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(54) Title: COMPOSITIONS FOR TREATING POST-CARDIAL INFARCTION DAMAGE

(57) Abstract: Methods and compositions for treating post-myocardial infarction damage are herein disclosed. In some embodiments, a carrier with a treatment agent may be fabricated. The carrier can be formulated from a bioerodable, sustained-release substance. The resultant loaded carrier may then be suspended in at least one component of a two-component matrix system for simultaneous delivery to a post-myocardial infarction treatment area.

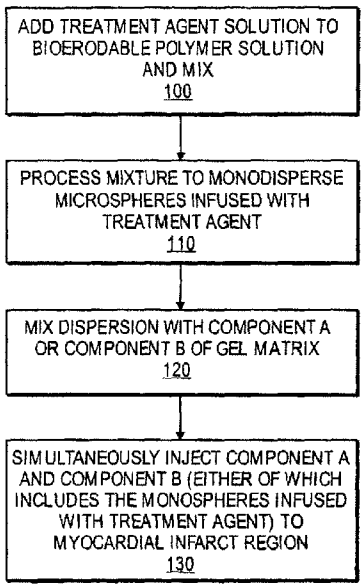

FIG. 2

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METHODS AND COMPOSITIONS FOR TREATING POST-CARDIAL INFARCTION DAMAGE

FIELD OF INVENTION

[0001] Post-myocardial infarction treatments and compositions.

BACKGROUND OF INVENTION

[0002] Ischemic heart disease typically results from an imbalance between the myocardial blood flow and the metabolic demand of the myocardium. Progressive atherosclerosis with increasing occlusion of coronary arteries leads to a reduction in coronary blood flow. "Atherosclerosis" is a type of arteriosclerosis in which cells including smooth muscle cells and macrophages, fatty substances, cholesterol, cellular waste product, calcium and fibrin build up in the inner lining of a body vessel. "Arteriosclerosis" refers to the thickening and hardening of arteries. Blood flow can be further decreased by additional events such as changes in circulation that lead to hypoperfusion, vasospasm or thrombosis.

[0003] Myocardial infarction (MI) is one form of heart disease that often results from the sudden lack of supply of oxygen and other nutrients. The lack of blood supply is a result of a closure of the coronary artery (or any other artery feeding the heart) which nourishes a particular part of the heart muscle. The cause of this event is generally attributed to arteriosclerosis in coronary vessels.

[0004] Formerly, it was believed that an MI was caused from a slow progression of closure from, for example, 95% then to 100%. However, an MI can also be a result of minor blockages where, for example, there is a rupture of the cholesterol plaque resulting in blood clotting within the artery. Thus, the flow of blood is blocked and downstream cellular damage occurs. This damage can cause irregular rhythms that can be fatal, even though the remaining muscle is strong enough to pump a sufficient amount of blood. As a result of this insult to the heart tissue, scar tissue tends to naturally form.

[0005] Various procedures, including mechanical and therapeutic agent application procedures, are known for reopening blocked arties. An example of a mechanical procedure

includes balloon angioplasty with stenting, while an example of a therapeutic agent application includes the administration of a thrombolytic agent, such as urokinase. Such procedures do not, however, treat actual tissue damage to the heart. Other systemic drugs, such as ACE-inhibitors and Beta-blockers, may be effective in reducing cardiac load post-MI, although a significant portion of the population that experiences a major MI ultimately develop heart failure.

[0006] An important component in the progression to heart failure is remodeling of the heart due to mismatched mechanical forces between the infracted region and the healthy tissue resulting in uneven stress and strain distribution in the left ventricle. Once an MI occurs, remodeling of the heart begins. The principle components of the remodeling event include myocyte death, edema and inflammation, followed by fibroblast infiltration and collagen deposition, and finally scar formation. The principle component of the scar is collagen. Since mature myocytes of an adult are not regenerated, the infarct region experiences significant thinning. Myocyte loss is the major etiologic factor of wall thinning and chamber dilation that may ultimately lead to progression of cardiac myopathy. In other areas, remote regions experience hypertrophy (thickening) resulting in an overall enlargement of the left ventricle. This is the end result of the remodeling cascade. These changes in the heart result in changes in the patient's lifestyle and their ability to walk and to exercise. These changes also correlate with physiological changes that result in increase in blood pressure and worsening systolic and diastolic performance.

SUMMARY OF INVENTION

[0007] Methods and compositions for treating post-myocardial infarction damage are herein disclosed. In some embodiments, a carrier may be loaded with a treatment agent. The carrier can be formulated from a bioerodable, sustained-release substance. The resultant loaded carrier may then be suspended in one component of a two-component matrix for simultaneous delivery to a post-myocardial infarction treatment area.

[0008] A device that includes a first and second needle useful for delivering individual components of a gel is herein disclosed. Various needle assembly configurations prevent inadvertent mixture of the gel components but ensure that the components can admix within a patient's tissue to form a gel composition.

[0009] In alternative embodiment, the distal ends of a first and second needle are moveable relative to each other. The needles can be biased toward a separated configuration, and the separation distance of the needle tips can shorten when the needles engage a patient's tissue.

[0010] A device is disclosed that includes a first and second needle useful for delivering individual components of a gel in which at least one of the needles can be actuated manually to move relative to the other needle. The device is useful for delivering individual components of a gel.

[0011] A method is provided for delivering a first and second gel component into a patient anatomy in order to form a gel composition.

BRIEF DESCRIPTION OF DRAWINGS

[0012] FIGS. 1A-1B illustrate the progression of heart damage once the build-up of plaque in an artery induces an infarct to occur;

[0013] FIG. 2 schematically represents a method for preparing a two-component gel matrix with a sustained carrier loaded with treatment agent interdispersed therein;

[0014] FIG. 3 schematically represents an alternative method for preparing a two-component gel matrix with a sustained carrier loaded with treatment agent interdispersed therein;

[0015] FIG. 4 schematically represents a second alternative method for preparing a two-component gel matrix with a sustained carrier loaded with treatment agent interdispersed therein;

[0016] FIGS. 5A-5B illustrate an embodiment of a dual-needle injection device which can be used to deliver the compositions of the present invention;

[0017] FIGS. 6A-6C illustrate an alternative embodiment of a dual-needle injection device which can be used to deliver the compositions of the present invention;

[0018] FIGS. 7A-7B illustrate an alternative embodiment of a needle assembly having needles configured side-by-side that can be used to deliver the compositions of the present invention;

[0019] FIGS. 8A-8B illustrate an alternative embodiment of a needle assembly having needles configured generally coaxially that can be used to deliver the compositions of the present invention;

[0020] FIGS. 9A-9B illustrate an alternative embodiment of a needle assembly with divergent lumen ports that can be used to deliver the compositions of the present invention;

[0021] FIGS. 10A-10B illustrate an alternative embodiment of a needle assembly with divergent lumen ports that can be used to deliver the compositions of the present invention;

[0022] FIGS. 11A-11C illustrate an alternative embodiment of a needle assembly having offset needles that can be used to deliver the compositions of the present invention;

[0023] FIGS. 12A-12C illustrate an alternative embodiment of a needle assembly having offset needles that can be used to deliver the compositions of the present invention;

[0024] FIGS. 13A-13B illustrate an alternative embodiment of a needle assembly having a guide needle and a delivery needle;

[0025] FIGS. 14A-14C illustrate alternative embodiments of a delivery needle in accordance with the present invention;

[0026] FIGS. 15A-15B illustrate an alternative embodiment of a needle assembly having biased offset needles that can be used to deliver the compositions of the present invention;

[0027] FIGS. 16A-16C illustrate an alternative embodiment of needle assemblies configured to provide beneficial delivery characteristics;

[0028] FIG. 17 illustrates an alternative embodiment of a needle assembly that can be used to deliver the compositions of the present invention; and

[0029] FIG. 18 illustrates an alternative embodiment of a distal portion of an injection device with a needle assembly that can be used to deliver the compositions of the present invention.

DETAILED DESCRIPTION

[0030] Methods and compositions for treating post-myocardial infarction damage are herein disclosed. In some embodiments, a carrier with a treatment agent may be fabricated. The carrier can be formulated from a bioerodable, sustained-release substance. The resultant loaded carrier may then be suspended in at least one component of a two-component matrix system for simultaneous delivery to a post-myocardial infarction treatment area.

[0031] FIGS. 1A-1B illustrate the progression of heart damage once the build-up of plaque induces an infarct to occur. FIG. 1A illustrates a site 10 where blockage and restricted blood flow can occur from, for example, a thrombus or embolus. FIG. 1B illustrates resultant damage area 20 to the left ventricle that can result from the lack of oxygen and nutrient flow carried by the blood to the inferior region left of the heart. The damage area 20 will likely undergo remodeling, and eventually scarring, resulting in a non-functional area.

Treatment Agents

[0032] Treatment agents to treat post-myocardial infarction treatment areas may include: (i) agents that promote angiogenesis (angiogenesis promoting factors); (ii) agents that promote cell survival (cell survival promoting factors); and (iii) agents that recruit endogenous progenitor and/or stem cells (endogenous recruiting factors). Various forms of treatment agents are intended to include, but are not intended to be limited to, drugs, biologically active agents, chemically active agents, therapeutic agents, and the like, and pharmaceutical compositions thereof, which can be used in the delivery of a treatment agent to a treatment site as described herein.

[0033] "Angiogenesis" is the promotion or causation of the formation of new blood vessels. After an MI, the infarct tissue as well as the border zone and the remote zone around the infarct tissue begin to remodel. Scar tissue forms in the infarct region as the granulation is replaced with collagen. Stress from blood pressure cause the scar to thin out and stretch. The perfusion in this region is typically 10% of the healthy zone, decreasing the number of active capillaries. Increasing the number of capillaries may lead to an increase in compliance of the ventricle due to filling up with blood. Other benefits of increasing blood flow to the infarcted region include providing a route for circulating stem cells to seed and proliferate in the infarct region. Angiogenesis may also lead to increased oxygenation for the surviving cellular islets

within the infarct region, or to prime the infarct region for subsequent cell transplantation for myocardial regeneration. In the border zone, surviving cells would also benefit from an increase in blood supply through an angiogenesis process. In the remote zone, where cardiac cells tend to hypertrophy and become surrounded with some interstitial fibrosis, the ability of cells to receive oxygen and therefore function to full capacity are also compromised; thus, angiogenesis would be beneficial in these regions as well.

[0034] In some embodiments, angiogenesis promoting factors include, but are not intended to be limited to, growth factors such as isoforms of vasoendothelial growth factor (VEGF), fibroblast growth factor (FGF, e.g. beta-FGF), Del 1, hypoxia inducing factor (HIF 1-alpha), monocyte chemoattractant protein (MCP-1), nicotine, platelet derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), transforming growth factor (TGF alpha), hepatocyte growth factor (HGF), estrogens, follistatin, proliferin, prostaglandin E1 and E2, tumor necrosis factor (TNF-alpha), interleukin 8 (Il-8), hematopoietic growth factors, erythropoietin, granulocyte-colony stimulating factors (G-CSF) and platelet-derived endothelial growth factor (PD-ECGF). In some embodiments, angiogenesis promoting factors include, but are not intended to be limited to, peptides, such as PR39, PR11 and angiogenin, small molecules, such as PHD inhibitors, or other agents, such as eNOS enhancers.

