagen of any type. Additional materials include further ECM components, for example proteoglycans.

[0056] Proteins, as used herein, refer to their broadest definition and encompass the various isoforms that are commonly recognized to exist within the different families of proteins and other molecules. There are multiple types of each of these proteins and molecules that are naturally occurring, as well as types that can be or are synthetically manufactured or produced by genetic engineering. For example, collagen occurs in many forms and types and all of these types and subsets are encompassed herein.

[0057] The term protein, and any term used to define a specific protein or class of proteins further includes, but is not limited to, fragments, analogues, conservative amino acid substitutions, non-conservative amino acid substitutions and substitutions with non-naturally occurring

amino acids with respect to a protein or type or class of proteins. For example, the term collagen includes, but is not limited to, fragments, analogues, conservative amino acid substitutions, and substitutions with non-naturally occurring amino acids or residues with respect to any type or class of collagen. The term "residue" is used herein to refer to an amino acid (D or L) or an amino acid mimetic that is incorporated into a protein by an amide bond. As such, the residue can be a naturally occurring amino acid or, unless otherwise limited, can encompass known analogues of natural amino acids that function in a manner similar to the naturally occurring amino acids (i.e., amino acid mimetics).

[0058] Furthermore, as discussed above, individual substitutions, deletions or additions which alter, add or delete a single amino acid or a small percentage of amino acids (preferably less than 10%, more preferably less than 5%) in an encoded sequence are conservatively modified variations where the alterations result in the substitution of an amino acid with a chemically similar amino acid.

[0059] It is to be understood that the term protein, polypeptide or peptide further includes fragments that may be 90% to 95% of the entire amino acid sequence, as well as extensions to the entire amino acid sequence that are 5% to 10% longer than the amino acid sequence of the protein, polypeptide or peptide.

[0060] In one example, the solution may comprise synthetic materials, such as biologically compatible synthetic materials. For example, synthetic materials may include polymers. Such polymers include but are not limited to the following: poly(urethanes), poly(siloxanes) or silicones, poly(ethylene), poly(vinyl pyrrolidone), poly(2-hydroxy ethyl methacrylate), poly(N-vinyl pyrrolidone), poly(methyl methacrylate), poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, poly(ethylene-co-vinyl acetate), poly(ethylene glycol), poly(methacrylic acid), polylactides (PLA), polyglycolides (PGA), poly(lactide-co-glycolid-es) (PLGA), polyanhydrides, and polyorthoesters or any other similar synthetic polymers that may be developed that are biologically compatible. Biologically compatible synthetic polymers further include copolymers and blends, and any other combinations of the foregoing either together or with other polymers generally. The use of these polymers will depend on given applications and specifications required.

[0061] Solutions may also include electrospun materials that are capable of changing into different materials during or after electrospinning. For example, procollagen will form collagen when combined with procollagen peptidase. Procollagen, procollagen peptidase, and collagen are all within the definition of materials. Similarly, the protein fibrinogen, when combined with thrombin, forms fibrin. Fibrinogen or thrombin that are electrospun as well as the fibrin that later forms are included within the definition of materials.

[0062] Solutions may comprise any solvent that allows delivery of the material or substance to the orifice, tip of

a syringe, or other site from which the material will be electrospun. The solvent may be used for dissolving or suspending the material or the substance to be electrospun. For example, solvents used for electrospinning have the principal role of creating a mixture with collagen and/or other materials to be electrospun, such that electrospinning is feasible.

[0063] The concentration of a given solvent is often an important consideration in electrospinning. In electrospinning, interactions between molecules of materials stabilize the solution stream, leading to fibre formation. The solvent should sufficiently dissolve or disperse the polymer to prevent the solution stream from disintegrating into droplets and should thereby allow formation of a stable stream in the form of a fibre. In one example, the solution has a concentration of about 0.005 g/mL to about 0.15 g/mL, about 0.01 g/mL to about 0.12 g/mL, or about 0.04 g/mL to about 0.09 g/mL.

[0064] Solvents useful for dissolving or suspending a material or a substance depend on the material or substance. For example, collagen can be electrodeposited as a solution or suspension in water, 2,2,2-trifluoroethanol, 1,1,1,3,3,3-hexafluoro-2-propanol (also known as hexafluoroisopropanol or HFIP), or combinations thereof. Fibrin monomer can be electrospun from solvents such as urea, monochloroacetic acid, water, 2,2,2-trifluoroethanol, HFIP, or combinations thereof. Elastin can be electrodeposited as a solution or suspension in water, 2,2,2-trifluoroethanol, isopropanol, HFIP, or combinations thereof, such as isopropanol and water. Other lower order alcohols, especially halogenated alcohols, may be used. Additional solvents that may be used or combined with other solvents include acetamide, N-methylformamide, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide, N-methyl pyrrolidone (NMP), acetic acid, trifluoroacetic acid, ethyl acetate, acetonitrile, trifluoroacetic anhydride, 1,1,1-trifluoroacetone, maleic acid, hexafluoroacetone.

[0065] Proteins and peptides associated with membranes are often hydrophobic and thus do not dissolve readily in aqueous solutions. Such proteins can be dissolved in organic solvents such as methanol, chloroform, and trifluoroethanol (TFE) and emulsifying agents. Any other solvents may be used, for example, solvents useful in chromatography, especially high performance liquid chromatography. Proteins and peptides are also soluble, for example, in HFIP, hexafluoroacetone, chloroalcohols in conjugation with aqueous solutions of mineral acids, dimethylacetamide containing 5% lithium chloride, and in acids such as acetic acid, hydrochloric acid and formic acid. In some embodiments, the acids are very dilute, in others the acids are concentrated. N-methyl morpholine-N-oxide is another solvent that can be used with many polypeptides. Other compounds, used either alone or in combination with organic acids or salts, include the following: triethanolamine; dichloromethane; methylene chloride; 1,4-dioxane; acetonitrile; ethylene glycol; diethylene glycol; ethyl acetate; glycerine; propane-1,3-diol;

furan; tetrahydrofuran; indole; piperazine; pyrrole; pyrrolidone; 2-pyrrolidone; pyridine; quinoline; tetrahydroquinoline; pyrazole; and imidazole. Combinations of solvents may also be used.

