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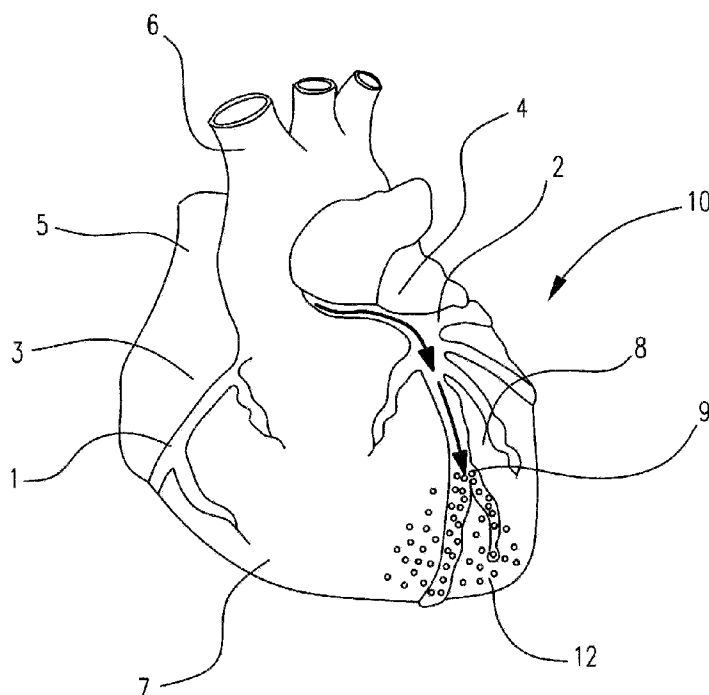
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(54) Title: METHODS, DEVICES AND COMPOSITIONS FOR CONTROLLED DRUG DELIVERY TO INJURED MYOCARDIUM

(57) Abstract: A method for modulating remodeling of an infarct region of a myocardium, the method including the controlled local delivery of therapeutic agent(s) employing microparticles as a carrier, and devices and compositions relating thereto.

FIG. 1





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**METHODS, DEVICES AND COMPOSITIONS
FOR CONTROLLED DRUG DELIVERY
TO INJURED MYOCARDIUM**

5 FIELD OF THE INVENTION

The present invention relates to the treatment of infarcted myocardium using controlled local drug delivery, and to methods, devices and compositions for such delivery.

10 BACKGROUND OF THE INVENTION

Ischemic heart disease is typically the result of an insufficient supply of blood to the heart muscle or myocardium often caused by constriction or obstruction of the blood vessels. For example, progressive atherosclerosis with increasing occlusion of coronary arteries leads to a reduction in coronary blood flow. Hypoperfusion,

15 vasospasm and thrombosis can lead to a further decrease in blood flow.

Myocardial infarction (MI) occurs when the blood supply to the heart is suddenly interrupted which results in insufficient oxygen and other nutrients.

Systemic delivery of drugs for the treatment of myocardial infarction has been relatively effective. However, a significant portion of the population ultimately
20 develops heart failure post-MI. Remodeling of the heart muscle such as the right or left ventricle, post-MI, is a significant component of the progression to heart failure due to uneven stress and strain distribution of the left ventricle post-MI.

Principle components of the remodeling event include myocyte death, edema and inflammation, followed by fibroblast infiltration and collagen deposition, and
25 finally scar formation. The principle component of scar tissue is collagen.

Myocyte loss is a major etiologic factor of wall thinning and chamber dilation that may ultimately lead to progression of cardiomyopathy, a heart disease

wherein the heart muscle, typically the left ventricle, is abnormally enlarged, thickened and/or stiffened, which can result in impairment of the heart muscle's ability to pump blood.

The controlled local delivery of drugs has become increasingly desirable
5 because higher doses can be maintained locally and the delivery of drugs directly to diseased tissue can be sustained over a longer period of time, can minimize side effects and is more effective against destructive myocardial remodeling post-MI.

SUMMARY OF THE INVENTION

10 The present invention relates to devices, methods and compositions for the modulation of remodeling of an infarct region of the myocardium post-myocardial (MI) infarction.

In one aspect, the present invention relates to a method for the controlled delivery of therapeutic agents into the myocardium for modulating remodeling of an
15 infarct region of the myocardium post-MI, the method including inserting a catheter into the myocardium, infusing at least one therapeutic agent into the infarct region, the at least one therapeutic agent effective for modulating remodeling of the infarct region.

Suitably, the carrier for the at least one therapeutic agent are polymeric microparticles or nanoparticles hereinafter referred to as particles. The therapeutic agent
20 may be encapsulated or entrapped in the particles, evenly distributed throughout the particles, or coated or adsorbed on the surface of the particles.

Suitably, for delivery in the vasculature the particles are in the microparticle size range having an average particle size of about 10 to about 25 microns in diameter, although for some applications this range may be varied.

Nanoparticles are also suitable for use in some embodiments described herein and generally have a diameter of about 1000 nm or less suitably from about 5 nm to about 750 nm, and more suitably from about 10 nm to about 500 nm.

The particles are suitably formed from a bioresorbable/biodegradable
5 polymeric composition.

Suitably, the at least one microparticles are infused into the lumen of the coronary artery and into the infarct region.

In some embodiments, the controlled delivery of the drug-loaded particle accompanies a vascular interventional procedure.

10 The present invention also relates to delivery devices for the controlled localized delivery of the drug-loaded particles described herein.

In one embodiment, individual particles are attached to the luminal side of a component of a catheter assembly, for example, the inner luminal surface of a catheter shaft for a perfusion catheter assembly, through a covalent linkage.

15 In another embodiment, a perfusion catheter assembly is equipped with pores which selectively allow microparticles such as drug-loaded particles of a specific size to pass therethrough, while preventing other larger particles from passing through.

In another embodiment, a perfusion catheter assembly in the form of a pre-loaded sack/balloon is disposed about a catheter shaft and the distal end of the
20 device contains a membrane with pores sized to selectively allow particles such as drug-loaded microparticles of a specific diameter to pass therethrough, while preventing particles of a larger size from passing through.

In another embodiment, drug-loaded particles are perfused out the distal tip of a perfusion catheter assembly, the distal tip having pores for selectively allowing
25 particles of a specific size to pass therethrough.

The methods, devices and compositions according to the invention can be employed in a variety of procedures including percutaneous coronary intervention (PCI) procedures, for treatment of peripheral artery disease (PAD), for treatment of diseases of the GI tract, treatment of renal vasculature, etc.

5 These and other aspects, embodiments and advantages of the present invention will become immediately apparent to those of ordinary skill in the art upon review of the Detailed Description and Claims to follow.

BRIEF DESCRIPTION OF THE DRAWINGS

10 FIG. 1 is a schematic diagram of the heart showing therapeutic agent delivery by intracoronary infusion.

FIG. 2 is a longitudinal cross-section of the distal end of one embodiment of a perfusion catheter assembly, the assembly including a perfusion balloon having drug-loaded particles pre-loaded into the balloon, the balloon, in a deflated state, shown
15 mounted on the catheter assembly.

FIG. 3 is a longitudinal cross-section of the distal of an embodiment of a perfusion catheter assembly similar to that shown in FIG. 2 showing a perfusion balloon in an inflated state.

FIG. 4 is a longitudinal cross-section of the distal end of an embodiment
20 of a perfusion catheter assembly similar to that shown in FIGS. 2-3 showing the balloon in an inflated state with drug-loaded particles perfusing therethrough.

FIG. 5 is a longitudinal cross-section of the distal end of one embodiment of a perfusion catheter assembly wherein the distal tip is equipped with a porous membrane.

FIG. 6 is a longitudinal cross-section of the distal end of one embodiment of a perfusion catheter assembly similar to that shown in FIG. 5 having perfusate of drug-loaded particles injected therein.

FIG. 7 is a longitudinal cross-section of the distal end of one embodiment of a perfusion catheter assembly similar to that shown in FIGS. 5 and 6 showing a perfusate of drug-loaded particles perfusing therethrough.

FIG. 8 is a longitudinal cross-section of the distal end of one embodiment of a perfusion catheter assembly with the perfusion balloon in a deflated state.

FIG. 9 is a longitudinal cross-section of the distal end of a perfusion catheter assembly similar to that shown in FIG. 8 with the perfusion balloon in an inflated state.

FIG. 10 is a longitudinal cross-section of the distal end of a perfusion catheter assembly similar to that shown in FIGS. 8 and 9 with the perfusion balloon in an inflated state illustrating drug-loaded particles perfusing through a membrane located on the distal tip.

FIG. 11 is a longitudinal cross section of a tubular member which may be employed for a variety of perfusion catheter assembly components, the tubular member having drug-loaded particles disposed on the inner lumen.

FIG. 12 is a longitudinal cross section of a tubular member similar to that shown in FIG. 11 illustrating perfusion of a solution therethrough.

FIG. 13 is a longitudinal cross section of a tubular member similar to that shown in FIGS. 11 and 12 illustrating perfusion of the drug-loaded particles out of a membrane on the distal end of the tubular member.

FIG. 14 is a longitudinal a tubular member which may be employed for a variety of perfusion catheter assembly components and a reservoir in fluid

communication therewith, the reservoir containing drug-loaded particles.

FIG. 15-18 illustrate coronary blood flow recovery post-infusion of incremental discrete doses of particles.

FIG. 19 illustrates a change in heart rate (HR) and mean arterial pressure (MAP) after infusion of microspheres of various diameters.

FIG. 20-22 illustrate the distribution of microparticles of various diameter sizes in an infarcted myocardium after infusion.

FIG. 23 is a graph summarizing dose feasibility for various particle sizes based on the average number of drug-loaded particles infused and the total mass of particles at the maximum tolerated dose as defined by recovery of normal coronary blood flow in a porcine model within 6 minutes.

DETAILED DESCRIPTION OF THE INVENTION

While this invention may be embodied in many different forms, there are described in detail herein specific preferred embodiments of the invention. This description is an exemplification of the principles of the invention and is not intended to limit the invention to the particular embodiments illustrated.

All US patents and applications and all other published documents mentioned anywhere in this application are incorporated herein by reference in their entirety. Any copending patent applications, mentioned anywhere in this application are also hereby expressly incorporated herein by reference in their entirety

For the purposes of this disclosure, like reference numerals in the figures shall refer to like features unless otherwise indicated.