[0035] Endogenous cardiomyocyte (myocytes) apoptosis is the major etiological factor of wall thinning and chamber dilation and may ultimately lead to progression of cardiac myopathy. After an infarction, mature myocytes of an adult are not regenerated which can lead to significant thinning in the infarct region. Thus, factors which promote cell survival applied to the infarct region are believed to be beneficial. In some embodiments, cell survival promoting factors include, but are not intended to be limited to, growth factors such as insulin-like growth factor (IGF-1) and human growth factor (HGF), which are known to mediate cell growth, differentiation and survival of a variety of cell types. In addition, small molecules such as, for example, HMG-CoA reductase inhibitors (statins) and capsase inhibitors can also promote cell survival and inhibit apoptosis.

[0036] To assist in the generation of new cells at the infarct region, autologous or allogeneic stem cells may be delivered to a patient. “Autologous” means the donor and recipient of the stem cells are the same. “Allogeneic” means the donor and recipient of the

stem cells are different. Cell survival promoting factors can also be used to increase the survivability of autologous and allogeneic implanted stem cells at the infarct region.

[0037] Cardiac progenitor cells are highly specialized stem cells which have shown the ability to differentiate into certain types of fully mature cardiac tissue. Examples of cardiac progenitor cells include, but are not limited to, c-Kit(+), Sca-1(+) and Isl-1(+). Thus, factors which recruit endogenous factors when applied to the infarct region are believed to be beneficial. In some embodiments, an endogenous recruiting factor can include, for example, HGF. HGF has been shown to control cell motility and promote cell migration. If applied post-infarction, HGF can assist in mobilizing and recruiting resident cardiac progenitor cells to the infarct region. In some embodiments, an endogenous recruiting factor can include, but is not intended to be limited to, stromal cell-derived factor 1 (SDF-1). SDF-1 is the ligand for the CXCR4 receptor, which is a surface receptor on circulating endothelial progenitor cells. Thus, when applied in or around the infarct region, SDF-1 may facilitate the homing of circulating endothelial progenitor cells to induce neovascularization.

[0038] It is contemplated that any of the above-described treatment agents can be used singularly or in combination thereof. In addition, other treatment agents, including but not limited to, anti-inflammatory, anti-platelet, anti-coagulant, anti-fibrin, anti-thrombotic, anti-mitotic, anti-biotic, anti-allergic, anti-oxidant, anti-proliferative, or anti-migratory agents, may be optionally used singularly or in combination thereof.

Sustained-release carriers

[0039] Bioerodable carriers (hereinafter interchangeably referred to as sustained-release carriers) infused with (or without) a treatment agent can be used for the sustained or controlled release of treatment agent for maximum benefit to the infarct region. It is believed that a large percentage of treatment agent delivered directly to the infarct region, or even diffused within a gel-like matrix, will be substantially washed away by the body's natural mechanisms, thus lessening the benefit of the treatment agent that may otherwise be obtained. Thus, sustained-release carriers infused with treatment agent that release the treatment agent over an extended time period can be beneficial by increasing the amount of time in which the infarct region is exposed to the treatment agent. Sustained-release carriers include, but are not limited to, (i) microparticles or nanoparticles (hereinafter interchangeably referred to as

microparticles), (ii) microfibers or nanofibers (hereinafter interchangeably referred to as microfibers) and (iii) liposomes and polymerosomes.

[0040] In addition, in some embodiments, a bioerodable carrier may be infused with (or without) a treatment agent and delivered to a treatment site to act as a "docking site" for endogenous myocardial stem cells and encourage their differentiation into cardiomyocytes.

A.

[0041] In some embodiments, the sustained-release carrier is a microparticle. Various methods can be employed to formulate and infuse or load the microparticles with treatment agent. In some embodiments, the microparticles are prepared by a water/oil/water (W/O/W) double emulsion method. In the W1 phase, an aqueous phase containing treatment agent, is dispersed into the oil phase consisting of polymer dissolved in organic solvent (e.g., dichloromethane) using a high-speed homogenizer. Examples of sustained-release polymers include, but are not limited to, poly(D,L-lactide-co-glycolide) (PLGA), poly(D,L-lactide) (PLA) or PLA-PEEP co-polymers, poly-ester-amide co-polymers (PEA) and polyphophazines. The primary water-in-oil (W/O) emulsion is then dispersed to an aqueous solution containing a polymeric surfactant, e.g., poly(vinyl alcohol) (PVA), and further homogenized to produce a W/O/W emulsion. After stirring for several hours, the microparticles are collected by filtration.

B.

[0042] In some embodiments, the sustained-release carrier is a microfiber or nanofiber. For example, the treatment agent (or no treatment agent) infused microfiber can be formulated by electrospinning. "Electrospinning" is a process by which microfibers are formed by using an electric field to draw a polymer solution from the tip of a capillary to a collector. A voltage is applied to the polymer solution which causes a stream of solution to be drawn toward a grounded collector. Electrospinning generates a web of fibers which can be subsequently processed into smaller lengths.

[0043] Examples of sustained-release polymers which can be used in electrospinning include, but are not limited to, PLGA, PLA or PLA-PEEP co-polymers, PEA, polyphosphazines and collagen. In one method, the treatment agent is mixed with a

bioerodable polymer solution, a solvent and a surfactant. Examples of surfactants can include, but are not limited to, anionic or cationic surfactants. Useful anionic surfactants include, but are not intended to be limited to, bis(2-ethylhexyl) sodium sulfosuccinate (AOT), bis (2-ethylhexyl) phosphate (NaDEHP), tauroglycocholate, and sodium lauryl sulfate. A useful cationic surfactant is tetradecyltrimethyl-ammonium bromide (TTAB). An example of a solvent includes, but is not limited to, hexafluoro isopropanol. The treatment agent-infused polymer solution is then subjected to electrospinning. As the solvent evaporates during electrospinning, the treatment agent incorporates and distributes within the polymer by non-covalent interactions. The resultant microfibers which can be from about 0.5 μm to about 3 μm in diameter form a web which may then be processed into smaller lengths of about 0.5 μm to about 500 μm. Based on the treatment agent, in some applications, microfibers may be a preferred sustained-release carrier due to the non-aqueous process by which they are formed. In some applications, microspheres may be preferable when the treatment agent is hydrophilic. In some applications, a microfiber is a preferred sustained-release carrier due to its release pharmacokinetic profile when compared to the release pharmacokinetic profile of a microsphere. In some cases, microspheres as well as microfibers can be used as a carrier of one or more than one treatment agent as the two types of carriers will provide different pharmacokinetic release profiles which may be advantageous for therapy.

[0044] In one embodiment, fibers can be electrospun from collagen and elastin dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP), forming a polymer solution. A treatment agent can be added to the polymer solution. A surfactant and a stabilizer can be used to evenly disperse the treatment agent in the solvent. The polymer solution can then be loaded into a syringe and placed in a syringe pump for metered dispensing at a predetermined rate. A positive output lead of a high voltage supply can be attached to a needle on the syringe. The needle can be directed to a stainless steel grounded target placed approximately 10 cm from the needle tip, which can be rotated at a predetermined speed to ensure an even coating. The distance of the needle from the target can be varied depending upon the diameter of the fibers needed. The resultant microfibers are from about 0.5 μm to about 3 μm in diameter and the resulting non-woven mat of fibers can then be processed into smaller lengths of about 0.5 μm to about 500 μm.

C.

[0045] In some embodiments, the sustained-release carrier is a liposome or a polymerosome. "Liposomes" are artificial vesicles that are approximately spherical in shape and can be produced from natural phospholipids and cholesterol. In one method, phospholipids are mixed with cholesterol in chloroform. Suitable phospholipids include, but are not limited to, dimyristoyl phosphatidyl choline or dipalmitoyl ethanolamine. In some embodiments, hydrophobic treatment agent can be added with an optional co-solvent, such as heptane or toluene. The liposomes may also be hydrophilically modified with an agent such as polyethylene glycol or dextran. After mixing, the solvent (and optional co-solvent) can be evaporated with heat or ambient temperature in a round bottom flask. Resultant lipids will be deposited on the glass surface. In some embodiments, hydrophilic treatment agent and water can be added to the flask and sonicated to form liposomes. The resultant suspension can be pressure filtered through ceramic pore size controlled filters to reduce liposome particle size. In the case of a polymerosome, a similar manufacturing technique can be used as that of a liposome. Polymerosomes can be formed from di-block co-polymers of differing solubility. For example, one block can be hydrophobic, e.g., poly lactic acid, polycaprolactone, n-butyl acrylate, and the other block can be hydrophilic, e.g., poly (ethylene glycol), poly(acrylic acid).

[0046]

Matrix Systems

[0047] A biocompatible matrix system can be used to suspend the treatment agent or the treatment agent-infused sustained-release carrier for delivery to the infarct region. In some embodiments, the matrix system can be a one-component or a two-component gel. In some embodiments, the matrix system is a two-component gel. Two-component gels can include, for example, fibrin glues (e.g., two components comprising fibrinogen and thrombin), self-assembled peptides or alginate constructs.

[0048] In some embodiments, the matrix system is a one-component gel. An example of a one-component gel includes an acrylate agent that is biocompatible. The one-component gel serves in one aspect to disperse the sustained-release carrier in order to form a more uniform scaffold over the entire infarct zone and may include border zone as well. For

example, the one-component gel may be sodium hyaluronate. The gel disperses the sustained-release carrier acting as a suspending media.

A.

[0049] In some applications, the two-component gelation system includes a fibrin glue. Fibrin glue consists of two main components, fibrinogen and thrombin. Fibrinogen is a plasma glycoprotein of about 340 kiloDaltons (kDa) in its endogenous state. Fibrinogen is a symmetrical dimer comprised of six paired polypeptide chains, alpha, beta and gamma chains. On the alpha and beta chains, there is a small peptide sequence called a fibrinopeptide which prevent fibrinogen from spontaneously forming polymers with itself. In some embodiments, fibrinogen is modified with proteins. Thrombin is a coagulation protein. When combined in equal volumes, thrombin converts the fibrinogen to fibrin by enzymatic action at a rate determined by the concentration of thrombin. The result is a biocompatible gel which gelates when combined at the infarct region. Fibrin glue can undergo gelation at about 10 to about 60 seconds. Examples of other fibrin glue-like systems include, but are not limited to, Tisseel™ (Baxter), CoSeal™ (Baxter), Crosseal™ (Omrix Biopharmaceuticals, Ltd.), Hemaseel® (Haemacure Corp.) and CoStasis® (Angiotech Pharmaceuticals).

B.