[0066] Synthetic polymers may be electrospun from, for example, HFIP, methylene chloride, ethyl acetate; acetone, 2-butanone (methyl ethyl ketone), diethyl ether; ethanol; cyclohexane; water; dichloromethane (methylene chloride); tetrahydrofuran; dimethylsulfoxide (DMSO); acetonitrile; methyl formate and various solvent mixtures. HFIP and methylene chloride are desirable solvents. Selection of a solvent will depend upon the characteristics of the synthetic polymer to be electrodeposited.

[0067] Selection of a solvent, for example, is based in part on consideration of secondary forces that stabilize polymer-polymer interactions and the solvent's ability to replace these with strong polymer-solvent interactions. In the case of polypeptides such as collagen, and in the absence of covalent crosslinking, the principal secondary forces between chains are: (1) coulombic, resulting from attraction of fixed charges on the backbone and dictated by the primary structure (e.g., lysine and arginine residues will be positively charged at physiological pH, while aspartic or glutamic acid residues will be negatively charged); (2) dipole-dipole, resulting from interactions of permanent dipoles; the hydrogen bond, commonly found in polypeptides, is the strongest of such interactions; and (3) hydrophobic interactions, resulting from association of non-polar regions of the polypeptide due to a low tendency of non-polar species to interact favorably with polar water molecules. Solvents or solvent combinations that can favorably compete for these interactions can dissolve or disperse polypeptides. For example, HFIP and TFE possess a highly polar OH bond adjacent to a very hydrophobic fluorinated region. Additionally, the hydrophobic portions of these solvents can interact with hydrophobic domains in polypeptides, helping to resist the tendency of the latter to aggregate via hydrophobic interactions. In some examples, solvents are selected based on their tendency to induce helical structure in electrospun protein fibres, thereby predisposing monomers of collagen or other proteins to undergo polymerization and form helical polymers that mimic the native collagen fibril. Examples of such solvents include halogenated alcohols, preferably fluorinated alcohols (HFIP and TFE) hexafluoroacetone, chloroalcohols in conjugation with aqueous solutions of mineral acids and dimethylacetamide, preferably containing lithium chloride. HFIP and TFE are especially preferred. In some examples, water is added to the solvents.

[0068] The solvent, moreover, may have a relatively high vapor pressure to promote the stabilization of an electrospinning solution stream to create a fibre as the solvent evaporates. In examples involving higher boiling point solvents, it is often desirable to facilitate solvent evaporation by warming the spinning solution, and optionally the solution stream itself, or by electrospinning

in reduced atmospheric pressure.

Bioactive Agents

[0069] In one example, a solution for electrospinning may further comprise bioactive materials, for example a therapeutically effective amount of one or more bioactive agents in pure form or in derivative form. Preferably, the derivative form is a pharmaceutically acceptable salt, ester or prodrug form. Alternatively, a medical device may be implanted in combination with the administration of a bioactive agent from a catheter positioned within the body near the medical device, before, during or after implantation of the device.

[0070] Bioactive agents that may be used in the present disclosure include, but are not limited to, pharmaceutically acceptable compositions containing any of the bioactive agents or classes of bioactive agents listed herein, as well as any salts and/or pharmaceutically acceptable formulations thereof.

[0071] The bioactive agent may be coated on any suitable part of the medical device. Selection of the type of bioactive agent and the portions of the medical device comprising the bioactive agent may be chosen to perform a desired function upon implantation. For example, the bioactive agent may be selected to treat indications such as coronary artery angioplasty, renal artery angioplasty, carotid artery surgery, renal dialysis fistulae stenosis, or vascular graft stenosis.

[0072] The bioactive agent may be selected to perform one or more desired biological functions. For example, the abluminal surface of the medical device may comprise a bioactive agent selected to promote the ingrowth of tissue from the interior wall of a body vessel, such as a growth factor. An anti-angiogenic or antineoplastic bioactive agent such as paclitaxel, sirolimus, or a rapamycin analogue, or a metalloproteinase inhibitor such as batimastat may be coated on the medical device to mitigate or prevent undesired conditions in the vessel wall, such as restenosis. Many other types of bioactive agents can be coated on the medical device.

[0073] Bioactive agents for use in electrospinning solutions of the present disclosure include those suitable for coating an implantable medical device. The bioactive agent can include, for example, one or more of the following: antiproliferative agents (sirolimus, paclitaxel, actinomycin D, cyclosporine), immunomodulating drugs (tacrolimus, dexamethasone), metalloproteinase inhibitors (such as batimastat), antisclerosing agents (such as collagenases, halofuginone), prohealing drugs (nitric oxide donors, estradiols), mast cell inhibitors and molecular interventional bioactive agents such as c-myc antisense compounds, thromboresistant agents, thrombolytic agents, antibiotic agents, anti-tumor agents, antiviral agents, anti-angiogenic agents, angiogenic agents, anti-mitotic agents, anti-inflammatory agents, angiostatin agents, endostatin agents, cell cycle regulating agents, genetic agents, including hormones such as estrogen,

their homologues, derivatives, fragments, pharmaceutical salts and combinations thereof. Other useful bioactive agents include, for example, viral vectors and growth hormones such as Fibroblast Growth Factor and Transforming Growth Factor-beta.

[0074] Medical devices comprising an antithrombogenic bioactive agent are particularly preferred for implantation in areas of the body that contact blood. For example, an antithrombogenic bioactive agent can be coated on the medical device surface. An antithrombogenic bioactive agent is any bioactive agent that inhibits or prevents thrombus formation within a body vessel. The medical device may comprise any suitable antithrombogenic bioactive agent. Types of antithrombotic bioactive agents include anticoagulants, antiplatelets, and fibrinolytics. Anticoagulants are bioactive agents which act on any of the factors, cofactors, activated factors, or activated cofactors in the biochemical cascade and inhibit the synthesis of fibrin. Antiplatelet bioactive agents inhibit the adhesion, activation, and aggregation of platelets, which are key components of thrombi and play an important role in thrombosis. Fibrinolytic bioactive agents enhance the fibrinolytic cascade or otherwise aid in dissolution of a thrombus. Examples of antithrombotics include but are not limited to anticoagulants such as thrombin, Factor Xa, Factor Vila and tissue factor inhibitors; antiplatelets such as glycoprotein IIb/IIIa, thromboxane A2, ADP-induced glycoprotein IIb/IIIa, and phosphodiesterase inhibitors; and fibrinolytics such as plasminogen activators, thrombin activatable fibrinolysis inhibitor (TAFI) inhibitors, and other enzymes which cleave fibrin.

