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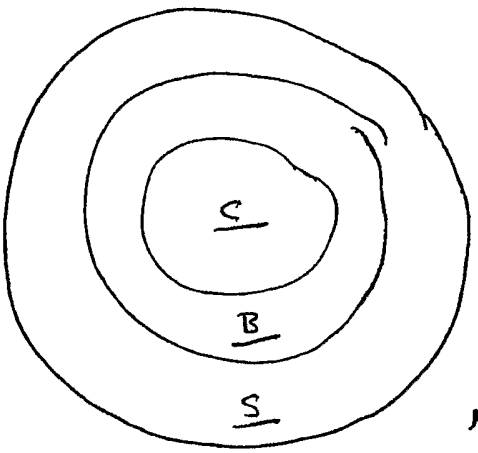
(54) Title: FERROMAGNETIC PARTICLES AND METHODS



(57) Abstract: Ferromagnetic particles and methods are disclosed.

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Ferromagnetic Particles and Methods

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, U.S. Patent Application Serial No. 10/651,475, entitled "Embolization," and filed on August 29, 2003, which is incorporated herein by reference.

TECHNICAL FIELD

This invention relates to ferromagnetic particles and methods.

BACKGROUND

Therapeutic vascular occlusions (embolizations) are used to prevent or treat pathological conditions *in situ*. Compositions including embolic particles are used for occluding vessels in a variety of medical applications. Delivery of embolic particles through a catheter is dependent on size uniformity, density and compressibility of the embolic particles.

SUMMARY

In one aspect, the invention features a method that includes providing a particle having a diameter of from about ten microns to about 3,000 microns. The particle includes a polymeric matrix, a ferromagnetic material and a therapeutic agent. The method also includes heating the particle to release the therapeutic agent from the particle.

In another aspect, the invention features a method that includes disposing a particle in a body lumen. The particle has a diameter of from about ten microns to about 3,000 microns, and the particle includes a polymeric matrix and a ferromagnetic material. The method also includes heating the particle to heat body tissue.

In a further aspect, the invention features a particle that includes a polymeric matrix and a ferromagnetic material contained within the polymeric matrix. The particle has a first density of pores in an interior region and a second density of pores at a surface region. The first density being different from the second density.

In an additional aspect, the invention features a particle that includes a gel polymeric matrix and a ferromagnetic material homogeneously distributed in the gel polymer.

Embodiments can include one or more of the following.

The particle can be heated, for example, to a temperature of at least about 40°C and/or a temperature of at most about 200°C.

In some embodiments, the method can include providing a plurality of particles. Each of the particles can have a diameter of from about ten microns to about 3,000 microns, and each of the particles can include a polymeric matrix, a ferromagnetic material and a therapeutic agent. The method can also include heating at least some of the plurality of particles to release the therapeutic agent from the particle.

Heating a particle can include exposing the particle to RF radiation.

The particle can be disposed in a body lumen before being heated. Heating the particle heats body tissue adjacent the particle.

The ferromagnetic material can include, for example, a transition metal, a metal alloy, and/or a metal oxide.

The ferromagnetic material can be, for example, in the shape of a particle, a fiber, a flake, and/or a powder.

The polymeric matrix (e.g., the gel polymeric matrix) can include, for example, a polyvinyl alcohol, a polyacrylic acid, a polymethacrylic acid, a poly vinyl sulfonate, a carboxymethyl cellulose, a hydroxyethyl cellulose, a substituted cellulose, a polyacrylamide, a polyethylene glycol, a polyamide, a polyurea, a polyurethane, a polyester, a polyether, a polystyrene, a polysaccharide (e.g. alginate), a polylactic acid, a polyethylene, a polymethylmethacrylate, a polycaprolactone, a polyglycolic acid, and/or a poly(lactic-co-glycolic) acid.

In some embodiments, the density of the ferromagnetic material in the interior region of the particle can be greater than a density of the ferromagnetic material at the surface region of the particle.

In certain embodiments, there can be substantially no ferromagnetic material at the surface region.

In some embodiments, the particle can further include a therapeutic agent contained within the polymeric matrix.

In certain embodiments, the particle can further include a coating surrounding the polymeric matrix, the coating comprising a therapeutic agent.

In some embodiments, the particle can further include a third region between the interior region and the surface region, the third region having a third density of pores less than the first density and less than the second density.

In certain embodiments, a therapeutic agent can be contained in the gel polymeric matrix.

In some embodiments, the particle can further include a coating surrounding the gel polymeric matrix, the coating containing a therapeutic agent.

Embodiments of the invention may have one or more of the following advantages.

In some embodiments, the positioning of the particle within a body lumen can be relatively easily and/or non-invasively controlled using a magnetic field (e.g., a magnetic field outside a subject, a magnetic field inside a subject, or both). As an example, the particle can be steered through a body lumen (e.g., to a relatively distal location of a lumen that might otherwise be difficult for the particle to reach) by applying a magnetic field to the particle. As another example, the ability of the particle to migrate from a desired location can be reduced by applying a magnetic field.

In certain embodiments, the particle can enhance tissue heating and/or ablation procedures. For example, when exposed to RF radiation, the particle can become heated and, in turn, heat the tissue.

Features and advantages are in the description, drawings, and claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a cross-sectional view of a particle.

FIG. 2 is a cross-sectional view of a particle.

FIG. 3 is a cross-sectional view of a particle.

FIG. 4 is a cross-sectional view of a particle.