[0050] In some embodiments, the two-component gel comprises self-assembled peptides. Self-assembled peptides generally include repeat sequences of alternating hydrophobic and hydrophilic amino acid chains. The hydrophilic amino acids are generally charge-bearing and can be anionic, cationic or both. Examples of cationic amino acids are lysine and arginine. Examples of anionic amino acids are aspartic acid and glutamic acid. Examples of hydrophobic amino acids are alanine, valine, leucine, isoleucine or phenylalanine. Self-assembled peptides can range from 8 to about 40 amino acids in length and can assemble into nanoscale fibers under conditions of physiological pH and osmolarity. In sufficient concentration and over time, the fibers can assemble into an interconnected structure that appears macroscopically as a gel. Self-assembled peptides typically undergo gelation between several minutes to several hours. Examples of self-assembled peptides include, but are not limited to: AcN-RARADADARARADADA-CNH_2 (RAD 16-II) wherein R is arginine, A is alanine, D is aspartic acid, and Ac indicates acetylation; VKVKVKVKV-PP-

TKVKVKVKV-NH_2 (MAX-1) wherein V is valine, K is lysine and P is proline; and AcN-AEAEAKAKAEAEAKAK-CNH_2 wherein A is alanine, K is lysine and E is glutamic acid (EAK16-II).

Example

[0051] In one example, the self-assembled peptide is RAD 16-II. At low pH and osmolarity, RAD 16-II forms a solution. At physiological pH and osmolarity, RAD 16-II forms a gel although gel formation can be slow. In some embodiments, RAD 16-II is mixed with phosphate buffer saline (PBS) to form a first component solution. In some embodiments, the first component solution can be co-injected with a second component comprising sodium chloride, sucrose or other osmolarity modifying substance using, for example, a dual-injection delivery assembly. In some embodiments, the components can be co-injected with carriers such as angiogenesis promoting factors, cell survival promoting factors and/or endogenous recruiting factors. These factors bind non-specifically to the self-assembled peptides by electrostatic interactions, and this binding can control or retard the release of the factors.

C.

[0052] In some embodiments, the two-component gel is an alginate construct. For example, the alginate construct may be collagen or gelatin grafted alginate. In one example, a first component can be a solution of about 0.5 percent to about 1.0 percent alginate while a second component can be a solution of about 40 mM to about 180 mM calcium chloride. One example of a suitable amount of components is about 200 microliters of alginate solution and about 200 microliters of calcium chloride. In one embodiment, a desired amount of a treatment agent may be introduced with the alginate solution.

Methods of Manufacture

[0053] FIG. 2 schematically represents a method for preparing a two-component gel matrix with a sustained carrier loaded with treatment agent interdispersed therein. A treatment agent, such as an angiogenesis promoting factor, cell survival promoting factor, endogenous recruiting factor or any combination thereof can be added to a bioerodable polymer such as PLGA or PEA and PLA-PEEP co-polymers or polyphosphazenes (100). In

some embodiments, a W/O/W process can be used. The mixture can be processed to monodisperse the resultant treatment agent loaded microspheres (110). The microspheres can be in a range from about 5 μm to about 200 μm, preferably from about 10 μm to about 50 μm. Next, the resultant dispersion can be added to one component of a two-component gel such as fibrin glue (120). In one embodiment, the two-component gel includes component A and component B, wherein component A is fibrinogen and component B is thrombin. Component A and component B can then be separately but simultaneously injected into the myocardial infarct region by a dual-injection delivery assembly for treatment thereof (130).

[0054] FIG. 3 schematically represents an alternative method for preparing a two-component gel matrix with a sustained carrier loaded with treatment agent interdispersed therein. A treatment agent, such as an angiogenesis promoting factor, cell survival promoting factor, endogenous recruiting factor or any combination thereof can be added to a bioerodable polymer such as PLGA or PEA and PLA-PEEP co-polymers or polyphosphazenes or collagen (200) with solvent. For collagen/elastin electrospun fibers, a suitable solvent can be HFP. In some embodiments, an aqueous system may be used. The mixture can then be subjected to electrospinning to create interwoven fibers (210) with a diameter in a range from about 0.2 μm to about 3 μm. The fibers may then be processed into smaller of length from about 0.5 μm to about 500 μm (220). The fibers may be processed by cryogenic grinding, subjected to ultrasound in water, or subjected to ultrasound in a volatile solvent that is a non-solvent for both the polymer and the encapsulated protein or other agent or subjected to any other suitable method to reduce their size. Next, the resultant fibers can be added to one component of a two-component gel such as fibrin glue (230). In one embodiment, the two-component gel includes component A and component B, wherein component A is fibrinogen and component B is thrombin. Component A and component B can then be separately but simultaneously injected into the myocardial infarct region by a dual-injection delivery assembly for treatment thereof (240).

[0055] FIG. 4 schematically represents another alternative method for preparing a two-component gel matrix with a sustained carrier loaded with treatment agent interdispersed therein. A phospholipid substance can be combined with cholesterol in a solvent such as chloroform (300) in a round bottom flask. In some embodiments, a hydrophobic treatment agent including an optional co-solvent can be added thereto (300A). The solvent(s) can be evaporated depositing lipids on the glass surface (310). Next, water is added and in some

embodiments, a hydrophilic treatment agent (320). Then, the mixture is sonicated to form liposomes (330) and optionally pressure-filtered to reduce liposome particle size (340). Next, the resultant liposomes can be added to one component of a two-component gel such as fibrin glue (350). In one embodiment, the two-component gel includes component A and component B, wherein component A is fibrinogen and component B is thrombin. Component A and component B can then be separately but simultaneously injected into the myocardial infarct region by a dual-injection delivery assembly for treatment thereof (360).

Example

[0056] In one embodiment, collagen electrospun fibers can be processed to a range from about 200 nm and about 1300 nm. The range of electrospun fibers is approximately the range of naturally occurring type 1 and type 3 fibers which make up the heart matrix. Thus, the electrospun fibers may mimic endogenous fibers and accelerate growth of repair tissue to the infarct region, in particular, on the heart. The fibers can be dispersed throughout one component of a two-component gel. The two components can then be delivered to myocardial infarct region. The fibers can provide "docking sites" for endogenous myocardial stem cells and encourage their differentiation into cardiomyocytes. The gel can provide temporary containment of the fibers and prevent premature removal by macrophage cells.

[0057] The fibers can be fabricated such that they include an agent or no agent. Examples of agents can include a chemoattractant, such as SDF-1, or a cell survival promoting factor, such as IGF-1. In one embodiment, SDF-1 may be incorporated within the electrospun fibers and the resultant agent infused electrospun fibers may be dispersed throughout one component of a two-component gel. When delivered, the release of SDF-1 may recruit endogenous stem cells to the infarct region where they will adhere to the electrospun fibers and differentiate into stem cells.

[0058] In another embodiment, IGF-1 may be incorporated within the electrospun fibers and the resultant agent infused electrospun fibers may be dispersed throughout one component of a two-component gel. Stem cells may be incorporated within the other component of the two-component gel. When delivered, the stem cells may be temporally immobilized in the gel and adhere to the electrospun fibers. IGF-1 may enhance stem cell survival.

[0059] It should be appreciated that any of the above-described methods may be combined to treat an infarct region.

Methods of Treatment

[0060] Devices which can be used to deliver each component of the gel include, but are not limited to, dual-needle left-ventricle injection devices and dual-needle transvascular wall injection. Methods of access to use the injection devices include access via the femoral artery or the sub-xiphoid. "Xiphoid" or "xiphoid process" is a pointed cartilage attached to the lower end of the breastbone or sternum, the smallest and lowest division of the sternum. Both methods are known by those skilled in the art.

[0061] FIGS. 5A-5B illustrate an embodiment of a dual-needle injection device which can be used to deliver the compositions of the present invention. Delivery assembly 400 includes lumen 410 which may house delivery lumens, guidewire lumens and/or other lumens. Lumen 410, in this example, extends between distal portion 405 and proximal end 415 of delivery assembly 400.

[0062] In one embodiment, delivery assembly 400 includes main needle 420 disposed within delivery lumen 430. Main needle 420 is movably disposed within delivery lumen 430. Main needle 420 is, for example, a stainless steel hypotube that extends a length of the delivery assembly. Main needle 420 includes a lumen with an inside diameter of, for example, 0.08 inches (0.20 centimeters). In one example for a retractable needle catheter, main needle 420 has a needle length on the order of 40 inches (1.6 meters) from distal portion 405 to proximal portion 415. Lumen 410 also includes separate, possibly smaller diameter, auxiliary lumen 440 extending, in this example, co-linearly along the length of the catheter (from a distal portion 405 to proximal portion 415). Auxiliary lumen 440 is, for example, a polymer tubing of a suitable material (e.g., polyamides, polyolefins, polyurethanes, etc.). At distal portion 405, auxiliary lumen 440 is terminated to auxiliary needle end 450 co-linearly aligned with a delivery end of needle 420. Auxiliary lumen 440 may be terminated to auxiliary needle end 450 with a radiation-curable adhesive, such as an ultraviolet curable adhesive. Auxiliary needle end 450 is, for example, a stainless steel hypotube that is joined co-linearly to the end of main needle 420 by, for example, solder (illustrated as joint 455). Auxiliary needle end 450 has a length on the order of about 0.08 inches (0.20 centimeters).

FIG. 5B shows a cross-sectional front view through line A-A' of delivery assembly 400. FIG. 5B shows main needle 420 and auxiliary needle 450 in a co-linear alignment.

[0063] Referring to FIG. 5A, at proximal portion 415, auxiliary lumen 440 is terminated to auxiliary side arm 460. Auxiliary side arm 460 includes a portion extending co-linearly with main needle 420. Auxiliary side arm 460 is, for example, a stainless steel hypotube material that may be soldered to main needle 420 (illustrated as joint 465). Auxiliary side arm 460 has a co-linear length on the order of about, in one example, 1.2 inches (3 centimeters).

[0064] The proximal end of main needle 420 includes adaptor 470 for accommodating a substance delivery device (e.g., a component of a two-component bioerodable gel material). Adaptor 470 is, for example, a molded female luer housing. Similarly, a proximal end of auxiliary side arm 460 includes adaptor 480 to accommodate a substance delivery device (e.g., a female luer housing).

[0065] The design configuration described above with respect to FIGS. 5A-5B is suitable for introducing two-component gel compositions of the present invention. For example, a gel may be formed by a combination (mixing, contact, etc.) of a first component and a second component. Representatively, a first component may be introduced by a one cubic centimeters syringe at adaptor 470 through main needle 420. At the same time or shortly before or after, second component including treatment agent loaded sustained-release particles may be introduced with a one cubic centimeter syringe at adaptor 480. When the first and second components combine at the exit of delivery assembly 400 (at an infarct region), the materials combine (mix, contact) to form a bioerodable gel.