[0075] Further examples of antithrombotic bioactive agents include anticoagulants such as heparin, low molecular weight heparin, covalent heparin, synthetic heparin salts, coumadin, bivalirudin (hirulog), hirudin, argatroban, ximelagatran, dabigatran, dabigatran etexilate, D-phenalanyl-L-poly-L-arginyl, chloromethyl ketone, dalteparin, enoxaparin, nadroparin, danaparoid, vapirost, dextran, dipyridamole, omega-3 fatty acids, vitronectin receptor antagonists, DX-9065a, CI-1083, JTV-803, razaxaban, BAY 59-7939, and LY-51,7717; antiplatelets such as eptifibatide, tirofiban, orbofiban, lotrafiban, abciximab, aspirin, ticlopidine, clopidogrel, cilostazol, dipyridamole, nitric oxide sources such as sodium nitroprussiate, nitroglycerin, S-nitroso and N-nitroso compounds; fibrinolytics such as alteplase, anistreplase, reteplase, lanoteplase, monteplase, tenecteplase, urokinase, streptokinase, or phospholipid encapsulated microbubbles; and other bioactive agents such as endothelial progenitor cells or endothelial cells.

[0076] Also particularly preferred are solutions comprising a thrombolytic bioactive agent. Desirably, the thrombolytic bioactive agent is coated on the luminal surface of the medical device. Thrombolytic agents are used to dissolve blood clots that may adversely affect blood flow in body vessels. A thrombolytic agent is any therapeutic agent that either digests fibrin fibres directly or

activates the natural mechanisms for doing so. The medical device can comprise any suitable thrombolytic agent. Examples of commercial thrombolytics, with the corresponding active agent in parenthesis, include, but are not limited to, Abbokinase (urokinase), Abbokinase Open-Cath (urokinase), Activase (alteplase, recombinant), Eminase (anistreplase), Retavase (reteplase, recombinant), and Streptase (streptokinase). Other commonly used names are anisoylated plasminogen-streptokinase activator complex; APSAC; tissue-type plasminogen activator (recombinant); t-PA; rt-PA.

[0077] The configuration of the bioactive agent on the medical device will depend in part on the desired rate of elution for the bioactive agent(s). For example, bioactive agents may be incorporated in the medical device by: 1) mixing a bioactive agent with a solution prior to spinning the solution; 2) using two spinnerets to spin a polymer and a bioactive agent separately and simultaneously, 3) impregnating a spun polymer with a bioactive agent, and 4) electrospinning a solution over the top of a bioactive agent coated medical device.

[0078] In one example, a bioactive agent may be admixed with a solution comprising polymers and/or proteins. Electrospinning the resulting solution yields fibres that contain the desired bioactive agents. This method may be particularly suited to creating fibres that are not susceptible to being rejected by the body. Additionally, the fibres may later be melted, compressed, or otherwise manipulated, thereby changing or eliminating the interstices between the fibres, without reducing the drug content of the fibres.

[0079] In a second example, two spinnerets may be used in close proximity to each other, each having a common target. A first spinneret may be loaded with a solution comprising polymers and the second spinneret may be loaded with a solution comprising at least one bioactive agent. The spinnerets are charged and their solutions are spun simultaneously at the common target, creating a material that includes polymer fibres and bioactive agent fibres. The bioactive agent being fed into the second spinneret may also be mixed with a second polymer to improve the spin characteristics of the bioactive agent.

[0080] In another example, a solution may be electrospun onto a medical device incorporating a bioactive agent. For example, the medical device may be initially coated with a bioactive agent in any suitable manner. The medical device may then be coated by electrospinning a solution, such that the electrospun solution creates a non-woven network of fibres that at least partially overlies the bioactive agent previously deposited on the medical device. The bioactive agent may be deposited on the medical device in any suitable manner. For example, the coating may be deposited onto the medical device by spraying, dipping, pouring, pumping, brushing, wiping, ultrasonic deposition, vacuum deposition, vapor deposition, plasma deposition, electrostatic deposition, epitaxial growth, or any other suitable method.

[0081] The therapeutically effective amount of bioac-

tive agent that is provided in connection with the various examples ultimately depends upon the condition and severity of the condition to be treated; the type and activity of the specific bioactive agent employed; the method by which the medical device is administered to the patient; the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[0082] Local administration of bioactive agents may be more effective when carried out over an extended period of time, such as a time period at least matching the normal reaction time of the body to an angioplasty procedure. At the same time, it may be desirable to provide an initial high dose of the bioactive agent over a preliminary period. For example, local administration of a bioactive agent over a period of days or even months may be most effective in treating or inhibiting conditions such as restenosis.

Bioadhesives

[0083] In one example, a solution for electrospinning may further comprise a bioadhesive. The bioadhesive may be included in any suitable part of the medical device. In one example, the bioadhesive is coated on the exterior surface of the medical device. Selection of the type of bioadhesive, the portions of the medical device comprising the bioadhesive, and the manner of attaching the bioadhesive to the medical device can be chosen to perform a desired function upon implantation. For example, the bioadhesive can be selected to promote increased affinity of the desired portion of medical device to the section of the body against which it is urged.

[0084] Bioadhesives for use in conjunction with the present disclosure include any suitable bioadhesives known to those of ordinary skill in the art. For example, appropriate bioadhesives include, but are not limited to, the following: (1) cyanoacrylates such as ethyl cyanoacrylate, butyl cyanoacrylate, octyl cyanoacrylate, and hexyl cyanoacrylate; (2) fibrinogen, with or without thrombin, fibrin, fibropectin, elastin, and laminin; (3) mussel adhesive protein, chitosan, prolamine gel and transforming growth factor beta (TGF- β); (4) polysaccharides such as acacia, carboxymethyl-cellulose, dextran, hyaluronic acid, hydroxypropylcellulose, hydroxypropyl-methylcellulose, karaya gum, pectin, starch, alginates, and tragacanth; (5) polyacrylic acid, polycarbophil, modified hydropromellose, gelatin, polyvinyl-pyrrolidone, polyvinylalcohol, polyethylene glycol, polyethylene oxide, aldehyde relative multifunctional chemicals, maleic anhydride copolymers, and polypeptides; and (6) any bioabsorbable and biostable polymers derivitized with sticky molecules such as arginine, glycine, and aspartic acid, and copolymers. Furthermore, commercially available bioadhesives that may be used in the present disclosure include,