In one aspect the present invention relates to the controlled local delivery of therapeutic agent(s) to an injured myocardium for modulation of remodeling of the

myocardium post-MI using polymeric particles as a carrier for the therapeutic agent(s).

FIG. 1 is a schematic diagram illustrating a myocardium 10 post-MI. Particles 20 are infused into a lumen of a major coronary vessel, in this embodiment the left anterior descending (LAD), and directly to the infarct region 12. In this embodiment, the infarct region 12 is shown in the left ventricle 8. Local delivery of the therapeutic agent(s) to the infarct region 12 may be beneficial because the drug delivery process has little or no impact on the surrounding healthy heart tissue. The therapeutic benefit is in the prevention of the loss of function of the myocardium in the region of the injury due to remodeling and scar formation which occurs as a result of the natural reparation process of the infarct post-MI which can ultimately result in thinning of the ventricular wall.

FIG. 1 is intended for illustrative purposes only. The present invention can be employed for delivery of therapeutic agents to other areas of the body as well, and in particular to other regions of the heart. For example, the present invention can be employed to deliver therapeutic agent to the heart through the circumflex branch of the coronary artery to the back of the left ventricle and through the right coronary artery to treat either of the ventricles, the right atrium and the sinoatrial node as well.

In this embodiment, the particles 20 are suitably in the microparticle size range, the microparticles 20 suitably having a diameter in the range of about 10 microns to about 25 microns, and more suitably about 10 microns to about 20 microns. The particles may be of a mixed population according to size within the stated range, or may have a uniform size population based on average diameter in the stated range. For example, the microparticles may have a mixed size population within a range of about 10 microns to about 25 microns, or the microparticles may have a uniform population with an average diameter of about 15 microns \pm 1.5 microns. Delivery of microparticles having a size of greater than about 25 microns can have a negative impact on the

coronary blood flow. For example, microparticles having an average diameter of about 30 microns or greater may result in ischemia due to microvascular plugging.

In this embodiment, the total mass of microparticles delivered in a single bolus of drug loaded microparticles is suitably about 10 mg or less. The infusion of a
5 greater mass of microparticles can negatively impact the coronary blood flow.

In this embodiment, the number of particles delivered in a single bolus is suitably between about 5×10^5 to about 1×10^7 for maintaining optimum therapeutic effect without any significant impact on the coronary blood flow. Therapeutic effect may be acute, chronic or both. For example, the drug released from these microparticles
10 may limit post-MI remodeling over a span of weeks. Depending on the therapeutic agent delivered, there can be acute cardioprotective effect.

The total number of particles delivered is also dependent on average particle size. For smaller particles, a larger number of total particles may be delivered. For particles having an average particle size of about 10 microns, up to about 1×10^7
15 particles may be delivered. For particles having an average particle size of about 20 microns, up to about 1×10^6 total particles may be delivered. For average particle sizes between about 10 microns and about 20 microns, the desirable number of particles delivered may vary.

The particles may be formed from any suitable polymer composition
20 including both either non-biodegradable or biodegradable polymers. More suitably, the particles are formed from biodegradable polymer material. The polymer may be natural or synthetic, with synthetic polymers being preferred due to the better characterization of degradation and, where appropriate, release profile of an incorporated agent. The polymer is selected based on the period over which degradation or release of an agent is

desired, generally in the range of at several weeks to several months, although shorter or longer periods may be desirable.

Suitable polymer materials that may be incorporated into the polymer composition include, but are not limited to, polyhydroxyalkanoates such as

- 5 poly(hydroxybutyrate) (PHB), poly(hydroxyvalerate) (PHV) and poly(hydroxybutyrate-co-valerate), polylactones such as polycaprolactone (PCL), poly(L-lactic acid) (PLA), poly(glycolic acid) (PGA), poly(D,L-lactic acid), poly(lactide-co-glycolide) (PLGA), poly(lactide-co-caprolactone), polydioxanone, polyorthoesters, polyanhydrides, poly(glycolic acid-co-trimethylene carbonate), polyphosphoesters, polyphosphoester
- 10 urethanes, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), polyurethanes, poly(iminocarbonate), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, starch, collagen, hyaluronic acid, other natural polymers such as alginate, polysaccharides such as dextran and cellulose, etc., and mixtures thereof.

- 15 The particles can also be formed from bioerodible hydrogels which are prepared from materials and combinations of materials such as polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl
- 20 methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

Other suitable polymers include, but are not limited to, polyvinylpyrrolidone, polyethylene oxide (polyethylene glycol), polyvinyl alcohol, etc.

See, for example, U.S. Patent Publication No. 2006/0078624, for suitable polymer compositions for particle formation, the entire content of which is incorporated by reference herein.

Particulate carriers formed from an α -hydroxy acid and α -amino acid monomers are disclosed in U.S. Patent No. 6,042,820, the entire content of which is incorporated by reference herein.

In some embodiments, the particles are formed from a polymer composition that includes at least one of L-lactic acid, D,L-lactic acid, glycolic acid, caprolactone, or copolymers thereof.

Preferred biodegradable polymers are polyglycolic acid, polylactic acid, copolymers of glycolic acid and L- or D,L-lactic acid, and copolymers of glycolide and L- or D,L-lactide. Those of skill in the art will appreciate that the molecular weight of the polymer, the ratio of one monomer to another, for example the lactide to glycolide ratio, and the compositions of the end groups can be varied to tailor the properties of the particle.

In some embodiments, polylactide-co-glycolide copolymers are employed in forming the particles. The ratio of lactide to glycolide may range from about 50:50 to about 85:15. In one embodiment, a ratio of 75:25 lactide to glycolide may be employed.

U.S. Patent Publications discussing drug-loaded particles include, for example, U.S. 2005/0220853, the entire content of which is incorporated by reference herein.

The particles may be hollow, i.e. having a polymeric outer shell, they may be solid wherein therapeutic agent may be distributed throughout or coated or other

wise bonded on the surface thereof, or they may have more than one phase, for example, a liquid core with a polymeric outer shell.

In one specific embodiment, the particle is a solid polymeric particle having therapeutic agent distributed throughout the polymeric material.

5 To form a particle having a solid core, the polymer used as polymeric core can be mixed with an effective amount of therapeutic agent(s). This may be referred to as “microencapsulation” of the therapeutic agent(s). Methods of microencapsulation include, but are not limited to, rotating disk, spray drying, fluidized bed, single, double or three-phase emulsion techniques, drop-by-drop, spray drying, phase separation, etc.

10 An example of rotating disk type microencapsulation method is described in U.S. Patent Publication No. 2004/0001890, the entire content of which is incorporated by reference herein.

Spray-drying is described in U.S. Patent Nos. 6,451,349 and 6,416,739, each of which is incorporated by reference herein in its entirety.

15 The particle may also have a solid core with a sustained release coating of therapeutic agent(s) on the outside surface. One way to do this is to dissolve the therapeutic agent(s) with a polymer in a solvent containing both therapeutic agent(s) and polymer and then coating the particle core. See U.S. 2004/0001890, the entire content of which is incorporated by reference herein.

20 In a specific embodiment, the particles are formed with a poly(lactide-co-glycolide) copolymer having a ratio of 50:50 lactide to glycolide and an ace (angiotensin converting enzyme) inhibitor using a single emulsion technique. The solvent employed may be any suitable organic solvent. Exemplary solvents include methylene chloride and ethyl acetate. The particle size may be controlled by the stir rate as well as by
25 filtering after the particles have been formed. See, for example, U.S. No. 6,720,008

discussing single emulsion techniques, the entire content of which is incorporated by reference herein in its entirety. Single emulsion techniques are well known. See, for example, U.S. Patent Pub. Nos. 20050175709, 2006/0177416 and 2006/0034923, each of which is incorporated by reference herein in its entirety.

- 5 Examples of ACE inhibitors include, but are not limited to, sulfhydryl-containing ACE inhibitors such as Captopril (Capoten®), dicarboxylate-containing ACE inhibitors such as Enalapril (Vasotec®/Renitec®), Quinapril® (Accupril®), Ramipril (Altace®/Tritace®/Ramace®/Ramiwin®) Perindopril (Coversyl®/Aceon®), Lisinopril (Lisodur®/Lopril®/Novatec®/Prinivil®/Zestril®), Benazepril (Lotensin®), and
- 10 phosphonate-containing ACE inhibitors such as Fosinopril (Monopril®) and their active forms including enalaprilat, benazeprilat, etc.

- Examples of commercially available polymers having a ratio of 50:50 lactide to glycolide based on mole-% such as MEDISORB® 5050DL available from Alkermes, Inc. in Blue Ash, Ohio and RESOMER® RG 502 available from Boehringer
- 15 Ingelheim in Germany.

 Other suitable commercially available products having different ratios of lactide to glycolide as a mole-% are MEDISORB® 6535 DL, 7525 DL, 8515 DL and Resomer® RG 752 having a ratio of 75:25 lactide to glycolide and Resomer® RG 206.

- Any of these copolymers are available in a wide range of molecular
- 20 weights and ratios of lactic acid to glycolic acid from about 5,000 daltons to about 500,000 daltons.

 Alternatively, for water-soluble drugs, a double emulsion may be employed wherein the first emulsion includes the water soluble drugs in the aqueous phase and the polymer is in the organic phase. A double emulsion method of forming

drug-loaded microparticles is described in U.S. Patent No. 7,247,319, the entire content of which is incorporated by reference herein.

The particles described herein may be employed for localized controlled release of the therapeutic agents, the release of which may be sustained over a period of 5 days, weeks, or even months. The release kinetics can be controlled by both the carrier as well as the therapeutic agent(s) itself.

Any therapeutic agent may be employed herein. As used herein, the terms, "therapeutic agent", "drug", "pharmaceutically active agent", "pharmaceutically active material", "beneficial agent", "bioactive agent", and other related terms may be 10 used interchangeably herein and include genetic therapeutic agents, non-genetic therapeutic agents and cells. A drug may be used singly or in combination with other drugs. Drugs include genetic materials, non-genetic materials, and cells.