[0066] FIGS. 6A-6C illustrate an alternative embodiment of a dual-needle injection device which can be used to deliver two-component gel compositions of the present invention. In general, the catheter assembly 500 provides a system for delivering substances, such as two-component gel compositions, to or through a desired area of a blood vessel (a physiological lumen) or tissue in order to treat a myocardial infarct region. The catheter assembly 500 is similar to the catheter assembly 500 described in commonly-owned, U.S. Patent Application No. 6,554,801, titled "Directional Needle Injection Drug Delivery Device", and incorporated herein by reference.

[0067] In one embodiment, catheter assembly 500 is defined by elongated catheter body 550 having proximal portion 520 and distal portion 510. FIG. 6B shows catheter assembly 500 through line A-A' of FIG. 6A (at distal portion 510). FIG. 6C shows catheter assembly 500 through line B-B' of FIG. 6A.

[0068] Guidewire cannula 570 is formed within catheter body (from proximal portion 510 to distal portion 520) for allowing catheter assembly 500 to be fed and maneuvered over guidewire 580. Balloon 530 is incorporated at distal portion 510 of catheter assembly 500 and is in fluid communication with inflation cannula 560 of catheter assembly 500.

[0069] Balloon 530 can be formed from balloon wall or membrane 335 which is selectively inflatable to dilate from a collapsed configuration to a desired and controlled expanded configuration. Balloon 530 can be selectively dilated (inflated) by supplying a fluid into inflation cannula 560 at a predetermined rate of pressure through inflation port 565. Balloon wall 335 is selectively deflatable, after inflation, to return to the collapsed configuration or a deflated profile. Balloon 530 may be dilated (inflated) by the introduction of a liquid into inflation cannula 560. Liquids containing treatment and/or diagnostic agents may also be used to inflate balloon 530. In one embodiment, balloon 530 may be made of a material that is permeable to such treatment and/or diagnostic liquids. To inflate balloon 530, the fluid can be supplied into inflation cannula 560 at a predetermined pressure, for example, between about one and 20 atmospheres. The specific pressure depends on various factors, such as the thickness of balloon wall 335, the material from which balloon wall 335 is made, the type of substance employed and the flow-rate that is desired.

[0070] Catheter assembly 500 also includes substance delivery assembly 505 for injecting a substance into a myocardial infarct region. In one embodiment, substance delivery assembly 505 includes needle 515a movably disposed within hollow delivery lumen 525a. Delivery assembly 505 includes needle 515b movably disposed within hollow delivery lumen 525b. Delivery lumen 525a and delivery lumen 525b each extend between distal portion 510 and proximal portion 520. Delivery lumen 525a and delivery lumen 525b can be made from any suitable material, such as polymers and copolymers of polyamides, polyolefins, polyurethanes and the like. Access to the proximal end of delivery lumen 525a or delivery lumen 525b for insertion of needle 515a or 515b, respectively is provided through hub 535.

Delivery lumens 525a and 525b may be used to deliver first and second components of a two-component gel composition to a myocardial infarct region.

[0071] Referring now to Figure 7A, an alternative embodiment of a distal needle portion 405 is shown. In this embodiment, a proximal edge of the distal end of main needle 420 is near the distal edge of the distal end of auxiliary needle 450. As shown, in this configuration it is possible for the planes encompassing the edges of the distal ends of both needles to be nearly co-planar. This is illustrated further in the cross-sectional view of the needle configuration shown in Figure 7B. As a result of the nearly co-planar configuration of the distal ends, the distal needle portion 405 can puncture tissue and spread the tissue cleanly as it is advanced further. This minimizes tissue damage and allows the tissue to recover more fully after the distal needle portion 405 is removed.

[0072] Figure 8A illustrates yet another alternative embodiment of a distal needle portion 405 in accordance with this invention. In this configuration, the distal portion of auxiliary needle 450 is positioned within the distal portion of main needle 420. The distal ends of the needles may be generally coaxial in order to maximize the flow area of the main needle 420. A sectional view of the needle configuration is shown in Figure 8B. Although the embodiment is shown in a generally coaxial configuration, the auxiliary needle may also be non-concentric with respect to the main needle. In this way, the flow characteristics of the distal needle portion 405 may be modified in accordance with the invention. This will also account for normal manufacturing tolerances. Further, alternative configurations in accordance with this embodiment can be used to affect the piercing capabilities of the distal needle portion 405.

[0073] It is an object of this invention to prevent the inadvertent mixture of the two gel components of the present invention prior to their delivery into the target tissue. Controlling the flow direction of injectate moved through the distal end of each needle will accomplish this. For example, by providing divergent flow paths for each gel component, when the gel components are injected while the distal needle portion is positioned within the turbulent blood flow of a heart chamber, the gel components will be quickly dispersed by the circulating blood before they are able to interact with each other. In contrast, when the distal needle portion 405 is inserted within the heart tissue and the gel components are injected

through the divergent flow paths, the resistance of the heart tissue will moderate the dispersal of the gel components, allowing them to admix and form a two-component gel composition.

[0074] In accordance with this invention, the distal needle portion 405 may be configured as shown in Figures 9A-9B. Distal needle portion 405 includes a main needle 420 aligned collinearly with auxiliary needle 450. Main needle 420 includes a lumen opening defined by a plane that intersects the axis of the needle lumen. Thus, a gel component moved through the main needle will exit the needle lumen along the axis of the needle lumen. In contrast, auxiliary needle 450 includes a lumen opening formed in the wall of the needle lumen such that the lumen opening is generally parallel with the needle lumen axis. Thus, a gel component moved through the auxiliary needle will exit the needle lumen in a direction that is generally perpendicular to the needle lumen axis. Therefore a gel component injected through the auxiliary needle 450 exits the distal needle portion 405 in a direction that diverges from the direction that a gel component injected through the main needle 420 will follow as it exits the distal needle portion 405.

[0075] As shown in Figure 9B, the auxiliary needle 450 of this embodiment includes a closed end. The schematic representation of this figure indicates that the end may be closed by forming a needle from one piece with a closed end. Alternatively, an open ended needle tube may be closed by inserting and bonding in place a needle plug. In this case, bonding of the plug may be accomplished by using adhesive or thermal welding, soldering, or any other suitable process that is well known in the art. It may be preferable, though not necessary, to form the plug from the same material as that used to form the auxiliary needle 450, to improve manufacturability.

[0076] An alternative configuration for a distal needle portion 405 that prevents the inadvertent mixture of injectate is shown in Figures 10A-10B. In this embodiment, the lumen openings of main needle 420 and auxiliary needle 450 are not co-planar. Further, in this embodiment, the distal ends of each needle are generally co-planar to each other and the distal edge of a distal end of the auxiliary needle 450 is positioned near the proximal edge of a distal end of the main needle 420. Therefore, a uniform surface is defined by the distal ends of both needles, which improves the piercing characteristics of the needle assembly. In further accordance with the invention, divergent pathways for the gel components are provided to prevent inadvertent mixture outside of the target tissue.

[0077] It will be appreciated that the main needle 420 and auxiliary needle 450 of the embodiments shown in Figures 7 through 10 are interchangeable. That is, while the main needle 420 of Figure 10A-10B is shown with a closed end, it is possible to instead close the end of auxiliary needle 450 in accordance with this invention. This interchangeability is applied to each of the embodiments and configurations discussed.

[0078] Another method of ensuring that injectate is not inadvertently mixed is to longitudinally space the distal ends of the needles while they are positioned outside of the target tissue. Figure 11A-11B shows a distal needle portion 405 with a main needle 420 and an auxiliary needle 450 in a longitudinally spaced configuration. In this embodiment, the needles can be moved relative to one another. It will be appreciated that when the distal needle portion 405 is placed within a chamber of a beating heart, the turbulent blood flow within the beating heart will disperse the injectate from each needle before the two components are able to traverse the offset distance 470 to admix. Therefore, inadvertent mixting is prevented.

[0079] Referring now to Figure 11C, when the distal needle portion 405 engages tissue 602, a reactive load is placed on main needle 420 by the tissue 602, causing the main needle 420 to retract relative to auxiliary needle 450 and reducing the offset distance 470. Eventually, both needles engage and puncture the tissue 602. Thus, the subsequent injection of two gel components through the separate needle lumens will result in delivery of the injectate to adjacent locations within the tissue 602, allowing them to effectively mix to form a two-component gel composition in accordance with this invention.

[0080] Figures 12A-12C illustrates an alternative embodiment in accordance with this invention, using an alternative configuration of distal needle portion 405. In this embodiment, the main needle 420 is at least partially enclosed within the auxiliary needle 450 and the distal end of the main needle is offset from the distal end of the auxiliary needle 450 by a distance 470 when in a first position. In this first position, which is shown in Figure 12A-12B within the chamber of a heart, gel components delivered through each of the needle lumens will be dispersed by the turbulent blood flow before the two components are able to traverse the offset distance 470 to admix.

[0081] Referring now to Figure 12C, when the distal needle portion 405 engages tissue 602, a reactive load is placed on main needle 420 by the tissue 602, causing the main needle

420 to retract relative to auxiliary needle 450 and reducing offset distance 470. Eventually, both needles engage and puncture the tissue 602. Thus, the subsequent injection of two gel components through the separate needles will result in delivery of the injectate to adjacent locations within the tissue 602, allowing them to effectively mix to form a two-component gel composition in accordance with this invention.

[0082] In the embodiments that include an offset distance between needle tips such as those described in Figures 11 through 12, it is desirable to ensure that both needle tips pierce the tissue nearly simultaneously. This can be accomplished by constructing the leading needle from a softer material than the other needle. For example, referring to Figure 12A-12C, if the main needle 420 is fabricated from a polymeric compound such as PEEK, nylon, PEBAX, polyurethane, or another suitable polymer, it will be less likely to pierce the tissue as the catheter is advanced. Instead, it will retract until the auxiliary needle 450 contacts and pierces the tissue, forming a pathway by which the distal needle portion 405 can enter the tissue 602 to deliver the two gel components.

[0083] Alternatively, the leading needle may have a blunted distal tip to prevent it from puncturing the tissue before the lagging needle has contacted the tissue also.

[0084] Referring now to Figure 13A, an alternative embodiment of a needle assembly 600 in accordance with this invention utilizes a guide needle 610 and a delivery needle 620 (hidden). The guide needle 610 is designed to facilitate the puncture of the target tissue, while the delivery needle 620 is intended to deliver the two gel components to the target site. The delivery needle 620 is at least partially positioned within the guide needle 610 and may be moveable within the guide needle. Therefore, the delivery needle may be configured in an initial leading or lagging position relative to the guide needle 610. In accordance with their purpose, the guide needle 610 and the delivery needle 620 may be fabricated from different materials. The guide needle 610 is preferably fabricated from a harder material than the delivery needle 620. Therefore, the guide needle 610 may be formed from a metal such as stainless steel or cobalt chromium, while suitable shape memory metals such as Nitinol may also be used. This provides a guide needle configuration that can puncture tissue easily. The delivery needle 620 may be formed from suitable polymeric compounds such as polyurethane, polyimide, polyamide, PEEK, nylon, Pebax and other suitable plastics that are well known in the art.