FIG. 5 is a cross-sectional view of a particle.

FIG. 6A is a schematic of an embodiment of a system for manufacturing particles, and FIG. 6B is an enlarged schematic of region 6B in FIG. 6A.

FIG. 7A is a schematic illustrating an embodiment of injection of an embolic composition including embolic particles into a vessel, and FIG. 7B is an enlarged view of the region 7B in FIG. 7A.

DETAILED DESCRIPTION

The particle typically includes a polymeric matrix (e.g., a gel polymeric matrix) and a ferromagnetic material.

The polymeric matrix can include one or more polymer materials. Typically, the polymer material(s) is biocompatible. Examples of polymer materials include polyvinyl alcohols, polyacrylic acids, polymethacrylic acids, poly vinyl sulfonates, carboxymethyl celluloses, hydroxyethyl celluloses, substituted celluloses, polyacrylamides, polyethylene glycols, polyamides, polyureas, polyurethanes, polyesters, polyethers, polystyrenes, polysaccharides, polylactic acids, polyethylenes, polymethylmethacrylates, polycaprolactones, polyglycolic acids, poly(lactic-co-glycolic) acids (e.g., poly(d-lactic-co-glycolic) acids), and copolymers or mixtures thereof. In some embodiments, the polymeric matrix can be substantially formed of a highly water insoluble, high molecular weight polymer. An example of such a polymer is a high molecular weight polyvinyl alcohol (PVA) that has been acetalized. The polymeric matrix can be substantially pure intrachain 1,3-acetalized PVA and substantially free of animal derived residue such as collagen. In some embodiments, the particle includes a minor amount (e.g., about 2.5 weight percent or less, about one weight percent or less, about 0.2 weight percent or less) of a gelling material (e.g., a polysaccharide, such as alginate). In certain embodiments, the majority (e.g., at least about 75 weight percent, at least about 90 weight percent, at least about 95 weight percent) of the polymeric matrix is formed of a bioabsorbable polymer (e.g., polysaccharide, such as alginate).

The polymer material(s) can be, for example, gel (uncrosslinked) polymer material(s) or a crosslinked polymer material(s). In some embodiments, the polymer material(s) can include cross-linked PVA, such as a cross-linked form of PVA noted above. In certain embodiments, the polymer material(s) can include alginate (e.g., sodium alginate) gel. In some embodiments, the polymeric matrix can include one or more gel polymer materials (e.g., an alginate gel) and/or one or more cross-linked polymeric materials (e.g., cross-linked PVA).

As used herein, a ferromagnetic material refers to a material that has a magnetic susceptibility of at least about 0.075 or more (e.g., at least about 0.1 or more; at least about 0.2 or more; at least about 0.3 or more; at least about 0.4 or more; at least about 0.5 or more; at least about one or more; at least about ten or more; at least about 100 or more; at least about 1,000 or more; at least about 10,000 or more) when measured at 25°C. A ferromagnetic material can be,

for example, a metal (e.g., a transition metal such as nickel, cobalt, or iron), a metal alloy (e.g., a nickel-iron alloy such as Mu-metal), a metal oxide (e.g., an iron oxide such as magnetite), a ceramic nanomaterial, a soft ferrite (e.g., nickel-zinc-iron), a magnet alloy (e.g., a rare earth magnet alloy such as a neodymium-iron-boron alloy or a samarium-cobalt alloy), an amorphous alloy (e.g., iron-silicon-boron), a non-earth alloy, or a silicon alloy (e.g., an iron-zirconium-copper-boron-silicon alloy, an iron-zirconium-copper-boron-silicon alloy). Magnetite is commercially available from FerroTec Corporation (Nashua, NH), under the tradename EMG 1111 Ferrofluid. Iron-copper-niobium-boron-silicon alloys are commercially available from Hitachi Metals of America under the tradename Finemet™. Iron-zirconium-copper-boron-silicon alloys are commercially available from MAGNETEC GmbH under the tradename Nanoperm®. In certain embodiments, the ferromagnetic material is a biocompatible material (e.g., magnetite). In some embodiments, the ferromagnetic material is a bioerodible material, such that the material can eventually break down in the body and either be dispersed throughout the body or excreted from the body. In certain embodiments, one or more of the polymeric matrix materials and one or more of the ferromagnetic materials can be biocompatible. For example, the polymeric matrix can be a polysaccharide (e.g., alginate), and the ferromagnetic material can be magnetite.

In general, the polymeric matrix can be porous or nonporous. In embodiments in which the particle is porous, the density of the pores can be homogeneous or nonhomogeneous, the size of the pores can be homogeneous or nonhomogeneous, and/or the mass density (the density of the polymeric matrix and ferromagnetic material mass per unit volume of the particle) can be homogenous or nonhomogeneous. For example, in some embodiments (e.g., when the particle is formed of a cross-linked PVA), a particle having a radius, r, can have a center region, C, from the center of the particle to a radius of about r/3, a body region, B, from about r/3 to about 2 r/3, and a surface region, S, from about 2r/3 to r. The regions can be characterized by the relative size of the pores present in the particle in each region, the density of pores (the number of pores per unit volume of the particle) in each region, and/or the mass density (the density of the polymeric matrix and ferromagnetic material mass per unit volume of the particle) in each region. In certain embodiments, the mean size of the pores in region C of the particle can be greater than the mean size of the pores at region S of the particle. In some embodiments, the mean size of the pores in region C of the particle is greater than the mean size of the pores in