In some embodiments, the present invention may be employed for the localized, controlled release of therapeutic agents for modulation of post-MI remodeling. 15 For modulation of post-MI remodeling, some therapeutic agent(s) may be more efficacious than others. Examples of agents useful for the mediation of post-MI remodeling include, but are not limited to, selective or non-selective matrix metalloproteinase inhibitors (MMPi) (tissue inhibitor of metalloproteinases or TIMPs including TIMP-1, TIMP-2, TIMP-3 and TIMP-4), mediation of renin angiotensin 20 aldosterone system (RAAS) pathways and myocardial salvage including the prevention of myocyte death and the promotion of myocyte proliferation, mediation of mitochondrial death pathways and apoptosis, etc.

RAAS may be mediated through the introduction of ACE inhibitors (or inhibitors of angiotensin-converting enzyme), angiotensin receptor antagonists or 25 blockers and aldosterone blockers, for example.

ACE inhibitors may be used to reduce the formation of angiotensin II, the production of which can ultimately result in elevated blood pressure. Examples of ACE inhibitors include, but are not limited to, sulfhydryl-containing ACE inhibitors such as Captopril sold under the tradename of Capoten®, dicarboxylate-containing ACE inhibitors such as quinapril sold under the tradename of Accupril® and phosphate-containing ACE inhibitors such as fosinopril sold under the tradename of Monopril®.

Angiotensin receptor antagonists include, but are not limited to, losartan (Cozaar®), valsartan (Diovan®), irbesartan (Avapro®), candesartan (Atacand®) and telmisartan (Micardis®).

10 An example of an aldosterone blockers include, but are not limited to, spironolactone and eplerenone.

Other examples of drugs which may be employed for mediation of remodeling include, but are not limited to statins such as atorvastatin (competitive inhibitors of HMG-CoA reductase), nitroglycerine, and TGF-beta inhibitors, 15 cardioprotective agents, anti-apoptotic agents, adenosine, myofibroblast proliferation/migration/maturation inhibitors, β -blockers such as Carvedilol, NEP (neutral endopeptidase) inhibitors such as omapatrilat, vasopectidase inhibitors, growth factors such as VEGF, PDGF, IGF, bFGF, SDGF, etc., PPAR (peroxisome proliferator-activated receptor) agonists, anti-inflammatory agents, etc.

20 Some therapies are suitably administered within about 72 hours of the MI event as this is when some early remodeling of the heart muscle may occur, while other therapies may be delivered beyond 72 hours, for example, up to about 2 weeks. As an example only, ACE inhibitors and therapies for mediation of RAAS pathways may suitably be delivered within about 72 hours. Suitably, matrix metalloproteinase 25 inhibitors are delivered within about one week, and more suitably within about 72 hours.

The mediation of early remodeling by the controlled local delivery of select therapeutic agents can be particularly efficacious because infarct expansion may occur early and results in ventricular dilatation and wall thinning, and causes elevation of diastolic and systolic wall stresses (increased blood pressure).

5 The present invention may be employed at the same time as vessel reperfusion, immediately after vessel reperfusion or as a separate interventional procedure. Suitably, however, local drug delivery is employed concurrently with or immediately after an interventional procedure such as percutaneous coronary intervention (PCI).

10 Any suitable delivery device may be employed herein. FIGS. 2-4 illustrate one embodiment of a perfusion catheter assembly 20 for delivery of drug-loaded particles 40, suitably in this embodiment in the microparticle size range. Perfusion catheter 20 is a dual-lumen catheter assembly including an inner shaft 22 and an outer shaft 24. Distal end 32 of perfusion balloon 26 is mounted on distal end of
15 inner shaft 22 and the proximal end 34 of perfusion balloon 26 is mounted on distal end of outer shaft 24.

Guide wire 46 is shown within the inner lumen 38 (guide wire lumen 38) defined by inner shaft 22.

Drug-loaded particles 40 are pre-loaded into balloon 26 which is shown
20 in a deflated state in FIG. 2. Balloon 26 may be inflated by perfusing a liquid carrier through lumen 28 of outer shaft 24 and into the balloon indicated by arrows in FIG. 3. The drug-loaded particles become dispersed or suspended in the liquid carrier. Shown at the distal end 32 of balloon 26 is a membrane 50. Membrane 50 has a pore size which allows particles of a certain specified size to pass through, but limits the passage of other
25 larger particles. The pores may be configured to allow particles of only one size, i.e. 15

microns \pm 1.5 microns) or may be configured to allow particles of a certain particle size range, i.e. 10-20 microns, to pass while limiting the passage of larger particles as shown in FIG. 4.

Of course, membrane 50, can be located anywhere on the balloon as
5 desired.

Furthermore, the membrane is provided for illustration only, and the device nor the scope of the invention are limited by this illustrative feature. Any suitable structure can be employed as a substitute for a membrane providing perfusion of selected particle sizes is allowed out of the device, while preventing other particle sizes
10 from entering a patient's system.

Perfusion of the inflation media through the balloon may be pulsatile so as to mix and agitate the particles and to prevent clogging of the membrane.

In use, the drug-loaded particles 40 can be infused into the lumen of the left anterior descending (LAD) 9 and is positioned at the infarcted region 12 as shown in
15 FIG. 1. Using this delivery approach, a guide catheter may be inserted through the femoral artery of a patient, and positioned at the ostium of the left coronary artery 2. The guide catheter is then employed to assist the placement of the balloon catheter assembly into the left coronary artery 10 and into the LAD 9 and into position at the infarct region 12. A guide wire is used to assist this placement.

20 Balloon 26 may then be inflated as illustrated in FIGS. 2-4 and the drug-loaded particles perfused into the infarct region 12 where they can lodge in the myocardial capillaries and release drug to the surrounding tissue in a controlled, sustained manner. The bioresorbable/biodegradable polymer used for forming the particle 40, whether a hollow shell or a solid particle having drug dispersed throughout
25 the solid, slowly allows the drug to elute over time.

Suitably, the drug-loaded particles are infused into the coronary artery in a single bolus. However, discrete incremental doses can also be employed.

The delivery of the drug-loaded particles can be done concurrently with a vessel reperfusion process such as PCI, immediately after a vessel reperfusion process, or in a separate interventional procedure. Suitably, the particles are delivered at the time of vessel reperfusion for optimum results.

Another embodiment of a perfusion catheter assembly is shown generally at 20 in FIGS. 5-7. Perfusion catheter assembly 20 is a dual lumen catheter assembly having an inner shaft 22 and an outer shaft. Inner shaft 22 defines a guide wire lumen 38. The distal end of the perfusion catheter assembly 20 is equipped with a distal tip 42 which further includes a porous membrane 50. Porous membrane 50 includes pores which are sized so as to allow passage of particles of specific diameter size only. In this embodiment, suitably the size of the particles is in the microparticle size range. Pores can be sized so as to allow particles of only a single diameter size to pass through such as 15 microns \pm 1.5 microns or of a given size range such as about 10 microns to about 20 microns in size while excluding particles of a larger size from passing through.

Again, referring to FIG. 1 for illustration only, the perfusion catheter assembly 20 can be employed to infuse drug-loaded particles 40 into a coronary artery such as the left coronary artery 2, into the lumen of the left anterior descending (LAD) 9 and into the infarcted region 12. Using this delivery approach, a guide catheter may be inserted through the femoral artery of a patient, and positioned at the ostium of the left coronary artery 2. The guide catheter is then employed to assist the placement of the perfusion catheter assembly 20 shown in FIG. 5 into the left coronary artery 10, into the LAD 9 and positioned at the infarct region 12. A guide wire is used to assist this placement.

The proximal end of the catheter assembly 20 may be further equipped with a port 54 for injecting a carrier fluid including the drug-loaded particles dispersed of suspended therein. Drug-loaded particles 40 in the carrier liquid are passed through the distal tip 42 and out through the porous membrane 40.

5 In one embodiment, the perfusion catheter assembly 20 includes both a balloon 26 and a distal tip 42 as shown in FIGS. 8-10. The distal tip includes porous membrane 40 having pores sized to allow selective perfusion of drug-loaded microparticles or nanoparticles as discussed above. FIG. 8 illustrates the balloon 26 in a deflated, folded, wrapped configuration. Balloon 26 is shown pre-loaded with the
10 particles 40. However, the drug-loaded particles may be injected into the catheter through a port which is in communication with an inflation lumen 28 rather than pre-loading the balloon as well. FIG. 9 illustrates balloon 26 in an inflated state and FIG. 10 illustrates particles of a selected size only being perfused through membrane 50 while larger particles are prevented from perfusing through membrane 50. In this
15 embodiment, the particles are suitably in the microparticle size range.

The catheter may also have more than one or two lumens, as in the case where the catheter includes both an occlusion or angioplasty balloon and a perfusion balloon. Of course, some devices employ two or more balloons as well.

20 In other embodiments, a perfusion catheter assembly includes drug loaded particles, suitably nanoparticles, that are covalently bonded to the inner lumen of a catheter component. Any suitable component which allows perfusion through the lumen may be employed including both the inner and outer shafts and balloons. Tubular member 56 with inner lumen 58 and inner surface 60 is shown in FIGS. 11-13 having particles 40, suitably nanoparticles, covalently bonded to inner surface 60.

Nanoparticles typically have a diameter of about 1000 nm or less, preferably from about 5 nm to about 750 nm, and more preferably from about 10 nm to about 500 nm.

Suitably, the covalent linkages may be readily cleaved, allowing the drug particles to release. In some embodiments, the linkage is formed so as to be readily cleaved through the use of enzymes. In other embodiments, the linkage is formed so as to be readily cleaved in the presence of water. Cleavage of the covalent linkages allows the drug-loaded nanoparticles to be perfused out of the lumen of the catheter component, to the treatment site within a patient.

A variety of covalent and non-covalent linking methods may be employed for attaching the nanoparticles to the inner lumen surface such as ester and thioester linkages, peptide linkages, and water soluble materials. Such attachment methods are known to those of skill in the art, some of which are listed below. These methods are illustrative only, and are not intended to limit the scope of the present invention in any way.

Ester and thioester linkages can be employed. Such linkages are hydrolyzable, the rate of which can be increased using esterases.

Peptide linkages are readily cleaved by appropriate enzymes.