[0085] Referring now to Figure 13B, a cross-sectional view of the needle assembly 600 shown in Figure 13A is illustrated. This illustrates that the delivery needle 620 includes at least two lumens defined by first lumen 622 and second lumen 624. Further, these lumens may be separated by a partition 626. The main function of the guide needle 610 in this embodiment is to puncture the target tissue thereby forming a channel for the insertion of delivery needle 620. The structure of delivery needle 620 allows different components of a therapeutic composition to be delivered through first lumen 622 and second lumen 624. The components are separated by partition 626 until they exit the distal end of needle assembly 600 and enter the target tissue, where the components admix to form a composition in accordance with this invention.

[0086] Figures 14A-14C are cross-sectional views of alternative embodiments of delivery needle 620 in accordance with this invention. Each of the variations includes the basic structural components of the delivery needle 620: a first lumen 622, a second lumen 624, and a partition 626. Figure 14A includes two elliptical lumens 622 and 624 and also exhibits a relatively high amount of material in the sidewall portion that contributes to improved torque transmission. In Figure 14B, the crescent-shaped second lumen 624 meshes with the circular first lumen 622. The cross-sectional areas of the first lumen 622 and second lumen 624 in this embodiment may be varied to achieve the desired flow rate through each lumen. In Figure 14C, the delivery needle is generally oval shaped and the first lumen 622 and second lumen 624 are D-shaped. This configuration resists torsion and provides a higher level of flexibility about a first axis 628 compared to the flexibility about a second axis 630. It will be appreciated that many other needle configurations may be contemplated by one skilled in the art that will ensure the separation of injectate during delivery in accordance with this invention.

[0087] As discussed in several of the embodiments above, the needle assembly may advantageously comprise a leading needle that is offset from another needle in a first configuration. This prevents mixing of gel components when they are released from the needle assembly outside of the presence of tissue, and therefore mitigates the risk of a thromboembolic event. A suitable offset distance for preventing inadvertent mixture of gel components outside of the target tissue is contemplated to be about 1-5 mm. In a second configuration, the leading needle is moved relative to the lagging needle by a reactive load applied by the target tissue until both needles contact and puncture the tissue. Following

tissue puncture, gel components may be delivered through each needle lumen to admix within the target tissue and form a two-component gel composition in accordance with this invention. The two needles may be configured to slide over one another. This can be enabled, for example, by housing the needles within a sheath over at least a portion of their length. Alternatively, the needle components may be constrained within bands placed at predetermined positions along the length of the catheter device.

[0088] Referring now to Figure 15A, a needle assembly 600 is shown in a first configuration prior to making contact with tissue 700. The needle assembly includes a first needle 640 with a distal end that leads the distal end of a second needle 642 in the first configuration. First needle 640 is further associated with first stop 644, while the second needle 642 is associated with a second stop 646. Biasing element 650 is associated with first stop 644 and second stop 646 and applies a separation force to the stops, which biases the distal ends of the first needle 640 and second needle 642 away from each other, as shown.

[0089] Referring now to Figure 15B, as the needle assembly 600 is advanced, the distal end of the leading needle 640 contacts tissue 700 and a reactive load is applied to the first needle 640. This reactive load opposes the biasing force of the biasing element 650 and the first needle 640 moves relative to second needle 642, reducing the offset distance of the distal ends of each needle. When the second needle 642 contacts the tissue 700, the needles puncture the tissue 700. Gel components can then be delivered through first needle 640 and second needle 642 into the tissue in order to form a gel composition therein.

[0090] Upon retraction of the needle assembly 600 from the tissue, the biasing element 650 will again force the separation of the distal ends of needle 640 and 642, thereby preventing gelation of the two gel components within the heart chamber and mitigating the risk of a thromboembolic event.

[0091] In this embodiment, the stops 644 and 646 may be formed from collars that are bonded to the surface of the needles as described. Bonding may be facilitated through the use of adhesive or thermal welding. Alternatively, the collars may be press fit with the corresponding needle components. The collars are sized and configured to provide adequate seating for the biasing element 650 without excessively impeding the flow of fluid within the needle components.

[0092] It may be desirable to vary the distance of the offset between the first and second needle. In this case, an adjustable stop may be provided to on one or both needles to affect this offset distance. The stop may be threaded, for example, and be engaged with a screw thread on the corresponding needle surface. Rotation of the needle via an association with a proximal handle component of the delivery device (not shown) would cause movement of the stop, which would in turn adjust the offset distance between the distal ends of the needle components.

[0093] Biasing element 650 is preferably formed from a compression spring that applies a separation load to first needle 640 and second needle 642. However, alternative embodiments are possible, such as the use of a volute, Belleville, tension, v-spring and leaf-type spring, or other configurations that may be contemplated by one skilled in the art.

[0094] Ideally, a needle assembly for delivering injectate into tissue will have a minimized cutting profile to reduce tissue damage caused by needle puncture. The ideal needle assembly will also prevent excessive back pressure in order to ease delivery of the injectate. These are competing goals since needle profile can be decreased to minimize puncture size while lumen profile can be increased to reduce back pressure.

[0095] Referring now to Figure 16A-16C, several embodiments of a needle assembly that minimize puncture area and reduce back pressure are shown. The embodiments generally include a tapered or stepped transition near the distal end of the needle.

[0096] Figure 16A shows a needle assembly 702 comprised of a first needle 710 and a second needle 712. Each needle includes a proximal portion 720 and a distal portion 722, these two portions being separated by a stepped transition zone 714 in the first needle and a stepped transition zone 716 in the second needle. It will be appreciated that the distal portion 722 has a reduced needle profile, which will minimize the cutting profile as it pierces into tissue. In contrast, the proximal portion 720 has a larger lumen profile, which reduces back pressure and eases delivery of an injectate through the needle assembly 702.

[0097] Referring now to Figure 16B, a needle assembly 702 in accordance with this invention is shown in which a distal portion 722 and a proximal portion 720 are separated by a tapered transition zone 714 in a first needle 710 and a tapered transition zone 716 in a second needle 712. This configuration provides the benefit of a needle assembly that

minimizes the cutting profile as it pierces tissue and reduces back pressure to ease delivery of injectate through the needle assembly 702.

[0098] Referring now to Figure 16C, an alternative embodiment of a needle assembly 702 in accordance with this invention is shown in which a distal portion 722 and a proximal portion 720 are separated by a stepped transition in first needle 710 and second needle 712. This configuration provides a needle assembly 702 that advantageously minimizes the cutting profile as it pierces tissue and reduces back pressure to ease delivery of injectate through the needle assembly 702. First needle 710 and second needle 712 are arranged in a side-by-side configuration, which optimizes the internal volume in each needle and further contributes to a reduction in back pressure in accordance with this invention.

[0099] An alternative embodiment of a needle assembly 800 in accordance with this invention is shown in Figure 17. In this embodiment, a first needle 802 and a second needle 804 are configured in a side-by-side fashion over a portion of their length and they are configured in a generally coaxial fashion over another portion of their length. The needles transition from one configuration to another configuration at a transition point 806 located at a discontinuity in the wall of the second needle 804. The first needle 802 may optionally be sealed to the second needle 804 at the transition point 806. It will be appreciated that this configuration creates a minimized needle profile in the distal portion of the needle assembly 800, while lumen profile may be optimized in the proximal portion of the needle assembly 800, in accordance with this invention.

[00100] Referring now to Figure 18, yet another embodiment in accordance with this invention is shown. An injection catheter 900 includes a needle assembly that comprises a first needle 902 disposed within a second needle 904, the second needle 904 of this embodiment is shorter than the first needle 902. The second needle 904 is associated with an intermediate catheter shaft 908 by a dynamic seal 906. This seal opposes fluid flow from within the catheter shaft so that fluid exits the injection catheter through second needle 904. Likewise, injectate may be delivered through the lumen of the first needle 902. An actuation element 910 is associated with the second needle 904 near a proximal end of the second needle 904. The actuation element 910 transmits loads to the second needle 904 that cause the needle to either extend or retract. Therefore, the distance between the distal ends of both needles can be controlled by the manipulation of the actuation element 910. In this way, the

puncturing of tissue and the creation of a composition therein can be controlled. Further, this configuration provides beneficial reduction in back pressure since the lumen of the catheter shaft is larger than the lumen of second needle 904.

[00101] Notwithstanding the description above, the needle components of this invention may be formed from any material that is suitable for the intended purpose. Needle components may therefore be formed from an appropriate metal, such as stainless steel, Nitinol, or cobalt-chromium alloys such as L605 or MP35N, any equivalents thereof, alloys thereof, and combinations thereof. Further, the one or both needle components may be formed from a suitable polymeric compound such as nylon, urethane, polyurethane, polyvinylchloride, polyester, PEEK, PTFE, PVDF, Kyner, polyimide, or polyethylene of various suitable densities. Further, one or both needle components may be a combination of metal and polymer materials, such as a polymer tube reinforced by a metal braid or coil, as are well known in the art.

[00102] The needle components described above are sized and configured to puncture the target tissue and effectively deliver the intended gel components therein. Accordingly, a wide range of needle sizes exist for achieving the goal of the invention. Nonetheless, it is contemplated that needle components in accordance with this invention may have an outer dimension at the distal end of between 23 and 33 Gauge.

[00103] In accordance with this invention, the bevel angle of the needles may be varied to facilitate tissue puncture. Therefore, the bevel angle could be in the range of 5 to 80 degrees. More preferably, the bevel angle could be in the range of 10 to 65 degrees, and even more preferably, the bevel angle could be in the range of 15 to 45 degrees. Further, it may only be necessary for one of the needle components to include a beveled tip. The beveled tip needle would facilitate tissue puncture, while the second needle may have a blunted or flat tip that is inserted within the punctured tissue.

[00104] From the foregoing detailed description, it will be evident that there are a number of changes, adaptations and modifications of the present invention which come within the province of those skilled in the part. The scope of the invention includes any combination of the elements from the different species and embodiments disclosed herein, as well as subassemblies, assemblies and methods thereof. However, it is intended that all such

variations not departing from the spirit of the invention be considered as within the scope thereof.

WHAT IS CLAIMED IS:

1. A device comprising:

a) a first delivery needle, and

b) a second delivery needle,

c) whereby a first gel component can be delivered through the first delivery needle without contacting a second gel component that may be disposed in the second delivery needle.

2. The device of claim 1, wherein the first delivery needle and the second delivery needle are arranged in a side-by-side configuration.

3. The device of claim 1, wherein the first delivery needle and the second delivery needle are arranged in a coaxial configuration.

4. The device of claim 1, further comprising a port disposed in the wall of the first delivery needle adapted such that a first gel component delivered through the port and a second gel component delivered through the second delivery needle will diverge.

5. The device of claim 2, adapted to have at least two configurations and wherein the distal end of the first delivery needle and the distal end of the second delivery needle are longitudinally separated by an offset distance.

6. The device of claim 5, wherein the offset distance is less in a second configuration than in the first configuration.

7. The device of claim 6, further including a biasing element associated with the first delivery needle and the second delivery needle, whereby the biasing element urges the device toward the first configuration.