but are not limited to: FOCALSEAL® (biodegradable eosin-PEG-lactide hydrogel requiring photopolymerization with Xenon light wand) produced by Focal; BERIPLAST® produced by Adventis-Bering; VIVOSTAT® produced by ConvaTec (Bristol-Meyers-Squibb); SEAL-AGENTM produced by Baxter; FIBRX® (containing virally inactivated human fibrinogen and inhibited-human thrombin) produced by CryoLife; TISSEEL® (fibrin glue composed of plasma derivatives from the last stages in the natural coagulation pathway where soluble fibrinogen is converted into a solid fibrin) and TISSUCOL® produced by Baxter; QUIXIL® (Biological Active Component and Thrombin) produced by Omrix Biopharm; a PEG-collagen conjugate produced by Cohesion (Collagen); HYSTOACRYL® BLUE (ENBUCRILATE) (cyanoacrylate) produced by Davis & Geck; NEXACRYLTM (N-butyl cyanoacrylate), NEXABONDTM, NEXABONDTM S/C, and TRAUMASEALTM (product based on cyanoacrylate) produced by Closure Medical (TriPoint Medical); DERMABOND® which consists of 2-octyl cyanoacrylate produced as DERMABOND® by (Ethicon); TISSUEGLU® produced by Medi-West Pharma; and VETBOND® which consists of n-butyl cyanoacrylate produced by 3M.

Medical Devices

[0085] The present disclosure is applicable to implantable or insertable medical devices of any shape or configuration. Typical subjects (also referred to herein as "patients") are vertebrate subjects (i.e., members of the subphylum cordata), including, mammals such as cattle, sheep, pigs, goats, horses, dogs, cats and humans.

[0086] Typical sites for placement of the medical devices include the coronary and peripheral vasculature (collectively referred to herein as the vasculature), heart, esophagus, trachea, colon, gastrointestinal tract, biliary tract, urinary tract, bladder, prostate, thorax, brain, wounds and surgical sites.

[0087] The medical device may be any device that is introduced temporarily or permanently into the body for the prophylaxis or treatment of a medical condition. For example, such medical devices may include, but are not limited to, stents, stent grafts, vascular grafts, catheters, guide wires, balloons, filters (e.g., vena cava filters), cerebral aneurysm filler coils, intraluminal paving systems, sutures, staples, anastomosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, slings, vascular implants, tissue adhesives and sealants, tissue scaffolds, hernia meshes, skin grafts, myocardial plugs, pacemaker leads, valves (e.g., venous valves), abdominal aortic aneurysm (AAA) grafts, embolic coils, various types of dressings (e.g., wound dressings), bone substitutes, intraluminal devices, vascular supports, or other known biocompatible devices.

[0088] The medical device may be made of one or more suitable biocompatible materials such as stainless

steel, nitinol, MP35N, gold, tantalum, platinum or platinum iridium, niobium, tungsten, iconel, ceramic, nickel, titanium, stainless steel/titanium composite, cobalt, chromium, cobalt/chromium alloys, magnesium, aluminum, or other biocompatible metals and/or composites or alloys such as carbon or carbon fibre, cellulose acetate, cellulose nitrate, silicone, cross-linked polyvinyl alcohol (PVA) hydrogel, cross-linked PVA hydrogel foam, polyurethane, polyamide, styrene isobutylene-styrene block copolymer (Kraton), polyethylene terephthalate, polyurethane, polyamide, polyester, polyorthoester, polyanhydride, polyether sulfone, polycarbonate, polypropylene, high molecular weight polyethylene, polytetrafluoroethylene, or other biocompatible polymeric material, or mixture of copolymers thereof; polyesters such as, polylactic acid, polyglycolic acid or copolymers thereof, a polyanhydride, polycaprolactone, polyhydroxybutyrate valerate or other biodegradable polymer, or mixtures or copolymers thereof; extracellular matrix components, proteins, collagen, fibrin or other therapeutic agent, or mixtures thereof.

[0089] It may be advantageous to prepare the surface of a medical device before electrospinning or otherwise depositing a coating thereon. Useful methods of surface preparation may include, but are not limited to: cleaning; physical modifications such as etching, drilling, cutting, or abrasion; chemical modifications such as solvent treatment; application of primer coatings or surfactants; plasma treatment; ion bombardment; and covalent bonding. Such surface preparation may activate the surface and promote the deposition or adhesion of the coating on the surface. Surface preparation may also selectively alter the release rate of a bioactive material. Any additional coating layers may similarly be processed to promote the deposition or adhesion of another layer, to further control the release rate of a bioactive agent, or to otherwise improve the biocompatibility of the surface of the layers. For example, plasma treating an additional coating layer before depositing a bioactive agent thereon may improve the adhesion of the bioactive agent, increase the amount of bioactive agent that can be deposited, and allow the bioactive material to be deposited in a more uniform layer.

[0090] A primer layer, or adhesion promotion layer, may be used with the medical device. This layer may include, for example, silane, acrylate polymer/copolymer, acrylate carboxyl and/or hydroxyl copolymer, polyvinylpyrrolidone/vinylacetate copolymer, olefin acrylic acid copolymer, ethylene acrylic acid copolymer, epoxy polymer, polyethylene glycol, polyethylene oxide, polyvinylpyridine copolymers, polyamide polymers/copolymers, polyimide polymers/copolymers, ethylene vinylacetate copolymer and/or polyether sulfones.

[0091] While various embodiments and examples have been described, it will be apparent to those of ordinary skill in the art that many more examples and implementations are possible within the scope of the disclosure. Accordingly, the disclosure is not to be restricted except in light of the attached claims and their equivalents.

lents.

[0092] All optional and preferred features and modifications of the described embodiments and dependent claims are usable in all aspects of the invention taught herein. Furthermore, the individual features of the dependent claims, as well as all optional and preferred features and modifications of the described embodiments are combinable and interchangeable with one another.

[0093] The disclosures in United States patent application number 13/356,324, from which this application claims priority, and in the abstract accompanying this application are incorporated herein by reference.

[0094] US 13/356,324 is a continuation-in-part of US 12/870,581, which is a divisional of US 12/274,530, which claims priority from US 60/991,365, filed Nov. 30, 2007, all of which are incorporated herein by reference in their entirety.