region B the particle, and/or the mean size of the pores in region B of the particle is greater than the mean size of the pores at region S of the particle. In some embodiments, the mean size of the pores in region C is about 20 microns or more (e.g., about 30 microns or more, from about 20 microns to about 35 microns). In certain embodiments, the mean size of the pores in region B is about 18 microns or less (e.g. about 15 microns or less, from about 18 microns to about two microns). In some embodiments, the mean size of the pores in region S is about one micron or less (e.g. from about 0.1 micron to about 0.01 micron). In certain embodiments, the mean size of the pores in region B is from about 50 percent to about 70 percent of the mean size of the pores in region C, and/or the mean size of the pores at region S is about ten percent or less (e.g., about two percent or less) of the mean size of the pores in region B. In some embodiments, the surface of the particle and/or its region S is/are substantially free of pores having a diameter greater than about one micron (e.g., greater than about ten microns). In certain embodiments, the mean size of the pores in the region from 0.8r to r (e.g., from 0.9r to r) is about one micron or less (e.g., about 0.5 micron or less, about 0.1 micron or less). In some embodiments, the pores in the region from the center of particle 10 to 0.9r (e.g., from the center of particle 10 to 0.8r) are about ten microns or greater and/or have a mean size of from about two microns to about 35 microns. In certain embodiments, the mean size of the pores in the region from 0.8r to r (e.g., from 0.9r to r) is about five percent or less (e.g., about one percent or less, about 0.3 percent or less) of the mean size of the pores in the region from the center to 0.9r. In some embodiments, the largest pores in the particle can have a size in the range of about one percent or more (e.g., about five percent or more, about ten percent or more) of the diameter of the particle. The size of the pores in the particle can be measured by viewing a cross-section of the particle. For irregularly shaped (nonspherical) pores, the maximum visible cross-section is used. Generally, the density of the pores in region C of the particle is greater than the density of the pores at region S of the particle. In some embodiments, the density of the pores in region C of the particle is greater than the density of the pores in region B of the particle, and/or the density of the pores in region B of the particle is greater than the density of the pores at region S of the particle. In general, the mass density in region C of the particle is less than the mass density at region S of the particle. In some embodiments, the mass density in region C of the particle is less than the mass density in region B of the particle, and/or the mass density in region B of the particle is less than the mass density at region S of the particle.

In general, the distribution of ferromagnetic material(s) can be homogeneous or nonhomogeneous. As an example, in embodiments in which the particle has regions S, C an B (see discussion above), the ferromagnetic material(s) can be contained within region S only, within region C only, with region B only, within regions S and C only, within regions S and B only, or within regions C and B only. As another example, in embodiments in which the polymeric matrix is formed of a gel (e.g., an alginate gel, such as a sodium alginate gel), the ferromagnetic material(s) can be present within an interior region of the particle only (e.g., within the inner two thirds of the particle only). Moreover, within a given region containing the ferromagnetic material(s), the density of ferromagnetic material(s) can be homogeneous or nonhomogeneous.

In certain embodiments a particle can include one or more therapeutic agents (e.g., drugs). The therapeutic agent(s) can be in and/or on the particle. Therapeutic agents include agents that are negatively charged, positively charged, amphoteric, or neutral. Therapeutic agents include genetic therapeutic agents, non-genetic therapeutic agents, and cells, and can be negatively charged, positively charged, amphoteric, or neutral. Therapeutic agents can be, for example, materials that are biologically active to treat physiological conditions; pharmaceutically active compounds; gene therapies; nucleic acids with and without carrier vectors; oligonucleotides; gene/vector systems; DNA chimeras; compacting agents (e.g., DNA compacting agents); viruses; polymers; hyaluronic acid; proteins (e.g., enzymes such as ribozymes); immunologic species; nonsteroidal anti-inflammatory medications; oral contraceptives; progestins; gonadotrophin-releasing hormone agonists; chemotherapeutic agents; and radioactive species (e.g., radioisotopes, radioactive molecules). Non-limiting examples of therapeutic agents include anti-thrombogenic agents; antioxidants; angiogenic and anti-angiogenic agents and factors; anti-proliferative agents (e.g., agents capable of blocking smooth muscle cell proliferation); calcium entry blockers; and survival genes which protect against cell death.

Exemplary non-genetic therapeutic agents include: anti-thrombotic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone); anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine and mesalamine; antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, cisplatin,

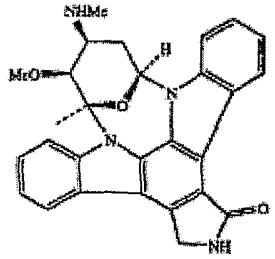
doxorubicin; vinblastine, vincristine, epothilones, endostatin, angiostatin, angiopeptin, monoclonal antibodies capable of blocking smooth muscle cell proliferation, and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, hirudin, antithrombin compounds, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides; vascular cell growth promoters such as growth factors, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; protein kinase and tyrosine kinase inhibitors (e.g., tyrphostins, genistein, quinoxalines); prostacyclin analogs; cholesterol-lowering agents; angiopoietins; antimicrobial agents such as triclosan, cephalosporins, aminoglycosides and nitrofurantoin; cytotoxic agents, cytostatic agents and cell proliferation affectors; vasodilating agents; and agents that interfere with endogenous vasoactive mechanisms.