8. The device of claim 7, wherein the biasing element is a spring.

9. The device of claim 8, wherein the spring is selected from the group consisting of compression, volute, Belleville, tension, v-spring and leaf-type springs.

10. The device of claim 3, wherein the distal end of the first delivery needle and the distal end of the second delivery needle are longitudinally separated by an offset distance in a first configuration.

11. The device of claim 10, adapted to have at least two configurations and wherein the distal end of the first delivery needle and the distal end of the second delivery needle are longitudinally separated by an offset distance that is less in a second configuration than in the first configuration.

12. The device of claim 11, further including a biasing element associated with the first delivery needle and the second delivery needle, whereby the biasing element urges the device toward the first configuration.

13. The device of claim 12, wherein the biasing element is a spring.

14. The device of claim 13, wherein the spring is selected from the group consisting of compression, volute, Belleville, tension, v-spring and leaf-type springs.

15. The device of claim 3, wherein the second delivery needle includes at least two lumens separated from each other, and separated from the first needle lumen.

16. The device of claim 1, wherein the proximal portion of the first delivery needle and second delivery needle have a larger lumen profile than the distal portion and the proximal portion connects to the distal portion through a transition portion.

17. The device of claim 16, wherein the transition portion has a step, a taper, or a combination of a step and taper.

18. A device comprising:

a) a first delivery needle, and

b) a second delivery needle wherein a lumen at the second needle is separated from the lumen of the first needle,

c) an actuation element associated with a proximal edge of the second delivery needle,

d) a catheter shaft, and

e) a dynamic seal formed between the catheter shaft inner lumen and the second delivery needle,

f) whereby a first component can be delivered through the first delivery needle without contacting a second component disposed in the second delivery needle.

19. A method of performing a medical procedure, comprising:

a) advancing within a patient's body lumen a device comprising a first delivery needle, and a second delivery needle,

b) delivering a first gel component through the first delivery needle,

c) delivering a second gel component through the second delivery needle, and

d) allowing the first and second gel components to admix within the patient's body tissue to form a gel composition.

20. The method of claim 19, wherein the device is further adapted to have at least two configurations and wherein the distal end of the first needle and the distal end of the second needle are longitudinally separated by an offset distance.

FIG. 1A

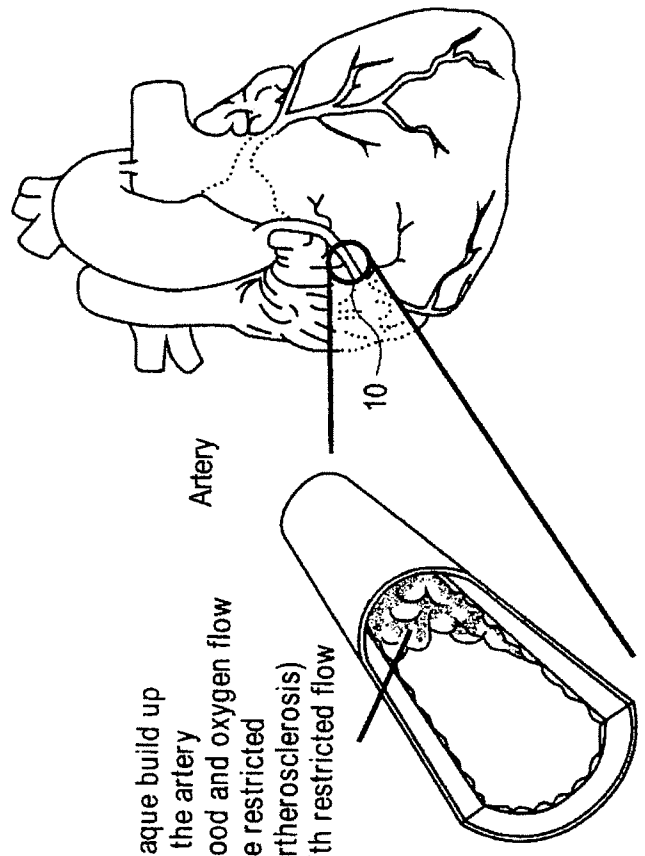
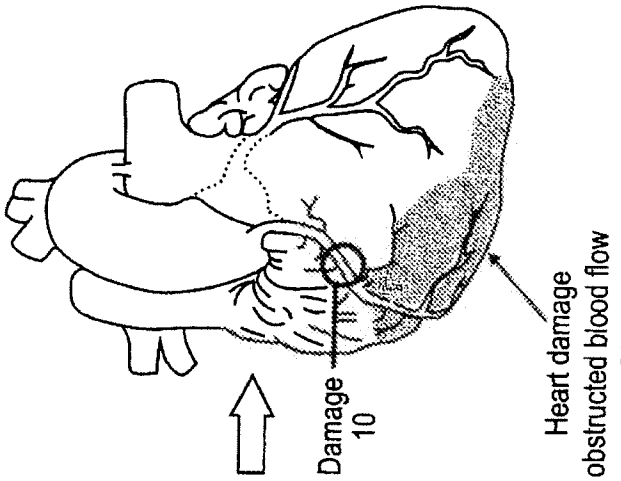

Plaque build up
in the artery
Blood and oxygen flow
are restricted
(artherosclerosis)
with restricted flow
Artery
10

FIG. 1B


Damage
10
Heart damage
obstructed blood flow
20

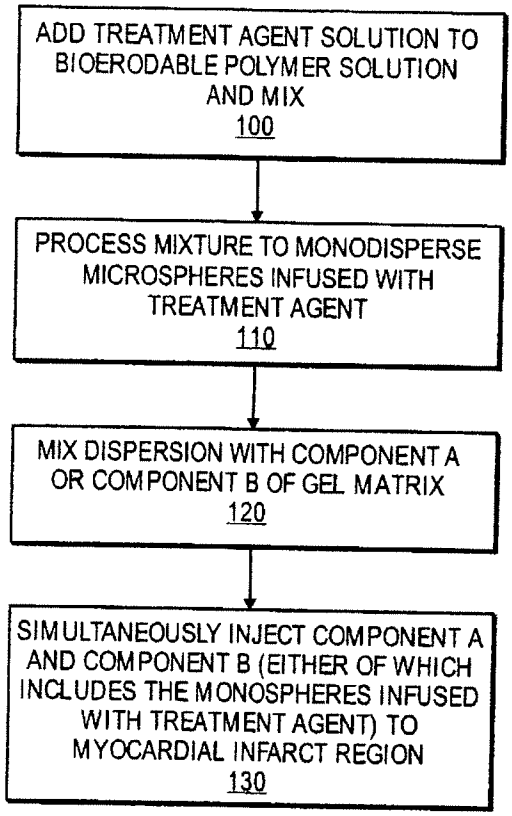

ADD TREATMENT AGENT SOLUTION TO BIOERODABLE POLYMER SOLUTION AND MIX
100
PROCESS MIXTURE TO MONODISPERSE MICROSPHERES INFUSED WITH TREATMENT AGENT
110
MIX DISPERSION WITH COMPONENT A OR COMPONENT B OF GEL MATRIX
120
SIMULTANEOUSLY INJECT COMPONENT A AND COMPONENT B (EITHER OF WHICH INCLUDES THE MONOSPHERES INFUSED WITH TREATMENT AGENT) TO MYOCARDIAL INFARCT REGION
130

FIG. 2

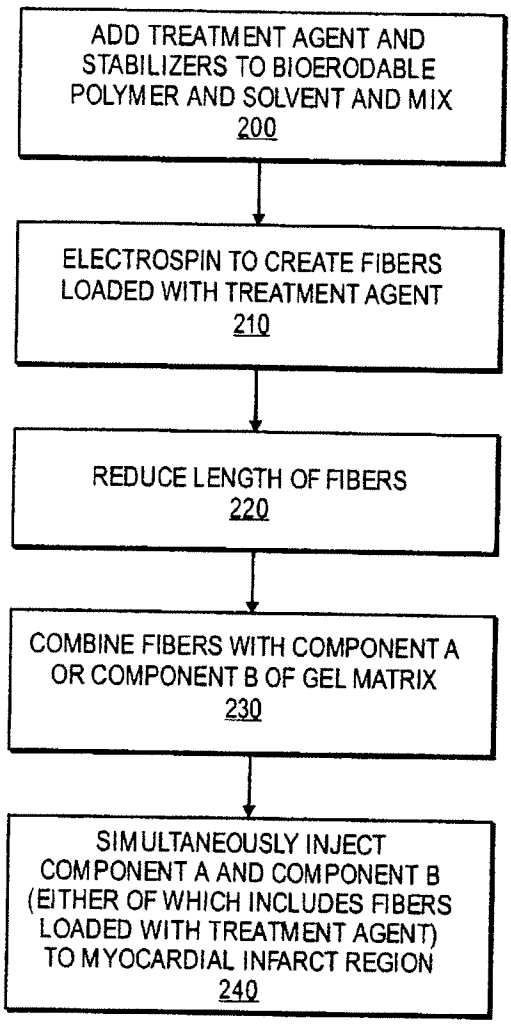

ADD TREATMENT AGENT AND STABILIZERS TO BIOERODABLE POLYMER AND SOLVENT AND MIX
200
ELECTROSPIN TO CREATE FIBERS LOADED WITH TREATMENT AGENT
210
REDUCE LENGTH OF FIBERS
220
COMBINE FIBERS WITH COMPONENT A OR COMPONENT B OF GEL MATRIX
230
SIMULTANEOUSLY INJECT COMPONENT A AND COMPONENT B (EITHER OF WHICH INCLUDES FIBERS LOADED WITH TREATMENT AGENT) TO MYOCARDIAL INFARCT REGION
240