Other types of covalent bonds, for example amide bonds and siloxane based linkages can also be used to attach the nanoparticle to the device surface.

Disulfide linkages are also readily severable and involve functionalization of the surface of the nano-particles such as with an -SH containing silane and the surface of the device with an activated disulfide linkage.

Alternatively, molecules may be covalently attached via linker molecules. Molecules may also be attached to the surface by non-covalent linkage, for example by

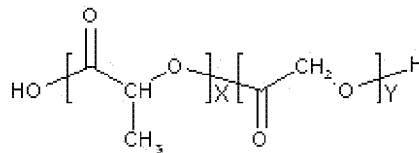
absorption via hydrophobic binding or Van der Waals forces, hydrogen bonding, acid/base interactions and electrostatic forces.

Layer-by-layer (LbL) adsorption is one specific method that can be employed in attachment of the drug-loaded nano-particles wherein the particle is formed using this method and the surface of the device is treated accordingly. Using LbL self-assembly techniques, the sequential absorption of oppositely charged species from solution, e.g. aqueous media, can be employed to prepare multi-layer films. The charge on the outer layer is reversed upon deposition of each subsequent polyelectrolyte layer. These techniques are also known in the art. See for example, commonly assigned US Patent Publication No. 2005/0129727, the entire content of which is incorporated by reference herein.

Other examples of linking methods are provided in U.S. Patent No. 7,195,780, wherein nanocaps are attached to nanotubes either through the use of covalent linkages or non-covalent techniques, the entire content of which is incorporated by reference herein.

One specific method of binding nanoparticles to the luminal surface of a device is to employ a polyalkylene glycol linker such as the heterobifunctional polyethylene glycol (PEG) liners disclosed in U.S. Patent Pub. No. 2006/0246524, the entire content of which is incorporated by reference herein. Suitably, the nanoparticles are coupled to the PEG via a hydrolyzable linker. This is a well known technique commonly referred to in the art as "PEGylation". Using this technique, chemically active or activated derivatives of the PEG polymer are first prepared to attach the PEG to the desired molecule. The selection of the functional group for the PEG derivative is based on the available reactive group on the molecule that will be coupled to the PEG. Commonly used end groups for heterobifunctional PEGs include, but are not limited to,

maleimide, vinyl sulfones, pyridyl disulfide, amine, carboxylic acids and NHS esters. If, for example, PLGA nanoparticles are attached via a PEG linker, no activation may be required. The carboxylic acid groups of PLGA may be directly reacted with PEG. If however, one wishes to attach PLGA via available hydroxyl groups, then PEG may be activated with a sulfonate group, for example. PLGA is shown below:



where X is the number of units of lactic acid and Y is the number of units of glycolic acid. For attaching nanoparticles to the luminal surface of a medical device, one would first coat the surface of the device with PEG macromolecules, prior to reacting with the PLGA nanoparticles.

Biocompatible adhesives may also be employed, for example, cyanoacrylates may be employed. Other adhesives include, but are not limited to, polyurethanes, epoxies, polyamides, polyimides, silicones, and so forth. The adhesive may be coated on the inner lumen surface, for example.

Water soluble gels or other hydrogels and fibrin gels may be employed for adhering the nanoparticles on the inner lumen surface.

In another embodiment, illustrated generally in FIG. 14, a delivery catheter assembly may include a reservoir 62 located at the proximal end of component of a catheter assembly. The reservoir 62 is in fluid communication with an inner lumen 58 of a tubular member 56 which may be employed in a catheter assembly for, as an example, an inner shaft (guide wire lumen) or an outer shaft, and extends substantially the entire length of the catheter assembly. Fluid communication can be provided by multiple openings 70 between the reservoir 62 and the lumen 58 of the tubular member

56 which forms part of the catheter assembly. Reservoir 62 contains the carrier liquid with the drug-loaded particles 40 dispersed or suspended therein. As fluid is infused into the lumen, the liquid carrier with drug-loaded particles 40 is pulled from the reservoir into the fluid flow and out the distal end of the lumen 58 as shown in FIG. 14.

5 Any therapeutic agent may be used in combination with the methods and devices disclosed herein. Examples of drugs which may be delivered using any of the above devices or methods may be found in commonly assigned U.S. Patent No. 7105175, 7014654, 6899731, 6855770 and 6545097, each of which is incorporated by reference herein in its entirety, and in commonly assigned U.S. Patent Application
10 Publication No. 2004/0215169, the entire content of which is incorporated by reference herein.

 The methods, devices and compositions disclosed herein may be employed for any application where it is desirable to have controlled local delivery of drugs. Examples include, but are not limited to, treatment of the coronary vasculature,
15 treatment of the gastrointestinal tract such as for the treatment of Crohn's disease, treatment of the peripheral vasculature, treatment of the renal vasculature such as for renal insufficiency, etc.

 The methods, devices and compositions of delivering therapeutic agents locally and for sustained periods of time can eliminate the need for additional procedures
20 and associated complications.

 The following non-limiting examples further illustrate some aspects of the present invention.

EXAMPLES

Particles were tested for optimum size, mass and total number of particles to be delivered in a single bolus. In these examples, the particles were polystyrene microparticles having an average particle size between about 10 and about 25 microns.

- 5 The particles were infused into the myocardium of porcine models just past the second diagonal of the LAD as shown in FIG. 1. The infusion rate was 1 mL/min. and the total number of particles was varied, as was the average particle size. The coronary blood flow recovery post-infusion was measured for each bolus administered.

FIGS. 15-18 illustrate the coronary blood flow recovery post-infusion for
10 a variety of different particle sizes and total particle number.

FIG. 15 is a graph illustrating the affect on coronary blood flow recovery post-infusion of microparticles having an average particle size of about 10 microns. As can be seen from the graph, up to about 1×10^7 microparticles may be delivered in a single bolus without having a significant impact on coronary blood flow.

- 15 FIG. 16 is a graph illustrating the affect on coronary blood flow recovery post-infusion of microparticles having an average particle size of about 15 microns. As can be seen from the graph, up to about 2×10^6 microparticles may be delivered in a single bolus without having a significant impact on coronary blood flow.

FIG. 17 is a graph illustrating the affect on coronary blood flow recovery
20 post-infusion of microparticles having an average particle size of about 20 microns. As can be seen from the graph, up to about 1×10^6 microparticles may be delivered in a single bolus without having a significant impact on coronary blood flow.

- A mixed particle size distribution of between about 10 and about 25 microns is illustrated in FIG. 18. The coronary blood flow recovery post-infusion was
25 negatively impacted with a total particle number of less than 5×10^5 . This may indicate

that particle sizes of larger than about 20 microns has a negative impact on coronary blood flow post-infusion.

FIG. 19 is a graph illustrating blood pressure and mean arterial pressure pre- and post-infusion. Particle sizes between about 10 and about 25 microns had an insignificant impact on the blood pressure and mean arterial pressure post-infusion.

FIGS. 20-22 are 3D bar graphs illustrating the distribution of the microparticles in infarcted myocardium. In each graph

10 N1 and N2 indicate normal myocardium;
A1 and A2 indicate adjacent infarct with normal and infarcted areas;
I1 and I2 indicate infarcted myocardium;
N1 is toward the septum;
Slice 1 is just above the apex of the heart with subsequent slices going up to the site of infusion at the second diagonal of the LAD.

15 FIG. 20 illustrates that microparticles having an average particle size of about 10 microns are well-distributed in the infarcted myocardium.

FIG. 21 illustrates that microparticles having an average particle size of about 15 microns are well-distributed in the infarcted myocardium.

20 FIG. 22 illustrates that microparticles having an average particle size of about 20 microns are well-distributed in the infarcted myocardium

Furthermore, little or no microparticles were found in the lung or liver of the porcine models in total numbers of less than about 10 microparticles per gram of tissue.

25 No detectable quantities of microparticles between about 10 microns and 20 microns in size were found in the circulating blood post-infusion.

FIG. 23 is a graph summarizing dose feasibility for various average particle sizes based on the average number of microparticles infused and the total mass of microparticles at the maximum tolerated dose. The maximum tolerated does in the

total number of microparticles that could be infused where the porcine model was able to recovery normal coronary blood flow (TIMI = 3) within 6 minutes post-infusion.

For this particular example, the optimum total mass of microparticles delivered by coronary infusion in a single bolus was found to be about 10 mg.

5 The above disclosure is intended to be illustrative and not exhaustive. This description will suggest many variations and alternatives to one of ordinary skill in this art. Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims.

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CLAIMS:

1. A method for modulating remodeling of an infarct region of a myocardium, the method comprising:
 - identifying an infarct region within a ventricle of the myocardium;
 - infusing microparticles into a coronary artery to said infarct region, said microparticles comprising a bioerodable polymer composition and comprising at least one therapeutic agent effective for modulating remodeling of the infarct region, said microparticles having a mixed diameter range of about 1 micron to about 45 microns.
2. The method of claim 1 wherein the mean diameter of said particles is between about 10 microns and about 25 microns.
3. The method of claim 1 wherein said microparticles have an average particle size of about 10 microns to about 20 microns.
4. The method of claim 1 further comprising inserting a catheter for the delivery of a therapeutic agent into said coronary artery to said infarct region, the catheter comprising an inner surface, the inner surface defining a lumen and infusing said microparticles through said lumen.
5. The method of claim 1 wherein said at least one therapeutic agent is encapsulated by said bioerodable polymer composition.
6. The method of claim 1 wherein said bioerodable polymer composition comprises at least one member selected from the group consisting of polyhydroxyalkanoates, polylactones, poly(L-lactic acid) (PLA), poly(glycolic acid), poly(D,L-lactic acid), poly(lactide-co-glycolide), polydioxanone, polyorthoesters, polyanhydrides, poly(glycolic acid-co-trimethylene carbonate), polyphosphoesters, polyphosphoester urethanes, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate),

poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyalkylene glycols, polyvinyl alcohols, biomolecules and mixtures thereof.

7. The method of claim 1 wherein said infarct region is within the left ventricle and said coronary artery is the left anterior descending coronary artery or the circumflex
5 branch of the coronary artery.

8. The method of claim 1 wherein said infarct region is in the right ventricle, the left ventricle, the right atrium, or the sinoatrial node and the artery is the right coronary artery.