Exemplary genetic therapeutic agents include: anti-sense DNA and RNA; DNA coding for: anti-sense RNA, tRNA or rRNA to replace defective or deficient endogenous molecules, angiogenic factors including growth factors such as acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor a, hepatocyte growth factor and insulin like growth factor, cell cycle inhibitors including CD inhibitors, thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, and the family of bone morphogenic proteins ("BMP's"), including BMP2, BMP3, BMP4, BMP5, BMP6 (Vgr1), BMP7 (OP1), BMP8, BMP9, BMP10, BM11, BMP12, BMP13, BMP14, BMP15, and BMP16. Currently preferred BMP's are any of BMP2, BMP3, BMP4, BMP5, BMP6 and BMP7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively or, in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them.

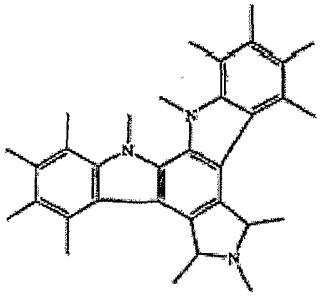
Vectors of interest for delivery of genetic therapeutic agents include: Plasmids, Viral vectors such as adenovirus (AV), adenoassociated virus (AAV) and lentivirus, Non-viral vectors such as lipids, liposomes and cationic lipids.

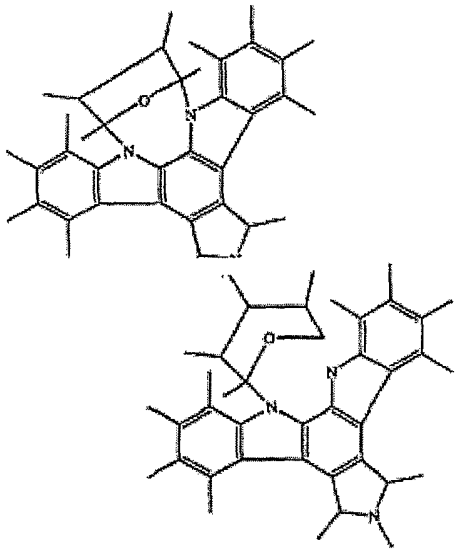
Cells include cells of human origin (autologous or allogeneic), including stem cells, or from an animal source (xenogeneic), which can be genetically engineered if desired to deliver proteins of interest.

Several of the above and numerous additional therapeutic agents appropriate for the practice of the present invention are disclosed in U.S. Patent No. 5,733,925, which is incorporated herein by reference. Therapeutic agents disclosed in this patent include the following: "Cytostatic agents" (i.e., agents that prevent or delay cell division in proliferating cells, for example, by inhibiting replication of DNA or by inhibiting spindle fiber formation). Representative examples of cytostatic agents include modified toxins, methotrexate, adriamycin, radionuclides (e.g., such as disclosed in Fritzberg et al., U.S. Patent No. 4,897,255), protein kinase inhibitors, including staurosporin, a protein kinase C inhibitor of the following formula:



as well as diindoloalkaloids having one of the following general structures:





as well as stimulators of the production or activation of TGF-beta, including Tamoxifen and derivatives of functional equivalents (e.g., plasmin, heparin, compounds capable of reducing the level or inactivating the lipoprotein Lp(a) or the glycoprotein apolipoprotein(a)) thereof, TGF-beta or functional equivalents, derivatives or analogs thereof, suramin, nitric oxide releasing compounds (e.g., nitroglycerin) or analogs or functional equivalents thereof, paclitaxel or analogs thereof (e.g., taxotere), inhibitors of specific enzymes (such as the nuclear enzyme DNA topoisomerase II and DNA polymerase, RNA polymerase, adenyl guanyl cyclase), superoxide dismutase inhibitors, terminal deoxynucleotidyl-transferase, reverse transcriptase, antisense oligonucleotides that suppress smooth muscle cell proliferation and the like.

Other examples of "cytostatic agents" include peptidic or mimetic inhibitors (i.e., antagonists, agonists, or competitive or non-competitive inhibitors) of cellular factors that may (e.g., in the presence of extracellular matrix) trigger proliferation of smooth muscle cells or pericytes: e.g., cytokines (e.g., interleukins such as IL-1), growth factors (e.g., PDGF, TGF-alpha or -beta, tumor necrosis factor, smooth muscle- and endothelial-derived growth factors, i.e., endothelin, FGF), homing receptors (e.g., for platelets or leukocytes), and extracellular matrix receptors (e.g., integrins). Representative examples of useful therapeutic agents in this category of cytostatic agents addressing smooth muscle proliferation include: subfragments of heparin, triazolopyrimidine (trapidil; a PDGF antagonist), lovastatin, and prostaglandins E1 or I2.

Agents that inhibit the intracellular increase in cell volume (i.e., the tissue volume occupied by a cell) such as cytoskeletal inhibitors or metabolic inhibitors. Representative examples of cytoskeletal inhibitors include colchicine, vinblastin, cytochalasins, paclitaxel and the like, which act on microtubule and microfilament networks within a cell. Representative examples of metabolic inhibitors include staurosporin, trichothecenes, and modified diphtheria and ricin toxins, Pseudomonas exotoxin and the like. Trichothecenes include simple trichothecenes (i.e., those that have only a central sesquiterpenoid structure) and macrocyclic trichothecenes (i.e., those that have an additional macrocyclic ring), e.g., a verrucarins or roridins, including Verrucarin A, Verrucarin B, Verrucarin J (Satratoxin C), Roridin A, Roridin C, Roridin D, Roridin E (Satratoxin D), Roridin H.