FIG. 3

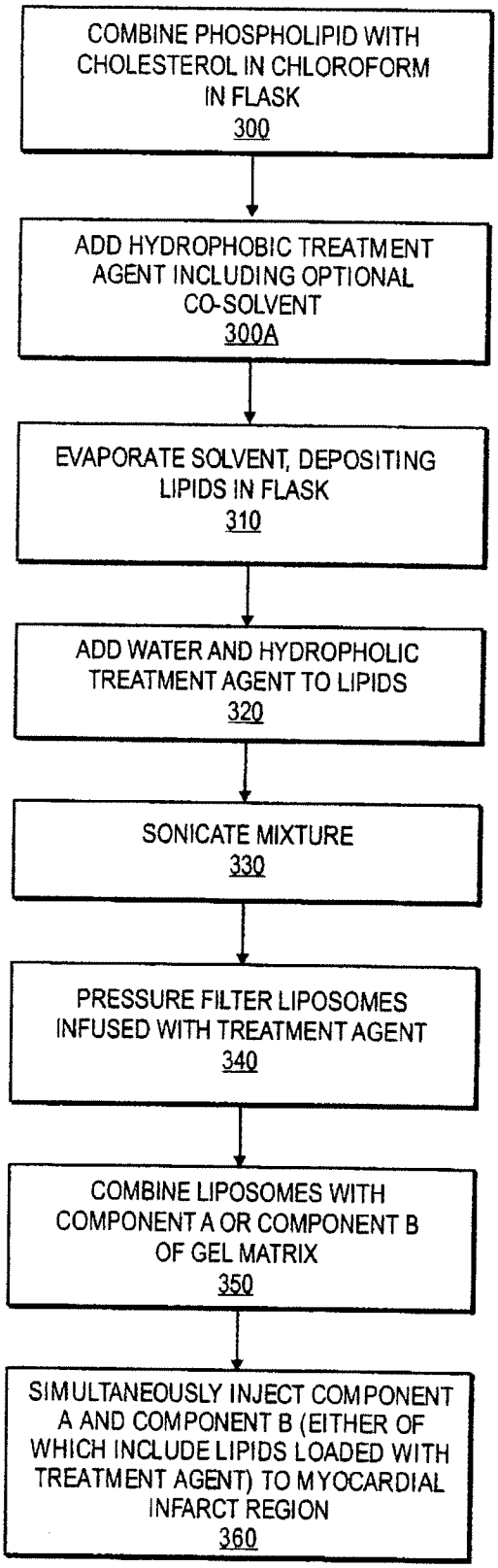
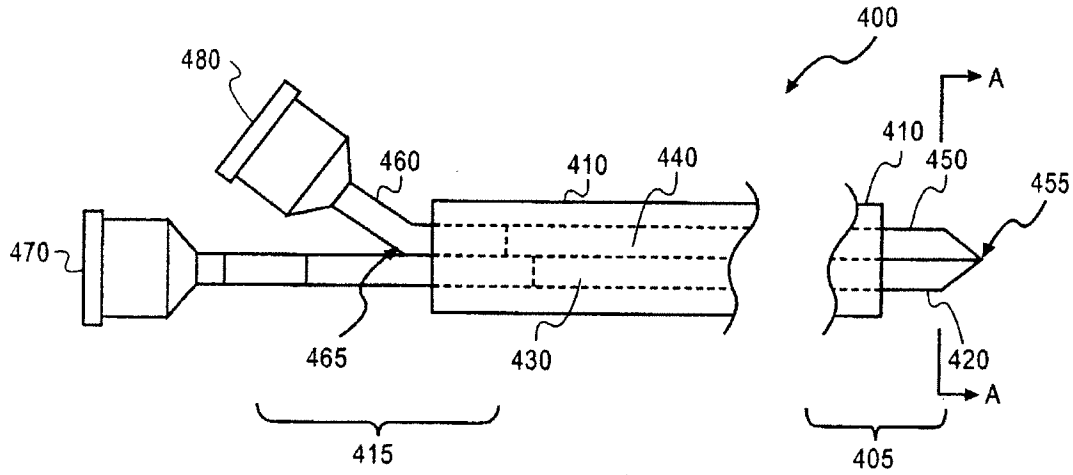

COMBINE PHOSPHOLIPID WITH CHOLESTEROL IN CHLOROFORM IN FLASK
300
ADD HYDROPHOBIC TREATMENT AGENT INCLUDING OPTIONAL CO-SOLVENT
300A
EVAPORATE SOLVENT, DEPOSITING LIPIDS IN FLASK
310
ADD WATER AND HYDROPHOLIC TREATMENT AGENT TO LIPIDS
320
SONICATE MIXTURE
330
PRESSURE FILTER LIPOSOMES INFUSED WITH TREATMENT AGENT
340
COMBINE LIPOSOMES WITH COMPONENT A OR COMPONENT B OF GEL MATRIX
350
SIMULTANEOUSLY INJECT COMPONENT A AND COMPONENT B (EITHER OF WHICH INCLUDE LIPIDS LOADED WITH TREATMENT AGENT) TO MYOCARDIAL INFARCT REGION
360

FIG. 4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480
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410
440
470
465
430
415
A
410
450
455
420
A
405

FIG. 5A

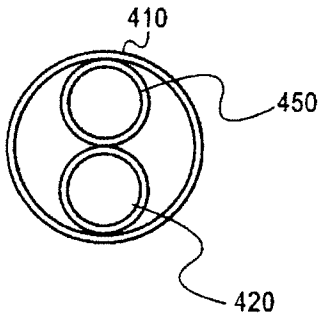
410
450
420

FIG. 5B

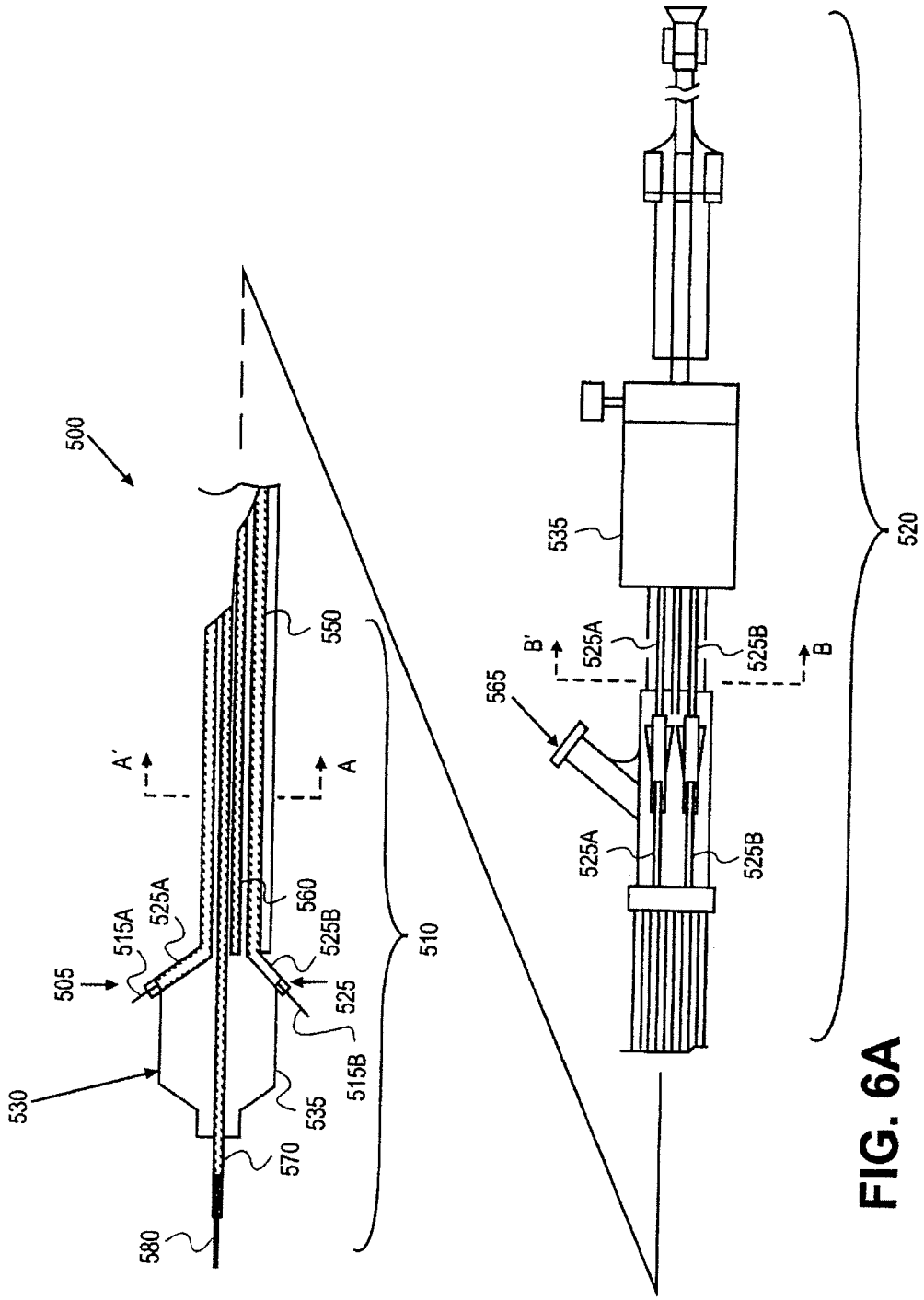
500
505
515A
525A
530
535
550
560
570
580
515B
525B
525
510
A'
A
B'
B
565
520