9. The method of claim 1 wherein said at least one therapeutic agent is a member
10 selected from the group consisting of therapeutic agents effective for inhibiting matrix metalloproteinase, therapeutic agents effective for mediating renin angiotensin aldosterone system pathways, therapeutic agents effective for inhibiting myocyte death and therapeutic agents effective for promoting myocyte survival, cardiac fibrosis and myocyte hypertrophy

15 10. The method of claim 1 wherein said method is performed concurrently with percutaneous coronary intervention.

11. The method of claim 1 wherein said catheter is a perfusion catheter comprising an expandable balloon, said expandable balloon comprising a porous membrane configured to allow said microparticles having a diameter of about 10 microns to about
20 25 to perfuse therethrough.

12. The method of claim 1 wherein said catheter is a perfusion catheter comprising a distal tip, said distal comprising a porous membrane configured to allow said microparticles having a diameter of about 10 microns to about 25 to perfuse therethrough.

13. The method of claim 1 comprising infusing a single bolus of said microparticles into said coronary artery, the total mass of said microparticles is about 10 mg or less.
14. The method of claim 1 comprising infusing a single bolus of said microparticles into said coronary artery, the total number of microparticles is between about 1×10^6 to
5 about 1×10^7 .
15. The method of claim 1 wherein said microparticles are covalently bonded to the inner surface of said catheter component through a linkage which is cleavable by enzymes or in the presence of water, said method further comprising perfusing a liquid comprising enzymes or water therethrough.
- 10 16. A perfusion catheter assembly for the delivery of microparticles, the perfusion catheter assembly configured and arranged to allow microparticles having a diameter of 25 microns or less to pass therethrough.
17. A perfusion catheter assembly for the delivery of microparticles, the perfusion catheter assembly comprising:
- 15 a porous membrane configured to allow microparticles having a diameter of about 25 microns or less to pass therethrough.
18. The perfusion catheter assembly of claim 17 wherein said porous membrane is configured to allow microparticles having a diameter of 20 microns or less to pass therethrough.
- 20 19. The perfusion catheter assembly of claim 17 comprising an expandable balloon, said expandable balloon comprising said porous membrane.
20. The perfusion catheter assembly of claim 17 wherein said balloon comprises a body portion and a proximal and distal end, said distal end comprising said porous membrane.

21. The perfusion catheter assembly of claim 17 comprising a distal tip, the distal tip comprising said porous membrane.
22. A catheter assembly for the controlled, local delivery of a therapeutic agent to a target site within a patient, the catheter comprising at least one component having an inner surface and an outer surface, the inner surface comprising microparticles covalently bonded thereto, the microparticles comprising a bioerodable polymeric composition and at least one therapeutic agent.
23. The catheter assembly of claim 22 wherein said at least one component is a catheter shaft.
24. The catheter assembly of claim 22, said microparticles comprising at least one member selected from the group consisting of polyhydroxyalkanoates, polylactones, poly(L-lactic acid) (PLA), poly(glycolic acid), poly(D,L-lactic acid), poly(lactide-co-glycolide), polydioxanone, polyorthoesters, polyanhydrides, poly(glycolic acid-co-trimethylene carbonate), polyphosphoesters, polyphosphoester urethanes, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, biomolecules and mixtures thereof.
25. The catheter assembly of claim 22 wherein said covalent bonds are cleaved in the presence of enzymes or water.
26. The catheter assembly of claim 22 wherein said microparticles are covalently bonded to said inner surface of said at least one component by ester linkages, thioester linkages, peptide linkages, water soluble linkages or combinations thereof.