Agents acting as an inhibitor that blocks cellular protein synthesis and/or secretion or organization of extracellular matrix (i.e., an "anti-matrix agent"). Representative examples of "anti-matrix agents" include inhibitors (i.e., agonists and antagonists and competitive and non-competitive inhibitors) of matrix synthesis, secretion and assembly, organizational cross-linking (e.g., transglutaminases cross-linking collagen), and matrix remodeling (e.g., following wound healing). A representative example of a useful therapeutic agent in this category of anti-matrix agents is colchicine, an inhibitor of secretion of extracellular matrix. Another example is tamoxifen for which evidence exists regarding its capability to organize and/or stabilize as well as diminish smooth muscle cell proliferation following angioplasty. The organization or stabilization may stem from the blockage of vascular smooth muscle cell maturation in to a pathologically proliferating form.

Agents that are cytotoxic to cells, particularly cancer cells. Preferred agents are Roridin A, Pseudomonas exotoxin and the like or analogs or functional equivalents thereof. A plethora of such therapeutic agents, including radioisotopes and the like, have been identified and are known in the art. In addition, protocols for the identification of cytotoxic moieties are known and employed routinely in the art.

A number of the above therapeutic agents and several others have also been identified as candidates for vascular treatment regimens, for example, as agents targeting restenosis. Such agents are appropriate for the practice of the present invention and include one or more of the following:

Calcium-channel blockers including:

Benzothiazapines such as diltiazem and clentiazem

Dihydropyridines such as nifedipine, amlodipine and nicardapine

Phenylalkylamines such as verapamil

Serotonin pathway modulators including:

5-HT antagonists such as ketanserin and naftidrofuryl

5-HT uptake inhibitors such as fluoxetine

Cyclic nucleotide pathway agents including:

Phosphodiesterase inhibitors such as cilostazole and dipyridamole

Adenylate/Guanylate cyclase stimulants such as forskolin

Adenosine analogs

Catecholamine modulators including:

α-antagonists such as prazosin and bunazosine

β-antagonists such as propranolol

α/β-antagonists such as labetalol and carvedilol

Endothelin receptor antagonists

Nitric oxide donors/releasing molecules including:

Organic nitrates/nitrites such as nitroglycerin, isosorbide dinitrate and amyl nitrite

Inorganic nitroso compounds such as sodium nitroprusside

Sydnonimines such as molsidomine and linsidomine

Nonoates such as diazenium diolates and NO adducts of alkanediamines

S-nitroso compounds including low molecular weight compounds (e.g., S-nitroso derivatives of captopril, glutathione and N-acetyl penicillamine), high molecular weight compounds (e.g., S-nitroso derivatives of proteins, peptides, oligosaccharides, polysaccharides, synthetic polymers/oligomers and natural polymers/oligomers)

C-nitroso-, O-nitroso- and N-nitroso-compounds

L-arginine

ACE inhibitors such as cilazapril, fosinopril and enalapril

ATII-receptor antagonists such as saralasin and losartin

Platelet adhesion inhibitors such as albumin and polyethylene oxide

Platelet aggregation inhibitors including:

Aspirin and thienopyridine (ticlopidine, clopidogrel)

GP IIb/IIIa inhibitors such as abciximab, epitifibatide and tirofiban

Coagulation pathway modulators including:

Heparinoids such as heparin, low molecular weight heparin, dextran sulfate and β-cyclodextrin tetradecasulfate

Thrombin inhibitors such as hirudin, hirulog, PPACK(D-phe-L-propyl-L-arg-chloromethylketone) and argatroban

FXa inhibitors such as antistatin and TAP (tick anticoagulant peptide)

Vitamin K inhibitors such as warfarin

Activated protein C

Cyclooxygenase pathway inhibitors such as aspirin, ibuprofen, flurbiprofen, indomethacin and sulfinpyrazone

Natural and synthetic corticosteroids such as dexamethasone, prednisolone, methprednisolone and hydrocortisone

Lipoxygenase pathway inhibitors such as nordihydroguairetic acid and caffeic acid

Leukotriene receptor antagonists

Antagonists of E- and P-selectins

Inhibitors of VCAM-1 and ICAM-1 interactions

Prostaglandins and analogs thereof including:

Prostaglandins such as PGE1 and PGI2

Prostacyclin analogs such as ciprostene, epoprostenol, carbacyclin, iloprost and beraprost

Macrophage activation preventers including bisphosphonates

HMG-CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin and cerivastatin

Fish oils and omega-3-fatty acids

Free-radical scavengers/antioxidants such as probucol, vitamins C and E, ebselen, trans-retinoic acid and SOD mimics

Agents affecting various growth factors including:

FGF pathway agents such as bFGF antibodies and chimeric fusion proteins

PDGF receptor antagonists such as trapidil

IGF pathway agents including somatostatin analogs such as angiopeptin and ocreotide

TGF-β pathway agents such as polyanionic agents (heparin, fucoidin), decorin, and TGF-β antibodies

EGF pathway agents such as EGF antibodies, receptor antagonists and chimeric fusion proteins

TNF-α pathway agents such as thalidomide and analogs thereof

Thromboxane A2 (TXA2) pathway modulators such as sulotroban, vapiprost, dazoxiben and ridogrel

Protein tyrosine kinase inhibitors such as tyrphostin, genistein and quinoxaline derivatives