Claims

1. An electrospinning apparatus including:

a first spinneret including a reservoir and an orifice, the first spinneret orifice including a proximal end fluidly coupled to the reservoir and a distal end through which a first solution may be electrospun, the first spinneret including a first electrical charge generated by a first voltage source coupled to the first spinneret;

a second spinneret including a reservoir and an orifice, the second spinneret orifice including a proximal end fluidly coupled to the reservoir and a distal end through which a second solution is electrospun, the second spinneret including a second electrical charge generated by a second voltage source coupled to the second spinneret, the first electrical charge of the first spinneret being adjustable independently of the second electrical charge of the second spinneret;

wherein the first spinneret orifice is located substantially opposite the second spinneret orifice, wherein the first and second spinnerets are for use in preparing a medical device defining a lumen with a proximal end, a distal end, a luminal surface and an abluminal surface,

wherein the first spinneret orifice distal end is configured to be located outside of the medical device lumen between the medical device proximal end and the medical device distal end and to directly face the medical device abluminal surface, and

wherein the second spinneret orifice distal end is configured to be located in the medical device lumen between the medical device proximal end and the medical device distal end and to directly face the medical device luminal surface.

2. Apparatus as claimed in claim 1, wherein a magnitude of the first electrical charge of the first spinneret is adjustable independently of a magnitude of the second electrical charge of the second spinneret.
3. Apparatus as claimed in claim 1 or 2, wherein a sign of the first electrical charge of the first spinneret is adjustable independently of a sign of the second electrical charge of the second spinneret.
4. Apparatus as claimed in claim 1, 2 or 3, wherein the first electrical charge of the first spinneret and the second electrical charge of the second spinneret are opposing electrical charges.
5. Apparatus as claimed in claim 1, 2 or 3, wherein a sign of the first electrical charge of the first spinneret is the same as a sign of the second electrical charge of the second spinneret.
6. Apparatus as claimed in any preceding claim, wherein a magnitude of the first electrical charge of the first spinneret is substantially the same as a magnitude of the second electrical charge of the second spinneret.
7. Apparatus as claimed in any preceding claim, wherein the medical device comprises a third electrical charge generated by a third voltage source, and the third electrical charge of the medical device is adjustable independently of the first electrical charge of the first spinneret and the second electrical charge of the second spinneret.
8. Apparatus as claimed claim 7, wherein a magnitude of the third electrical charge of the medical device is greater than a magnitude of the first electrical charge of the first spinneret and a magnitude of the second electrical charge of the second spinneret.
9. Apparatus as claimed in claim 7 or 8, wherein a sign of the first electrical charge of the first spinneret is positive, a sign of the second electrical charge of the second spinneret is positive, and a sign of the third electrical charge of the medical device is negative.
10. Apparatus as claimed in claim 7 or 8, wherein a sign of the first electrical charge of the first spinneret is negative, a sign of the second electrical charge of the second spinneret is negative, and a sign of the third electrical charge of the medical device is positive.
11. Apparatus as claimed in any preceding claim, wherein the first solution is different from the second solution.
12. Apparatus as claimed in any preceding claim, where-

in an electrical conductivity of the first solution is different than an electrical conductivity of the second solution.

- 5 13. A method for preparing a medical device, the method including:
 - 10 providing the medical device, the medical device including a first surface and an opposing second surface;
 - 15 providing an electrospinning apparatus, the electrospinning apparatus including a first spinneret and a second spinneret located substantially opposite the first spinneret, the first spinneret including a reservoir and an orifice fluidly coupled to the first spinneret reservoir, the second spinneret including a reservoir and an orifice fluidly coupled to the second spinneret reservoir;
 - 20 applying a first electrical charge to the first spinneret with a first voltage source;
 - 25 applying a second electrical charge to the second spinneret with a second voltage source, the first electrical charge of the first spinneret being adjustable independently of the second electrical charge of the second spinneret;
 - 30 locating the first spinneret orifice nearby the medical device first surface;
 - 35 locating the second spinneret orifice nearby the medical device second surface;
 - 40 simultaneously electrospinning a first solution onto the medical device first surface with the first spinneret and a second solution onto the medical device second surface with the second spinneret.
14. A method as claimed in claim 13, further including applying a third electrical charge to the medical device with a third voltage source, the third electrical charge of the medical device being adjustable independently of the first electrical charge of the first spinneret and the second electrical charge of the second spinneret.
15. A method as claimed in claim 13 or 14, wherein an electrical conductivity of the first solution is different than an electrical conductivity of the second solution.