FIG. 1

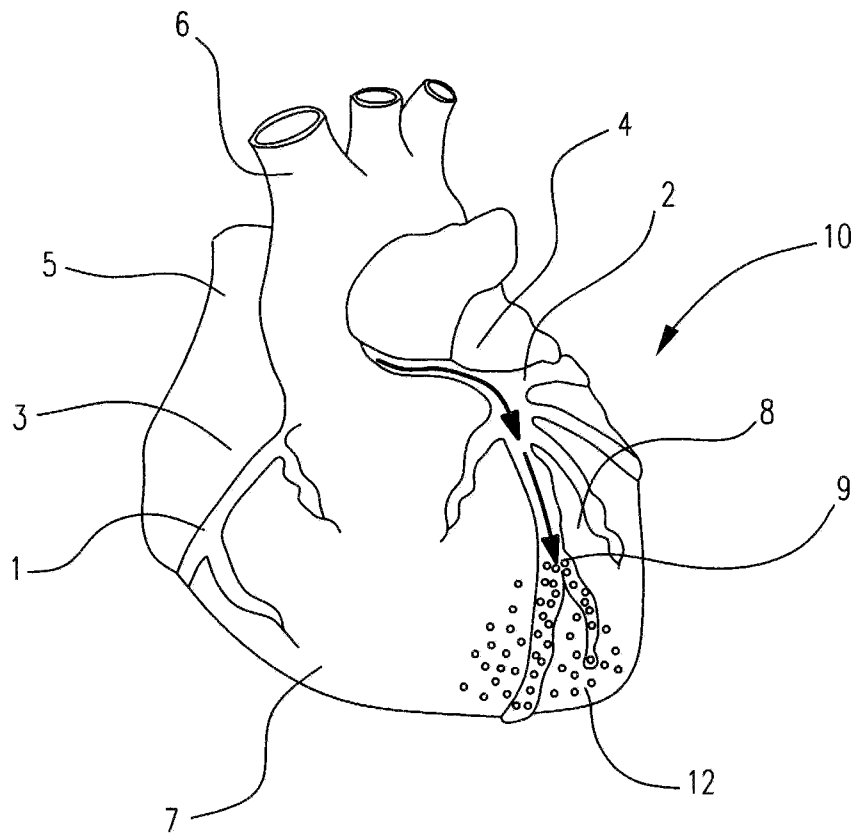


FIG. 2

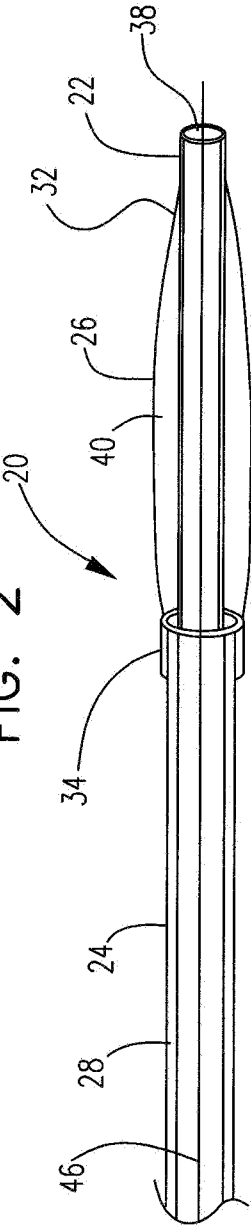


FIG. 3

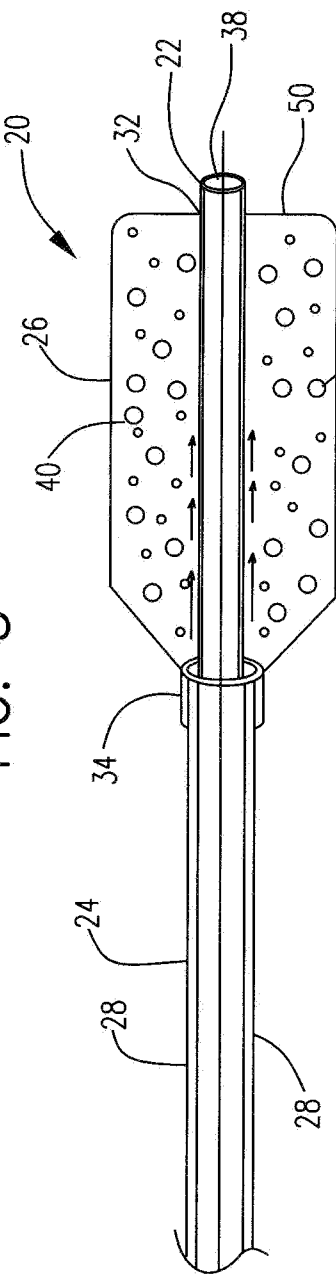


FIG. 4

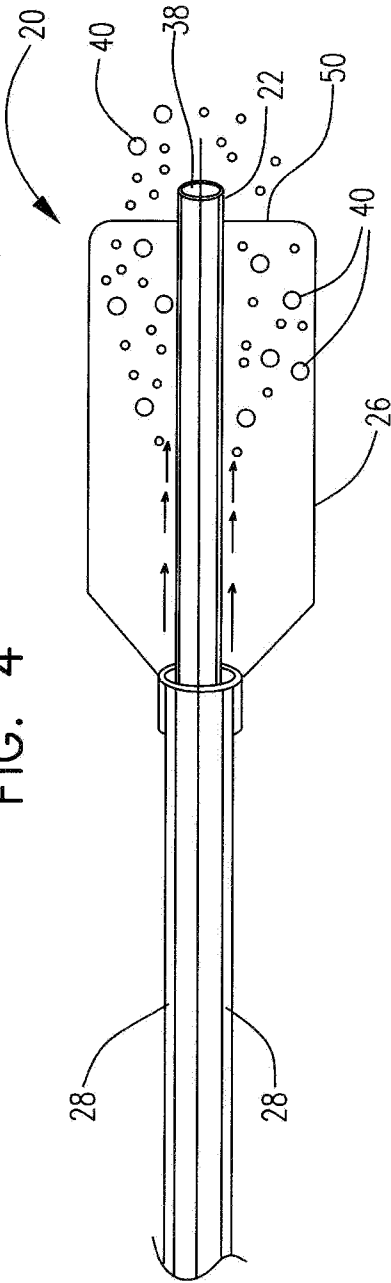


FIG. 5

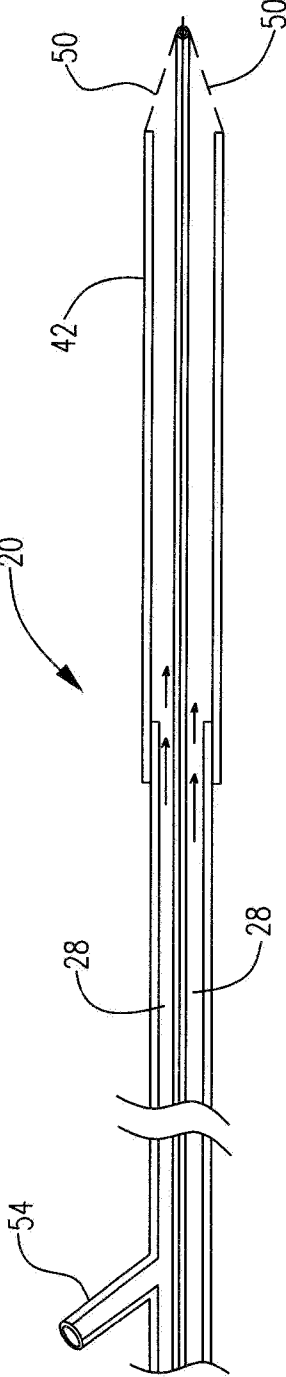


FIG. 6

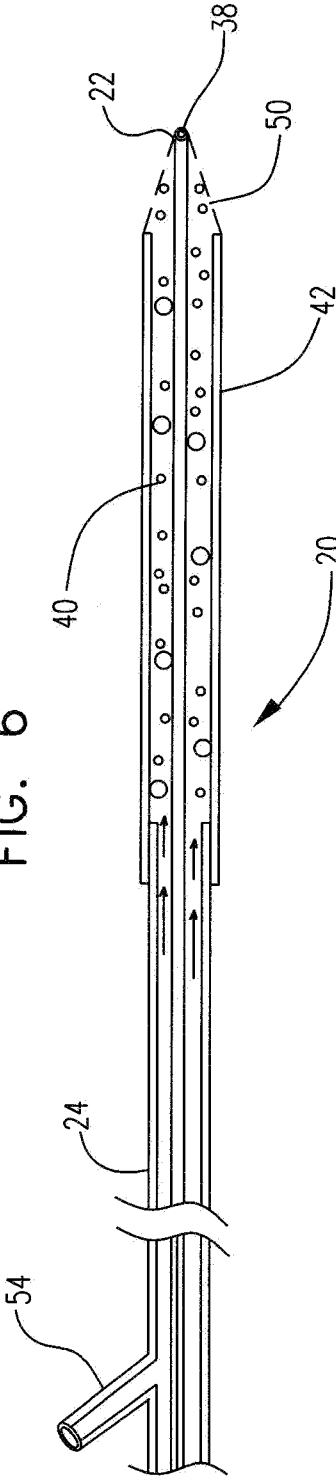


FIG. 7

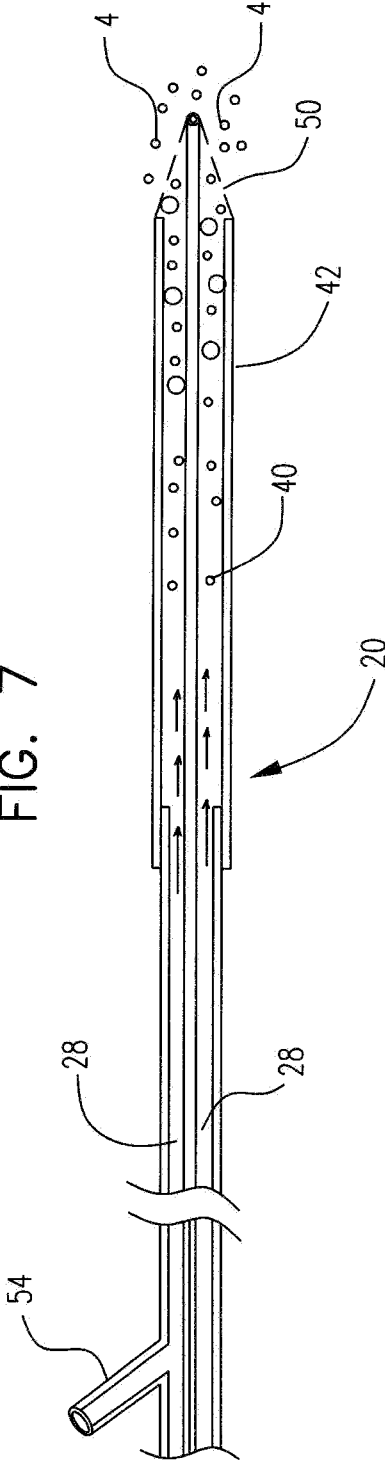


FIG. 8

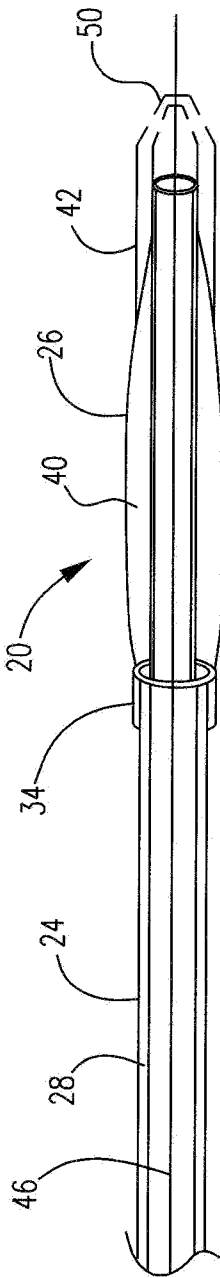


FIG. 9

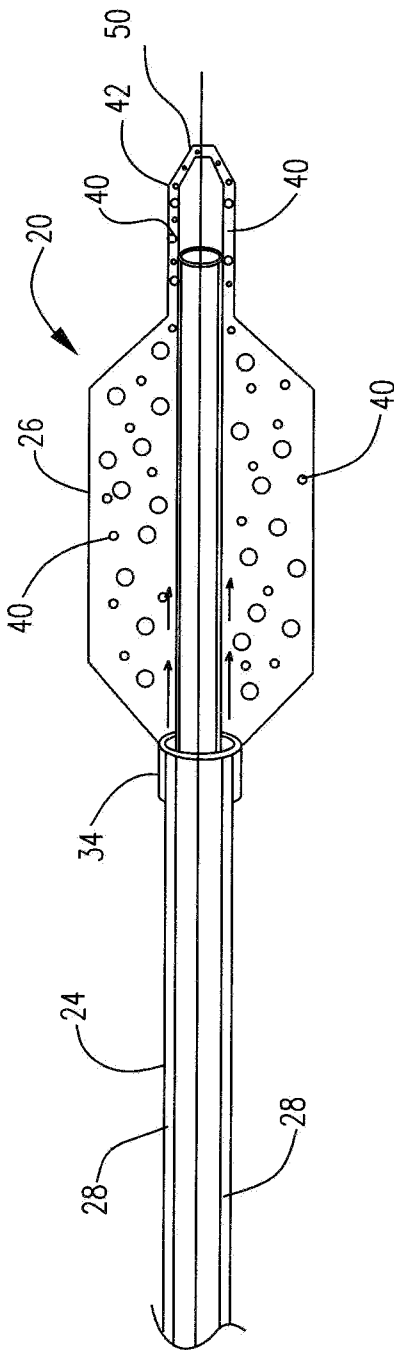


FIG. 10

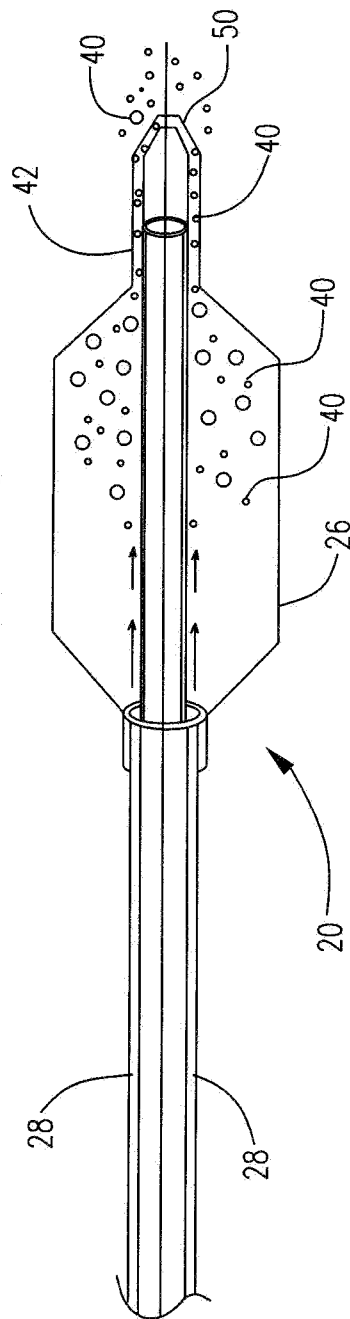


FIG. 11