MMP pathway inhibitors such as marimastat, ilomastat and metastat

Cell motility inhibitors such as cytochalasin B

Antiproliferative/antineoplastic agents including:

Antimetabolites such as purine analogs(6-mercaptopurine), pyrimidine analogs (e.g., cytarabine and 5-fluorouracil) and methotrexate

Nitrogen mustards, alkyl sulfonates, ethylenimines, antibiotics (e.g., daunorubicin, doxorubicin), nitrosoureas and cisplatin

Agents affecting microtubule dynamics (e.g., vinblastine, vincristine, colchicine, paclitaxel and epothilone)

Caspase activators

Proteasome inhibitors

Angiogenesis inhibitors (e.g., endostatin, angiostatin and squalamine)

Rapamycin, cerivastatin, flavopiridol and suramin

Matrix deposition/organization pathway inhibitors such as halofuginone or other quinazolinone derivatives and tranilast

Endothelialization facilitators such as VEGF and RGD peptide

Blood rheology modulators such as pentoxifylline.

In some embodiments, particle 100 can include a combination of any of the above therapeutic agents.

Therapeutic agents are described, for example, in co-pending Published Patent Application No. US 2004/0076582 A1, published on April 22, 2004, and entitled "Agent

Delivery Particle", which is incorporated herein by reference, and in Pinchuk et al., U.S. Patent No. 6,545,097, which is incorporated herein by reference.

In some embodiments a particle can be coated (e.g., with a bioabsorable material). For example, a particle can include a polyvinyl alcohol matrix polymer with a sodium alginate coating. The coating can contain, for example, one or more therapeutic agents. In certain embodiments, a particle can be coated to include a high concentration of one or more therapeutic agents and/or loaded into the interior of the particle. The surface can release an initial dosage of therapeutic agent after which the body of the particle can provide a burst release of therapeutic agent. The therapeutic agent on the surface can be the same as or different from the therapeutic agent in the body of the particle. The therapeutic agent on the surface can be applied by exposing the particle to a high concentration solution of the therapeutic agent. The therapeutic agent coated particle can include another coating over the surface the therapeutic agent (e.g., a degradable and/or bioabsorbable polymer which erodes when the particle is administered). The coating can assist in controlling the rate at which therapeutic agent is released from the particle. For example, the coating can be in the form of a porous membrane. The coating can delay an initial burst of therapeutic agent release. The coating can be applied by dipping or spraying the particle. The erodible polymer can be a polysaccharide (such as an alginate). In some embodiments, the coating can be an inorganic, ionic salt. Other erodible coatings include water soluble polymers (such as polyvinyl alcohol, e.g., that has not been cross-linked), biodegradable poly DL-lactide-poly ethylene glycol (PELA), hydrogels (e.g., polyacrylic acid, haluronic acid, gelatin, carboxymethyl cellulose), polyethylene glycols (PEG), chitosan, polyesters (e.g., polycaprolactones), and poly(lactic-co-glycolic) acids (e.g., poly(d-lactic-co-glycolic) acids). The coating can include therapeutic agent or can be substantially free of therapeutic agent. The therapeutic agent in the coating can be the same as or different from an agent on a surface layer of the particle and/or within the particle. A polymer coating, e.g. an erodible coating, can be applied to the particle surface in cases in which a high concentration of therapeutic agent has not been applied to the particle surface. In some embodiments, the coating can include one or more ferromagnetic materials. Alternatively or additionally, the particle interior can include one or more ferromagnetic materials. The coating can include a higher, equal, or lower concentration of ferromagnetic material relative to the particle interior. Coatings are described, for example, in

co-pending Published Patent Application No. US 2004/0076582 A1, published on April 22, 2004, and entitled "Agent Delivery Particle", which is incorporated herein by reference supra.

In certain embodiments, a particle can be formed with a relatively large interior region that is not solid (e.g., liquid or gas). The interior region can be, for example, centered at the center of the particle. In some embodiments, the interior region can correspond to at most about 50% (e.g., at most about 40%, at most about 30%, at most about 20%) of the volume of the particle and/or at least about five percent (e.g., at least about 10%) of the volume of the particle. In some embodiments, the nonsolid interior region can contain one or more therapeutic agents.

In general, the particles are dimensioned for use in embolization procedures. In some embodiments, a particle has a diameter of about 3,000 microns or less (e.g., about 2,500 microns or less; about 2,000 microns or less; about 1,500 microns or less; about 1,200 microns or less; about 1,000 microns or less; about 900 microns or less; about 700 microns or less; about 500 microns or less; about 400 microns or less; about 300 microns or less; about 100 microns or less) and/or about ten microns or more (e.g., about 100 microns or more; about 300 microns or more; about 400 microns or more; about 500 microns or more; about 700 microns or more; about 900 microns or more; about 1,000 microns or more; about 1,200 microns or more; about 1,500 microns or more; about 2,000 microns or more; about 2,500 microns or more). In certain embodiments, the diameter of a particle can be from about 100 microns to about 700 microns; from about 500 microns to about 700 microns; from about 100 microns to about 500 microns; from about 100 microns to about 300 microns; from about 300 microns to about 500 microns; from about 500 microns to about 1,200 microns; from about 500 microns to about 700 microns; from about 700 microns to about 900 microns; from about 900 microns to about 1,200 microns.