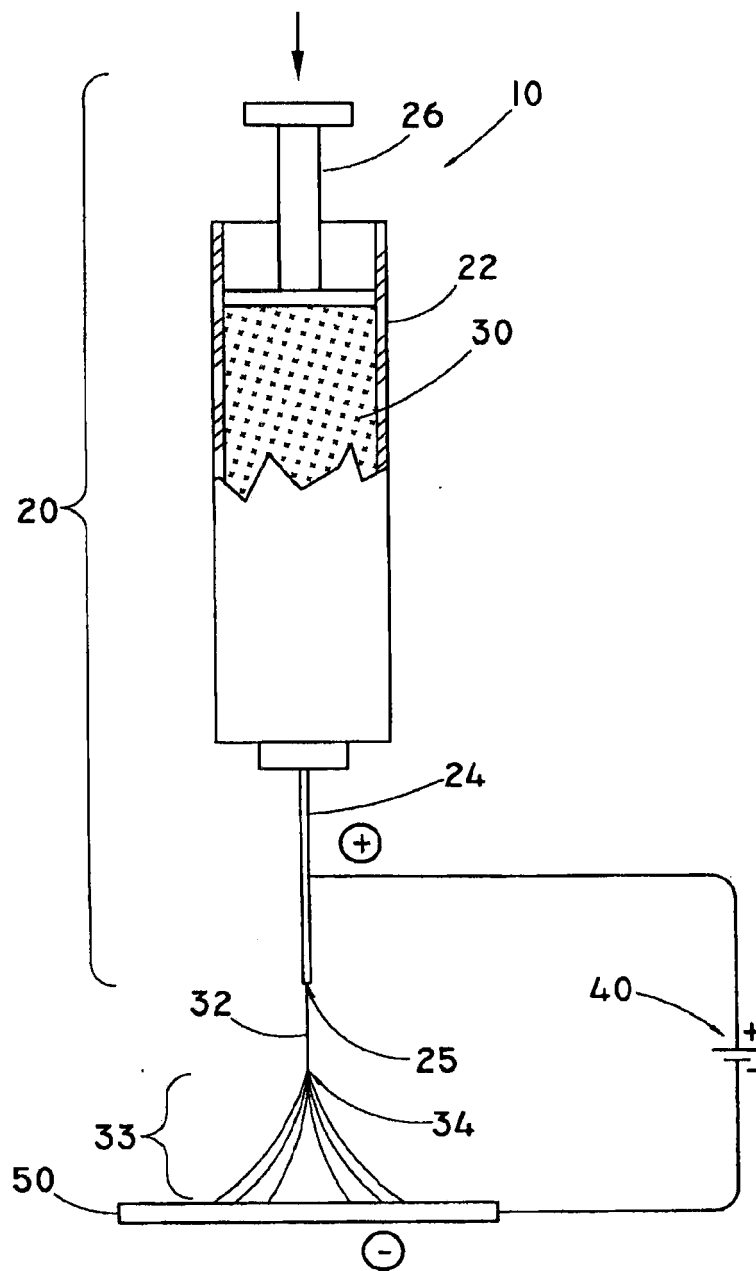


FIG. 1

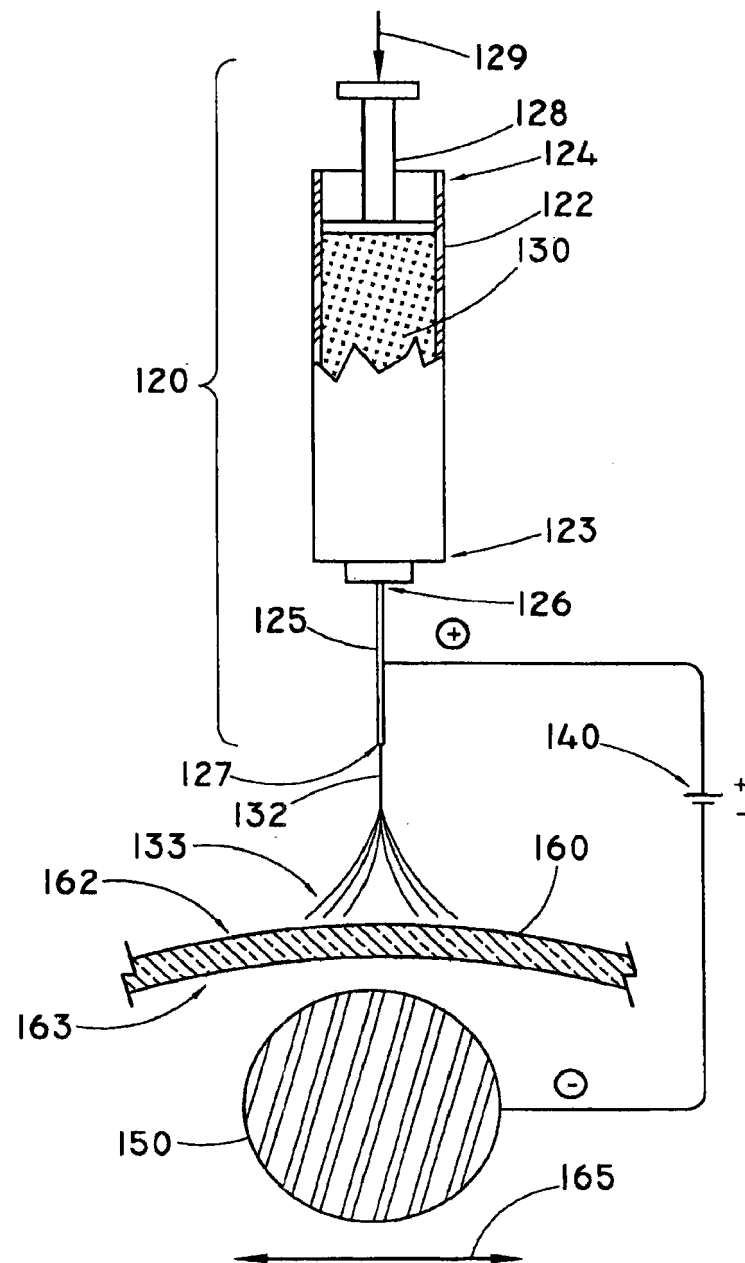
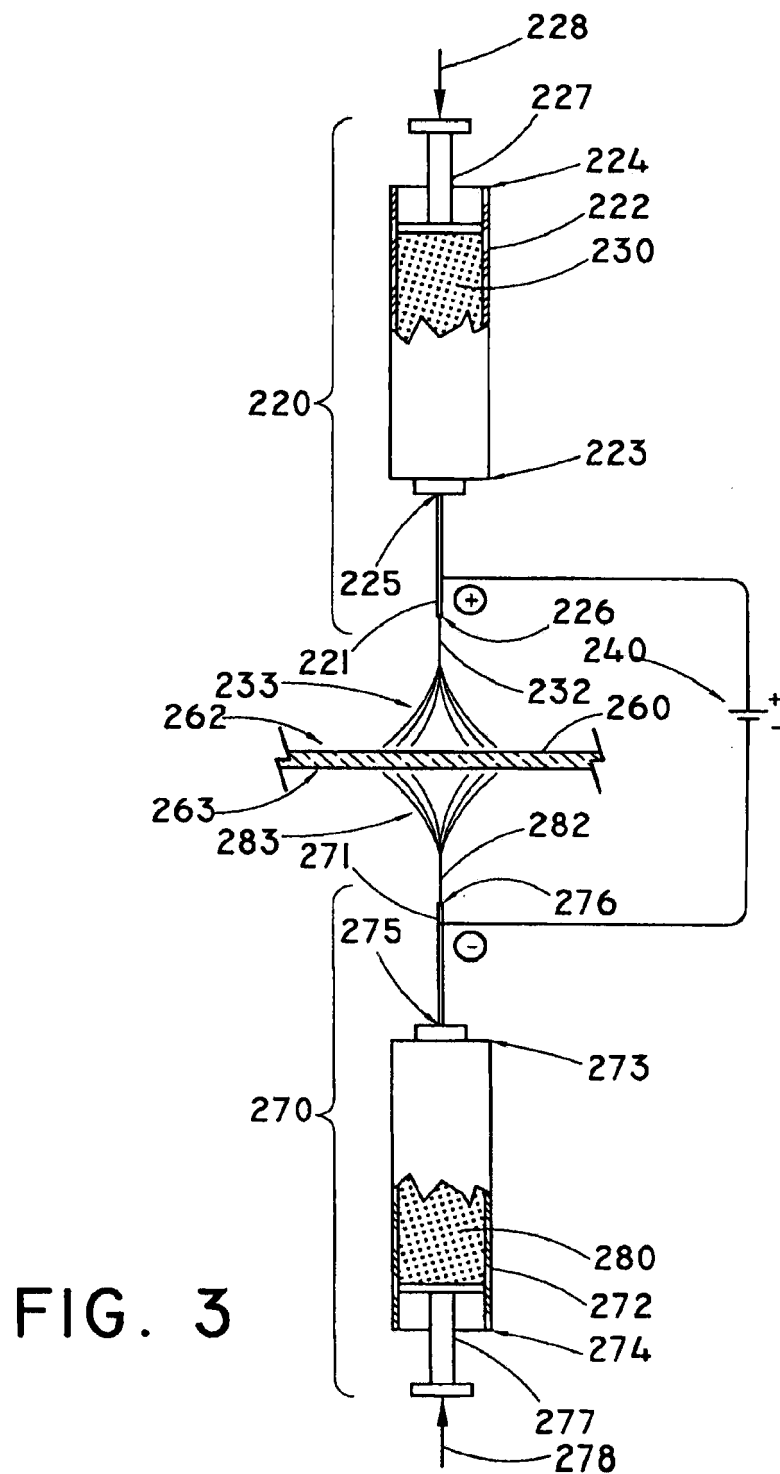