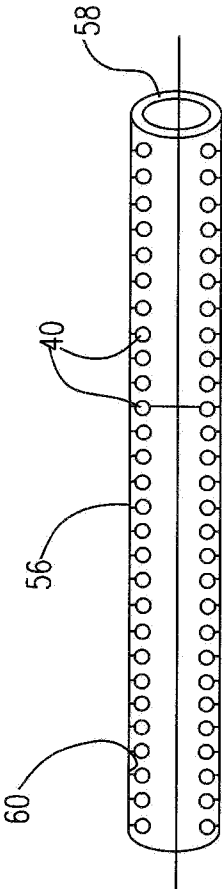


FIG. 12

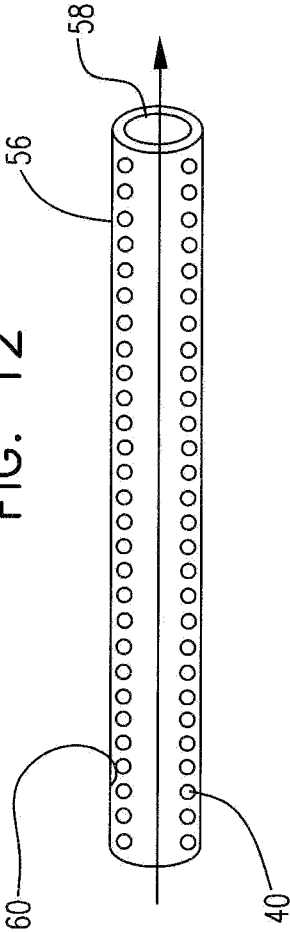


FIG. 13

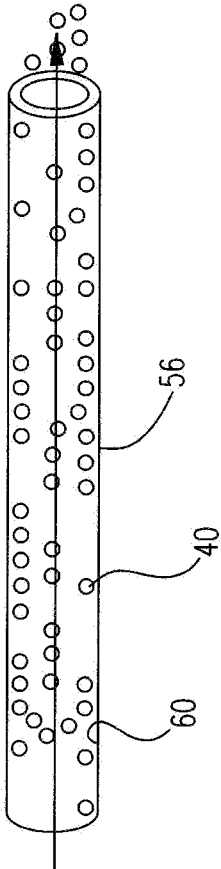
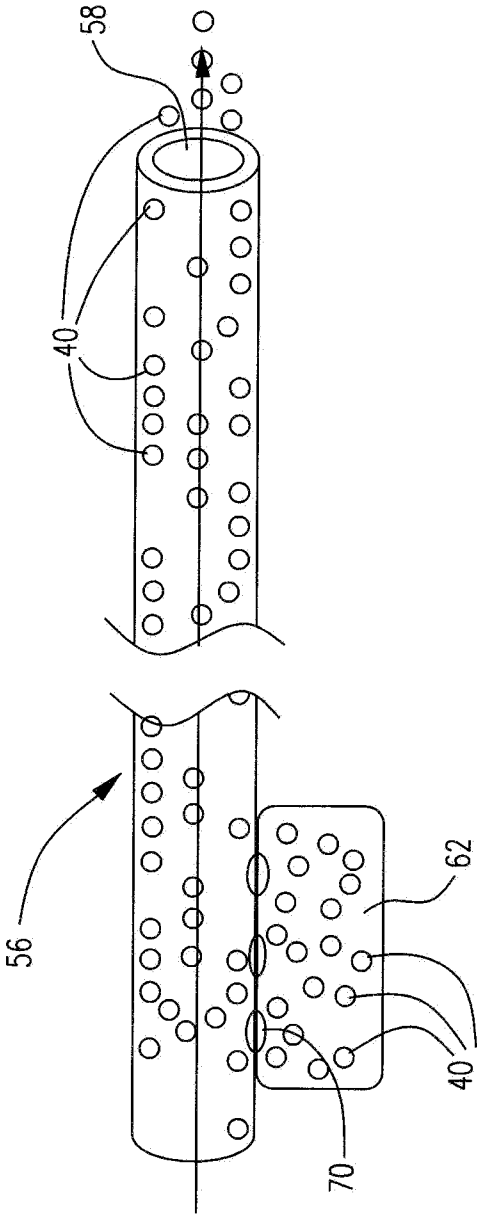


FIG. 14



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FIG. 15

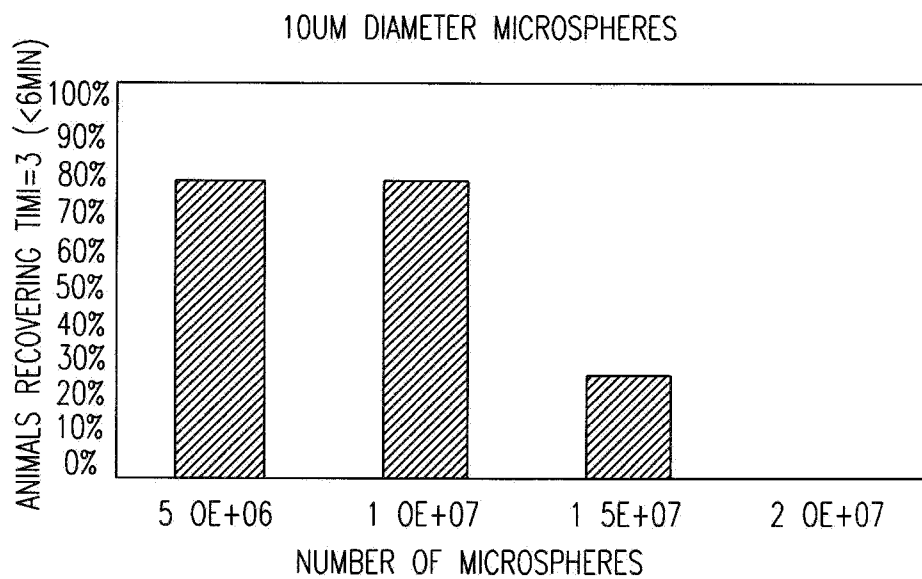
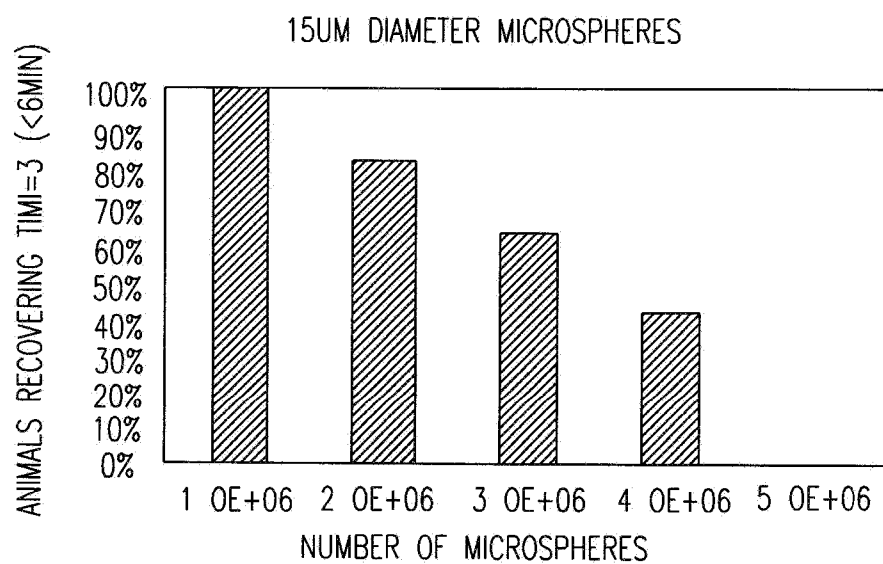


FIG. 16



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FIG. 17

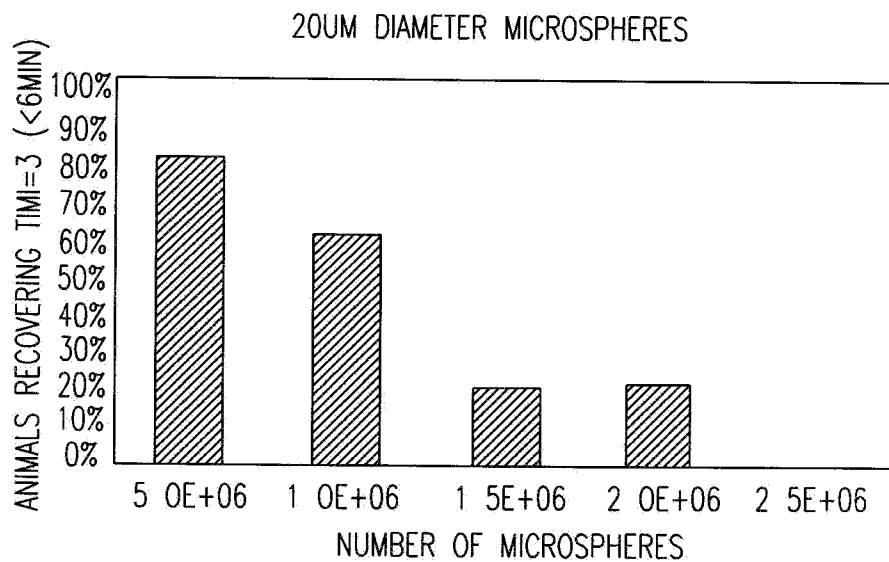
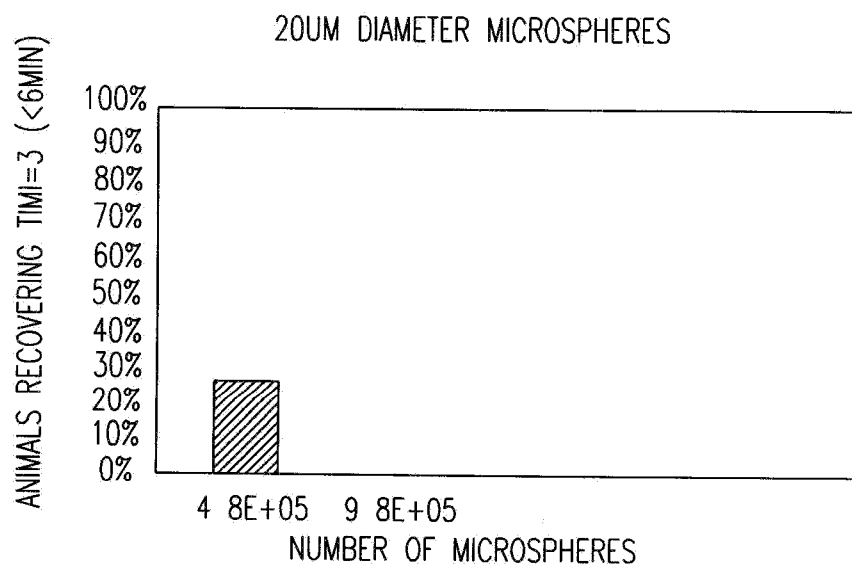
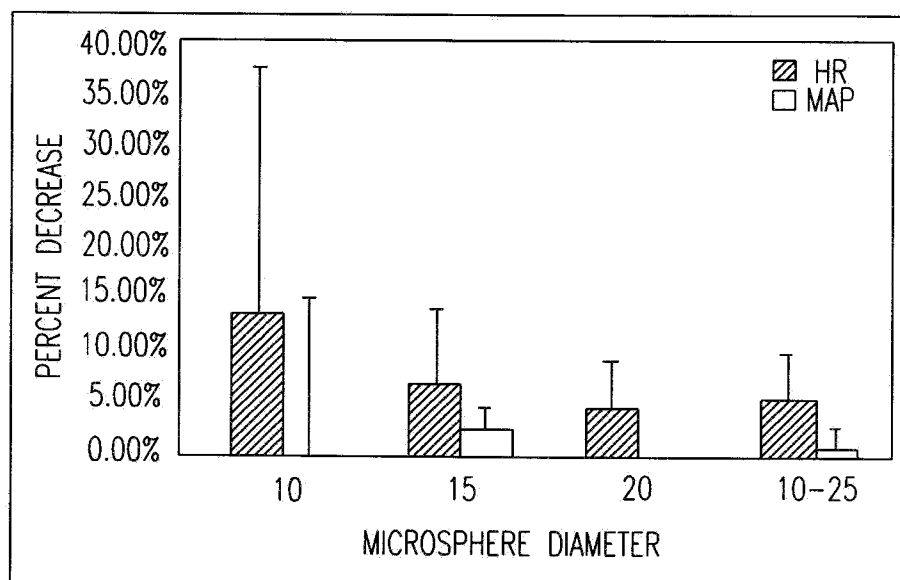