Generally, the amount of polymeric material contained in a particle can be varied as desired. In some embodiments, a particle can include about 99.9 percent by weight or less (e.g., about 99.5 percent by weight or less, about 99 percent by weight or less, about 95 percent by weight or less, about 90 percent by weight or less, about 80 percent by weight or less, about 70 percent by weight or less, about 60 percent by weight or less, about 50 percent by weight or less, about 40 percent by weight or less, about 30 percent by weight or less, about 20 percent by weight or less) and/or about ten percent by weight or more (e.g., about 20 percent by weight or more, about 30 percent by weight or more, about 40 percent by weight or more, about 50 percent by weight or more, about 60 percent by weight or more, about 70 percent by weight or more,

about 80 percent by weight or more, about 90 percent by weight or more, about 95 percent by weight or more) of polymeric material.

In general, the amount of ferromagnetic material contained within a particle can be selected as desired. In certain embodiments, a particle can include from about 0.1 percent by weight to about 90 percent by weight (e.g., from about 0.1 percent by weight to about 75 percent by weight, from about 0.1 percent by weight to about 50 percent by weight, from about one percent by weight to about 25 percent by weight) of the ferromagnetic material(s).

A ferromagnetic material can generally be in any desired form (e.g., a solid, a liquid) and any desired shape (e.g., one or more particles, one or more fibers, one or more flakes, and/or one or more powders). In some embodiments, the ferromagnetic material (e.g., a particle of ferromagnetic material, a fiber of ferromagnetic material, a flake of ferromagnetic material, a powder of ferromagnetic material) can have a width or diameter, and/or length, of less than about 40 microns (e.g., less than about 35 microns, less than about 30 microns, less than about 25 microns, less than about 20 microns, less than about 15 microns, less than about ten microns, less than about five microns, less than about one micron, less than about 0.5 micron, less than about 0.1 micron, less than about 0.05 micron, less than about 0.03 micron, less than about 0.01 micron) and/or more than about 0.005 micron (e.g., more than about 0.01 micron, more than about 0.03 micron, more than about 0.05 micron, more than about 0.1 micron, more than about 0.5 micron, more than about one micron, more than about five microns, more than about ten microns, more than about 15 microns, more than about 20 microns, more than about 25 microns, more than about 30 microns, more than about 35 microns). In some embodiments, a ferromagnetic material (e.g., a particle of ferromagnetic material, a fiber of ferromagnetic material, a flake of ferromagnetic material, a powder of ferromagnetic material) can have a width or diameter, and/or a length, of from about two microns to about 20 microns (e.g., from about ten microns to about 12 microns). As used herein, a fiber of ferromagnetic material has a ratio of its largest linear dimension to its smallest linear dimension of at least about 2:1 (e.g., at least about 3:1, at least about 5:1, at least about 10:1, at least about 15:1). In some embodiments, a fiber of ferromagnetic material has a ratio of its largest linear dimension to its smallest linear dimension of at most about 20:1 (e.g., at most about 15:1, at most about 10:1, about most about 5:1, at most about 3:1). In some embodiments, a ferromagnetic material includes a mixture of fibers having two or more different aspect ratios.

The density of the particle (e.g., as measured in grams of material per unit volume) is generally such that it can be readily suspended in a carrier fluid (e.g., a pharmaceutically acceptable carrier, such as a saline solution, a contrast solution, or a mixture thereof) and remain suspended during delivery. In some embodiments, the density of the particle is from about 1.1 grams per cubic centimeter to about 1.4 grams per cubic centimeter. As an example, for suspension in a saline-contrast solution, the density of the particle can be from about 1.2 grams per cubic centimeter to about 1.3 grams per cubic centimeter.

In embodiments in which the particle has regions S, C and B described above, the region of small pores near the surface of the particle can be relatively stiff and incompressible, which can enhance resistance to shear forces and abrasion. In addition, the variable pore size profile can produce a symmetric compressibility and, it is believed, a compressibility profile. As a result, the particle can be relatively easily compressed from a maximum, at rest diameter to a smaller, compressed first diameter. Compression to an even smaller diameter, however, may involve substantially greater force. Without wishing to be bound by theory, it is believed that a variable compressibility profile can be the result of a relatively weak, collapsible inter-pore wall structure in the center region of the particle (where the pores are relatively large), and a stiffer inter-pore wall structure near the surface of the particle (where the pores are more numerous and relatively small). It is further believed that a variable pore size profile can enhance elastic recovery after compression. It is also believed that the pore structure can influence the density of the particle and the rate of carrier fluid or body fluid uptake.

In some embodiments, a plurality of the particles (e.g., in an embolic composition) can be delivered through a catheter having a lumen with a cross-sectional area that is smaller (e.g., about 50 percent or less) than the uncompressed cross-sectional area of the particles. In such embodiments, the particles are compressed to pass through the catheter for delivery into the body. Typically, the compression force is provided indirectly, by depressing the syringe plunger to increase the pressure applied to the carrier fluid. In general, the particles are relatively easily compressed to diameters sufficient for delivery through the catheter into the body. The relatively robust, rigid surface region of the particles can resist abrasion when the particles contact hard surfaces such as syringe surfaces, hard plastic or metal stopcock surfaces, and/or the catheter lumen wall (made of, e.g., Teflon) during delivery. Once in the body, the particles can substantially recover to original diameter and shape for efficient transport in the carrier and body

fluid stream. At the point of occlusion, the particles can again compress as they aggregate in the occlusion region. The particles can form a relatively dense occluding mass. The compression of the particles in the body is generally determined by the force provided by body fluid flow in the lumen. In some embodiments, the compression may be limited by the compression profile of the particles, and the number of particles needed to occlude a given diameter may be reduced.