FIG. 6A

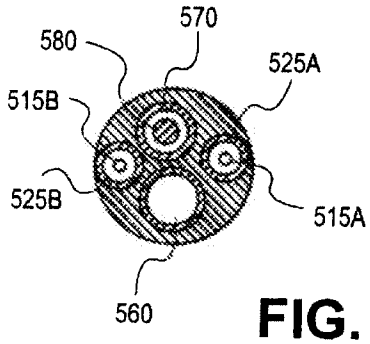

FIG. 6B

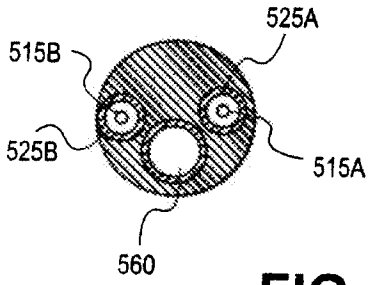

FIG. 6C

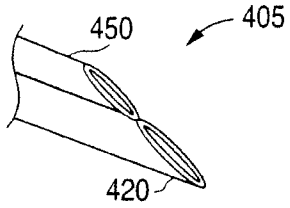

FIG. 7A

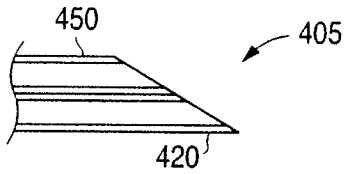

FIG. 7B

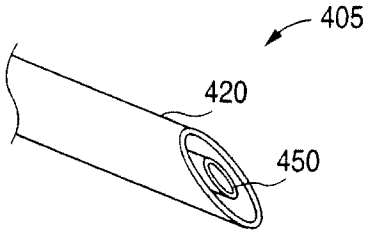

FIG. 8A

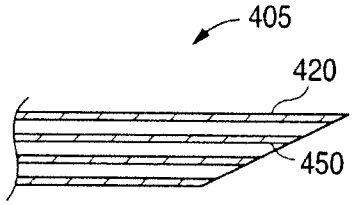

FIG. 8B

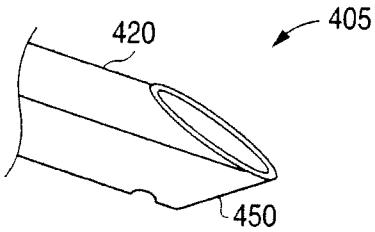

FIG. 9A

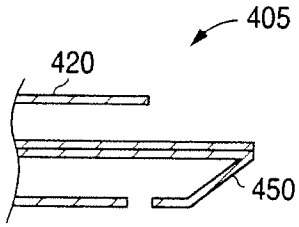

FIG. 9B

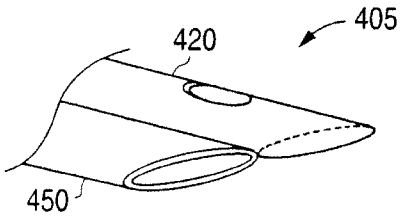

FIG. 10A

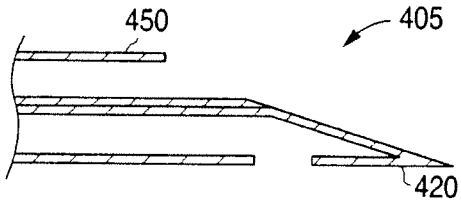

FIG. 10B

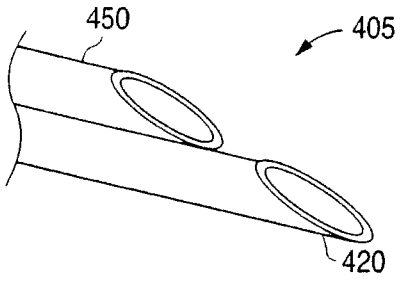

FIG. 11A

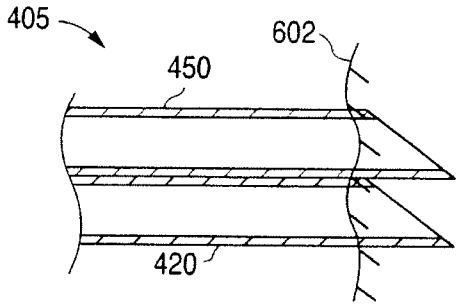

FIG. 11C

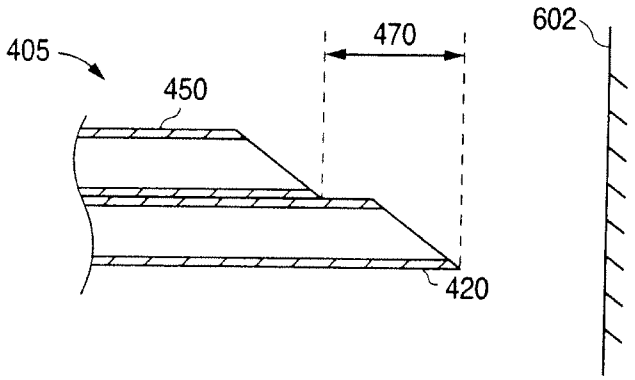

FIG. 11B

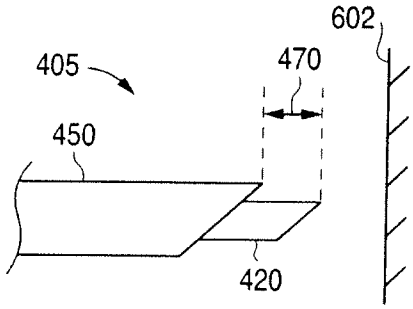

FIG. 12A

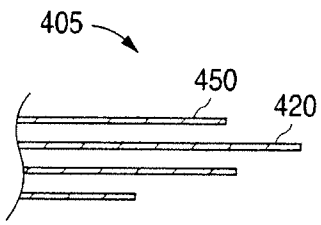

FIG. 12B

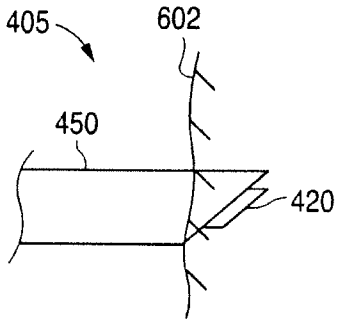

FIG. 12C

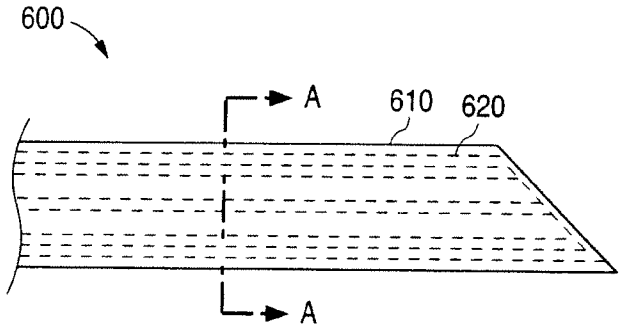

FIG. 13A

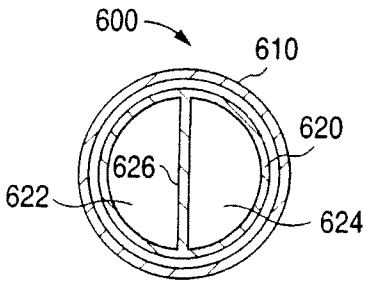

FIG. 13B

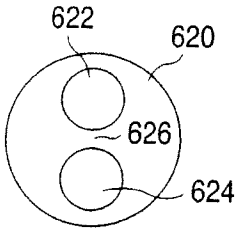

FIG. 14A

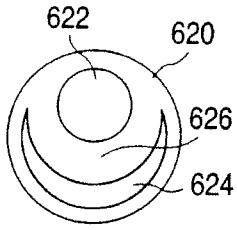

FIG. 14B

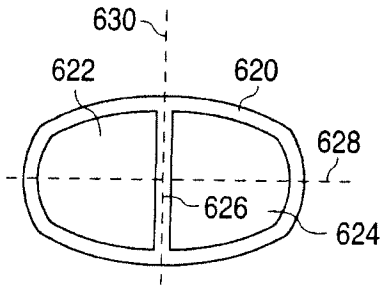

FIG. 14C

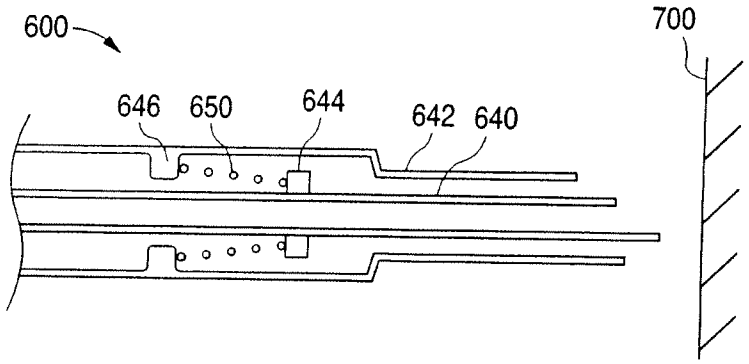

FIG. 15A

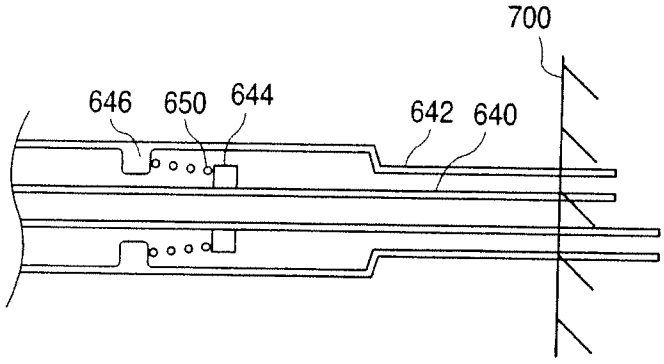

FIG. 15B

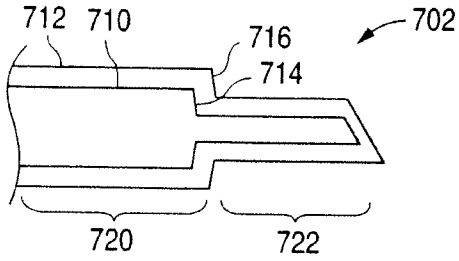

FIG. 16A

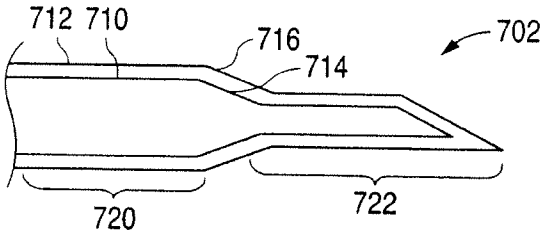

FIG. 16B

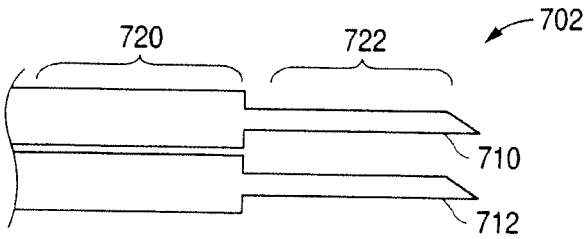

FIG. 16C

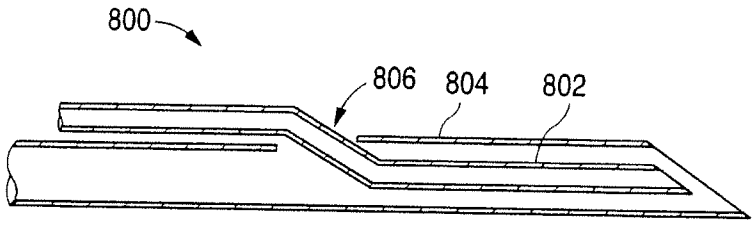

FIG. 17

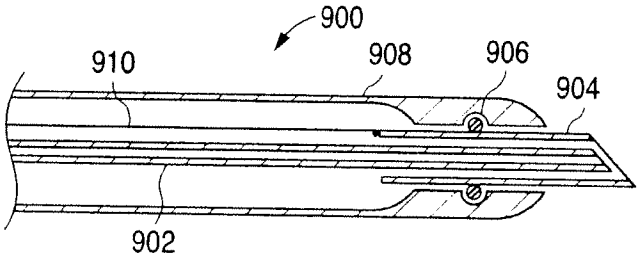

FIG. 18

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/079111

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M

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

Electronic data base consulted during the international search (name of data base and, where 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	US 5 419 777 A (HOFLING BERTHOLD [DE]) 30 May 1995 (1995-05-30)	1,2
A	abstract; figures 1-8	3-17
X	WO 2006/027549 A (PSIMEDICA LTD [GB]; WATSON JEREMY PAUL [GB]; CONNOR STEPHEN EDWARD [GB) 16 March 2006 (2006-03-16)	1,3
A	abstract; figures 1,3	2,4-17
X	US 3 804 097 A (RUDIE P) 16 April 1974 (1974-04-16)	1,2
A	abstract; figures 1-4	3-17
A	US 3 144 868 A (JASCALEVICH MARIO E) 18 August 1964 (1964-08-18) the whole document	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 December 2008	06/03/2009

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, Fax: (+31-70) 340-3016	Mausser, Thomas

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/079111

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

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

1. [X] Claims Nos.: 19,20
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-17

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-17

   A device comprising a first and second delivery needle.
   Technical problem to be solved: To deliver two medicamentations independently

   ---

2. claim: 18

   A device comprising an actuation device and a dynamic seal.
   Technical problem to be solved: To avoid contact of the delivered components.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/079111

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5419777 A	30-05-1995	AT 165740 T	15-05-1998
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