FIG. 18



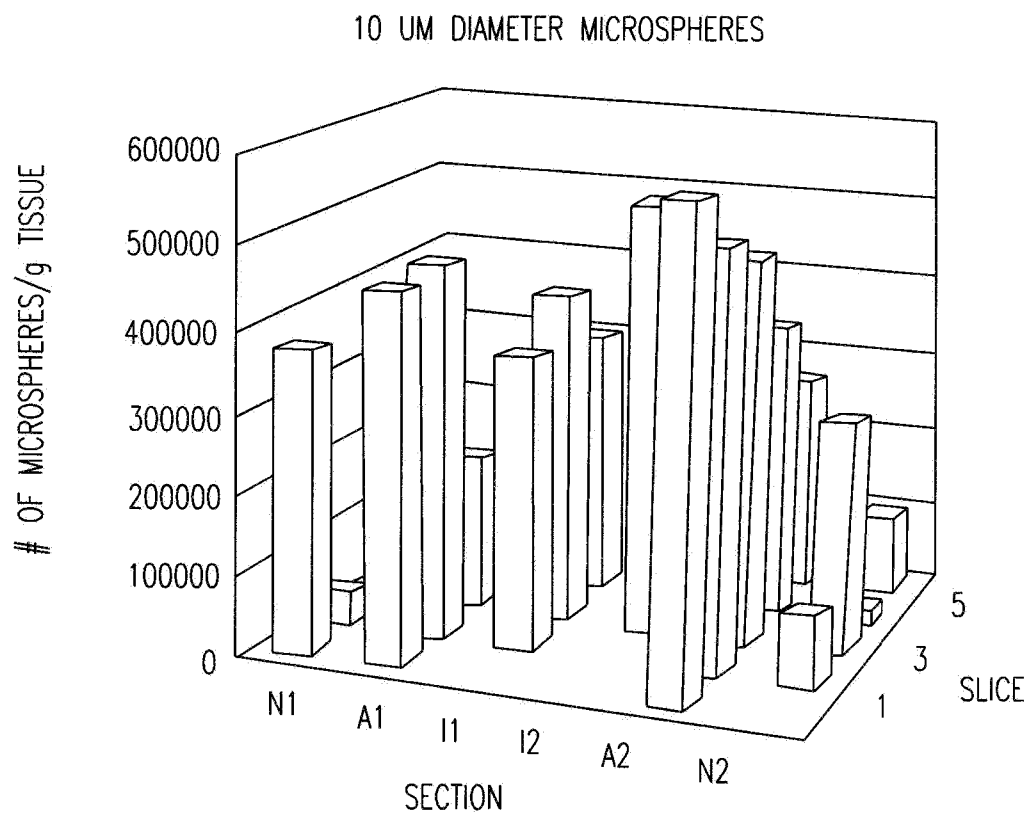
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FIG. 19



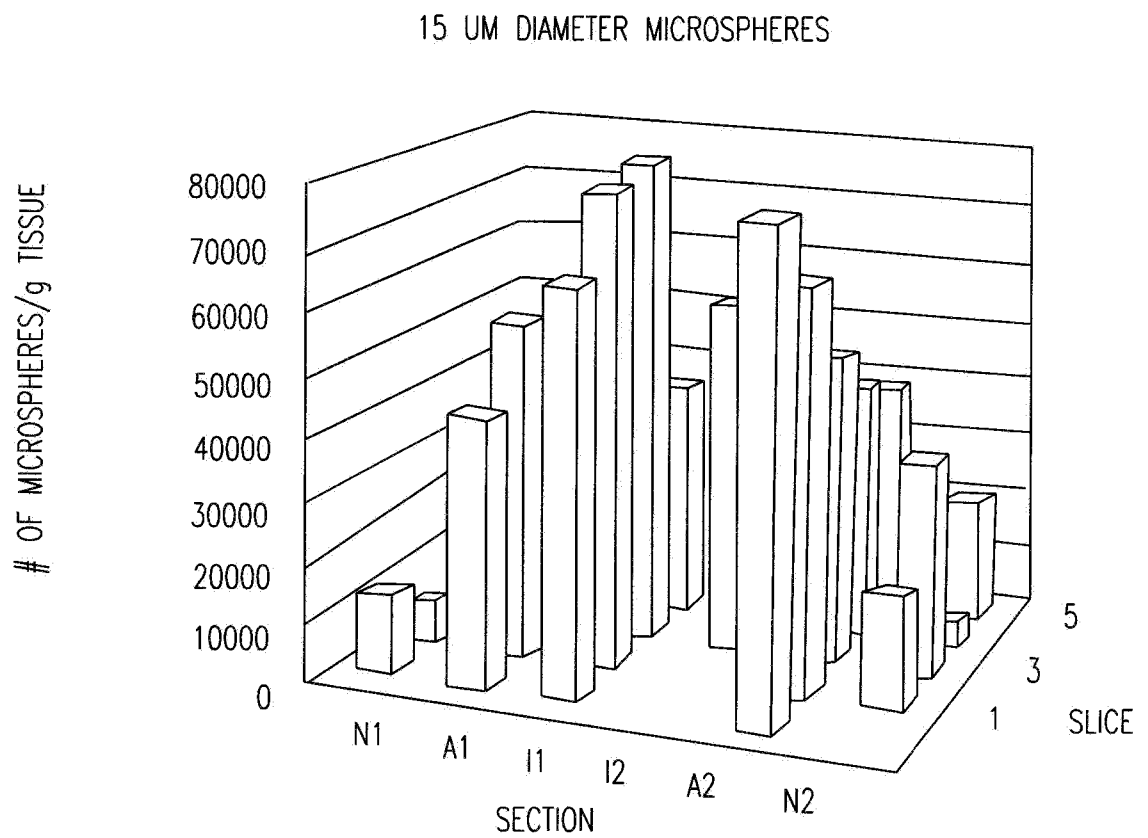
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FIG. 20



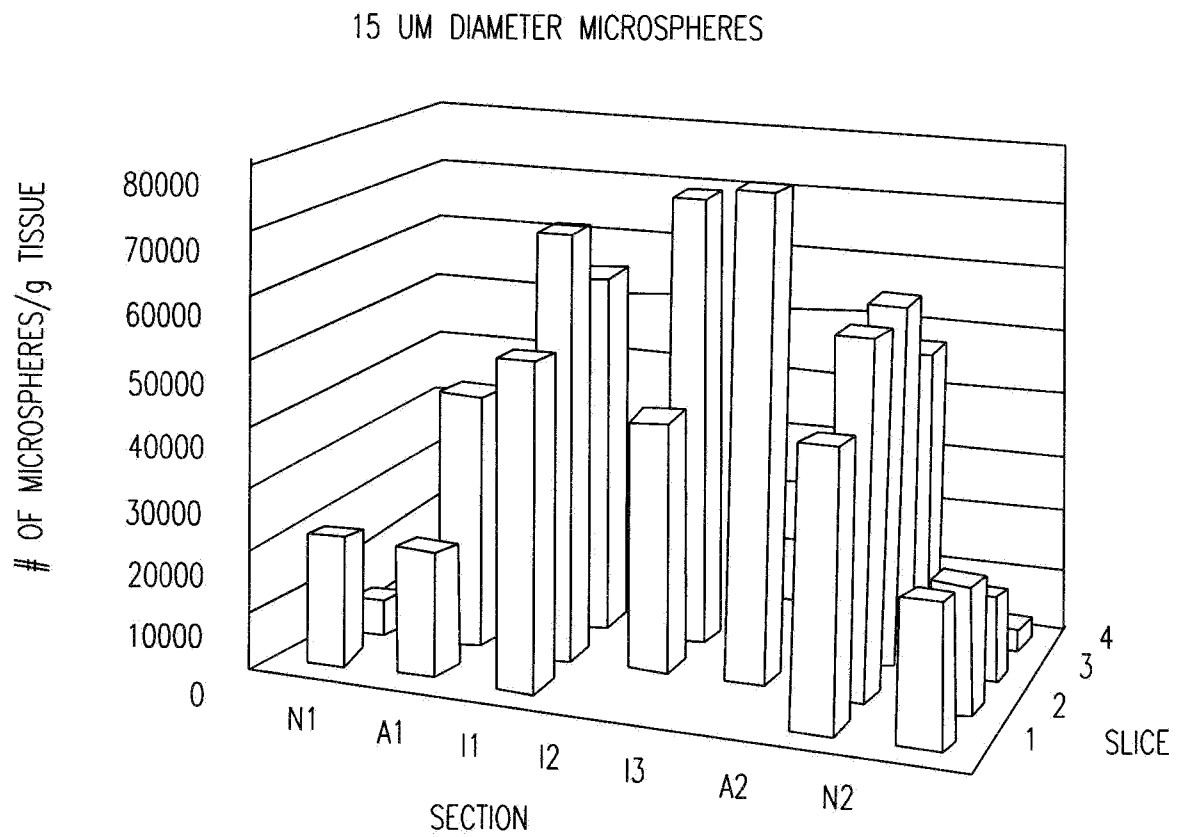
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FIG. 21



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FIG. 22



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FIG. 23