FIG. 2



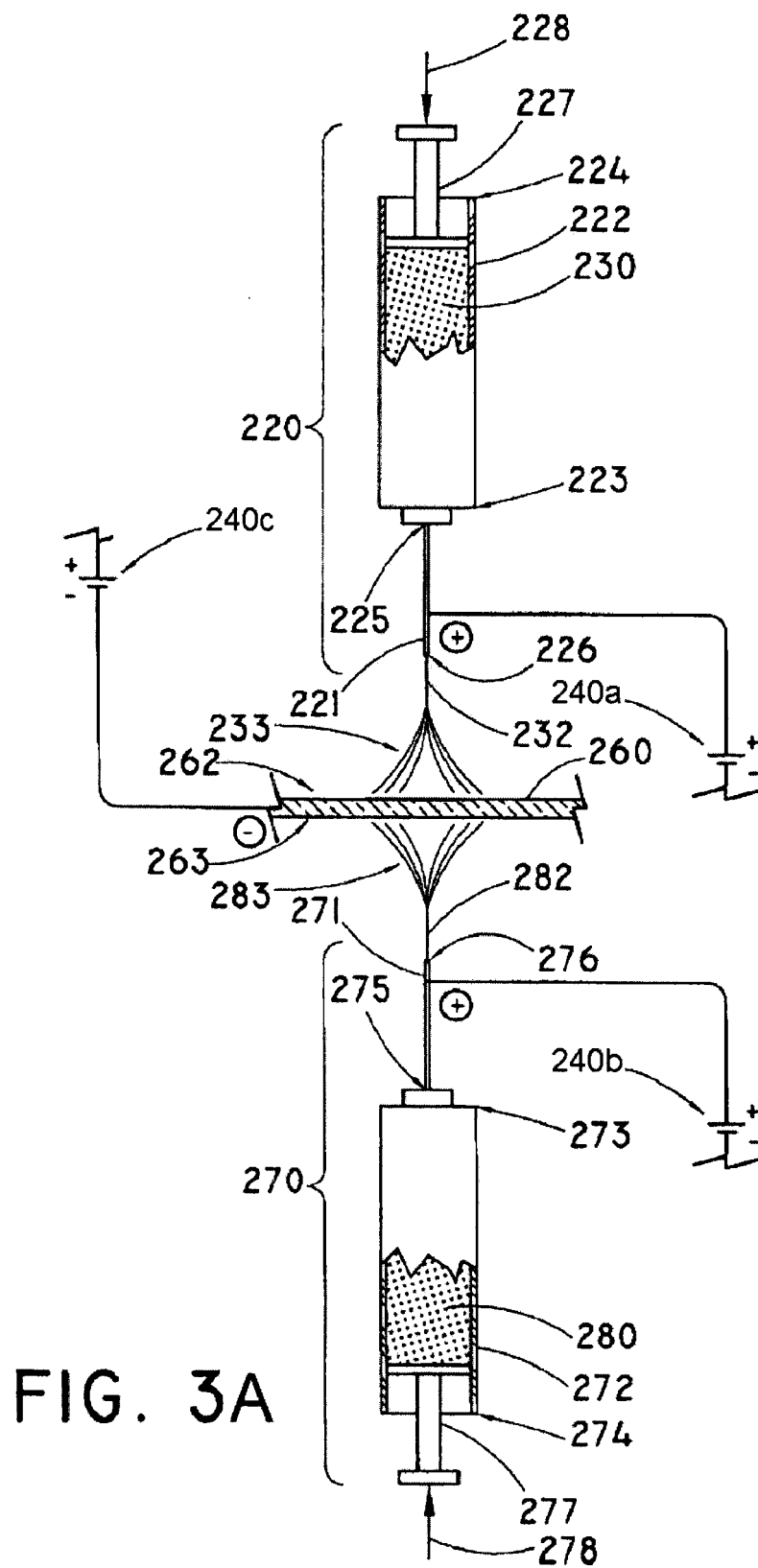


FIG. 3A

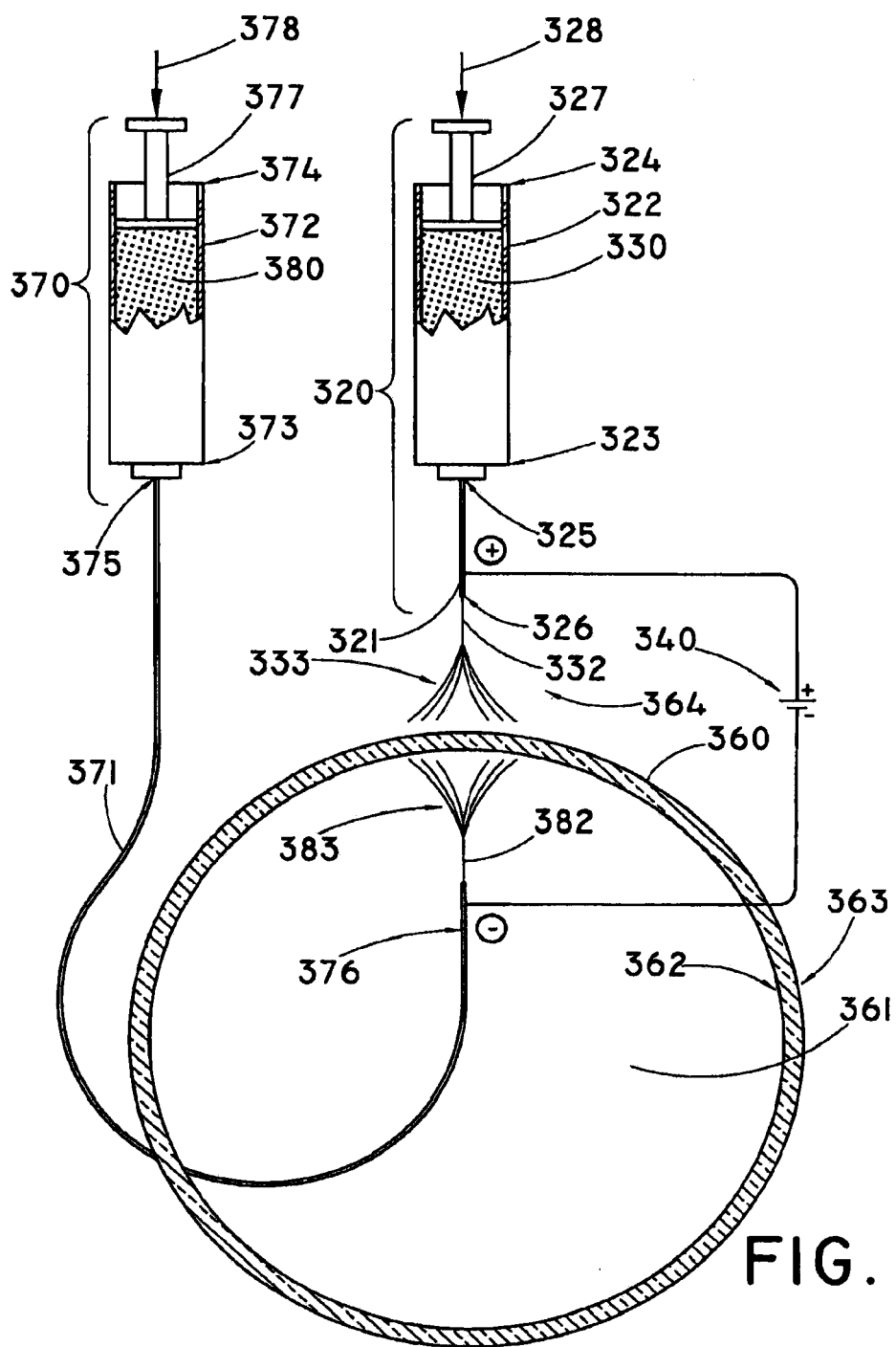
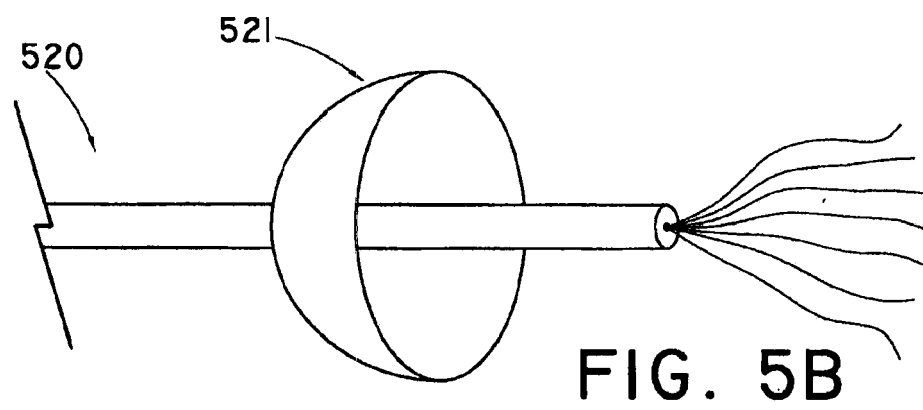
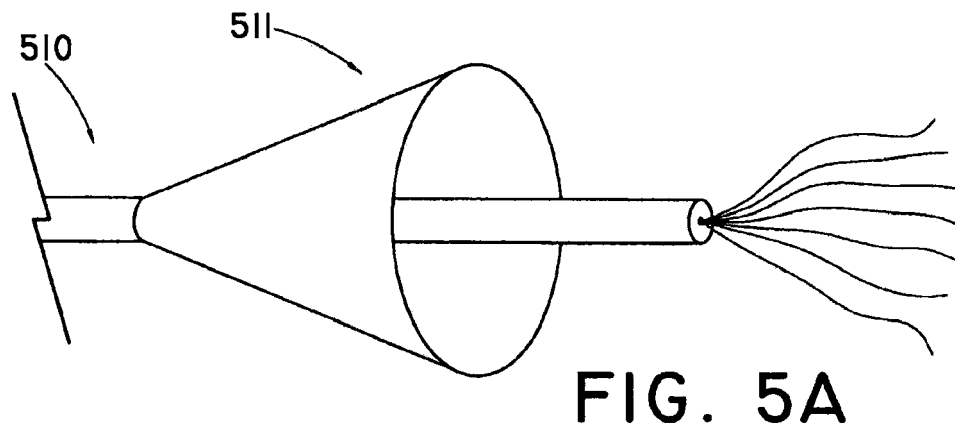


FIG. 4





EUROPEAN SEARCH REPORT

Application Number
EP 13 15 2391

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X,D	US 7 799 261 B2 (ORR DAVID E [US] ET AL) 21 September 2010 (2010-09-21) * abstract; claims 1-5; figures 3-4 * * column 1, line 55 - column 2, line 26 * * column 6, line 32 - column 8, line 62 * -----	1-15	INV. D01D5/00 B05B5/08 B05D1/04
A	US 2006/264140 A1 (ANDRADY ANTHONY L [US] ET AL) 23 November 2006 (2006-11-23) * abstract; figure 2 * * paragraphs [0035], [0037] * -----	1-15	
			TECHNICAL FIELDS SEARCHED (IPC)
			D01D B05B B05D D04H
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 21 March 2013	Examiner Malik, Jan
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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EPO FORM 1503 03.82 (P04C01)

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ON EUROPEAN PATENT APPLICATION NO.**

EP 13 15 2391

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21-03-2013

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