In certain embodiments, the sphericity of the particle after compression in a catheter (e.g., after compression to about 50 percent or more of the cross-sectional area of the particle) is about 0.8 or more (e.g., about 0.85 or more, about 0.9 or more, about 0.95 or more, about 0.97 or more). The particle can be, for example, manually compressed, essentially flattened, while wet to about 50 percent or less of its original diameter and then, upon exposure to fluid, regain a sphericity of about 0.8 or more (e.g., about 0.85 or more, about 0.9 or more, about 0.95 or more, about 0.97 or more). The sphericity of a particle can be determined using a Beckman Coulter RapidVUE Image Analyzer version 2.06 (Beckman Coulter, Miami, FL). Briefly, the RapidVUE takes an image of continuous-tone (gray-scale) form and converts it to a digital form through the process of sampling and quantization. The system software identifies and measures particles in an image in the form of a fiber, rod or sphere. The sphericity of a particle, which is computed as Da/Dp (where $Da = \sqrt{(4A/\pi)}$; $Dp = P/\pi$; A = pixel area; P = pixel perimeter), is a value from zero to one, with one representing a perfect circle.

Figs. 1-5 are cross-sectional views of exemplary particles. Fig. 1 shows a particle 10 (e.g., with PVA as the polymeric matrix) having regions B, C and S. In some embodiments, particle 10 includes one or more ferromagnetic materials homogeneously distributed in regions B, C and S. In certain embodiments, particle 10 includes one or more ferromagnetic materials homogeneously distributed in regions B and C only. Optionally, particle 10 can include one or more therapeutic agents in regions B, C and/or S. Fig. 2 shows a particle 20 including particle 10 with a coating 22 formed of a second polymeric material (e.g., alginate). In some embodiments, one or more ferromagnetic materials are homogeneously distributed in regions B, C and S, and coating 22 contains one or more therapeutic agents. Fig. 3 shows a gel particle 30 formed of a polymeric material (e.g., an alginate, such as sodium alginate) or a mix of polymeric materials (e.g., a mix of alginate and PVA). In some embodiments, gel particle 30 includes one or more therapeutic agents homogeneously distributed in gel particle 30. In certain embodiments, one or more ferromagnetic materials are homogeneously distributed in an interior

region (e.g., the inner two thirds, the inner half) of gel particle 30. Optionally, gel particle 30 can contain one or more therapeutic agents. The therapeutic can be homogeneously distributed in gel particle 30, or a portion of gel particle 30 (e.g., the inner two thirds, the inner half). Fig. 4 shows a particle 40 formed of particle 30 and a coating 42 of a second polymeric material, which may the same as or different from the first polymeric material. Fig. 5 shows a particle 50 including a nonsolid (e.g., liquid) interior region 52, a first layer 54 of a first polymeric material (e.g., alginate, a mixture of alginate and a PVA), and a second layer 56 of a second polymeric material which may the same as or different from the first polymeric material. One or more ferromagnetic materials can be contained in region 52, layer 54 and/or layer 56. One or more therapeutic agents can be contained in region 52, layer 54 and/or layer 56.

In general, various methods can be used to prepare a particle. In certain embodiments, an emulsion-based process is used to form a particle. Such processes are disclosed, for example, in International Application WO 00/23054 and U.S. Patent No. 6,270,802, both of which are hereby incorporated by reference. In some embodiments, a particle is formed using a drop generator.

FIG. 6A shows an embodiment of a system for producing particle 10. The system includes a flow controller 300, a drop generator 310, a gelling vessel 320, a reactor vessel 330, a gel dissolution chamber 340 and a filter 350. As shown in FIG. 6B, flow controller 300 delivers a solution that contains the material of the polymeric matrix (e.g., one or more polymers) and a gelling precursor (e.g., alginate) to a viscosity controller 305, which heats the solution to reduce viscosity prior to delivery to drop generator 310. The solution passes through an orifice in a nozzle in drop generator 310, forming drops of the solution. The drops are then directed into gelling vessel 320, where the drops contact a gelling agent (e.g., calcium chloride) and are stabilized by gel formation. The gel-stabilized drops are transferred from gelling vessel 320 to reactor vessel 330, where the polymer in the gel-stabilized drops is reacted (e.g., cross-linked), forming precursor particles. The precursor particles are transferred to gel dissolution chamber 340, where the gelling precursor is removed. The particles are then filtered in filter 350 to remove debris, and are sterilized and packaged as an embolic composition including the particles. Methods of making particles are described, for example, in published U.S. patent application 2004-0096662, published on May 20, 2004, and entitled "Agent Delivery Particle".

In some embodiments, a particle (e.g., a particle containing a first polymeric material, such as a PVA, coated with a second polymeric material, such as an alginate) can be formed

using a concentric nozzle. Methods of forming particles using a concentric nozzle are described, for example, in U.S. Patent Application 10/858,253, filed on June 1, 2004, and entitled Embolization. Alternatively or additionally, a particle having a first polymeric material coated with a second polymeric material can be formed, for example, by forming the first polymeric material followed by spray coating the second polymeric material, or soaking the first polymeric material in a liquid containing the second polymeric material.

In some embodiments in which a drop generator is used in the preparation of a particle, the ferromagnetic material(s) can be included in the solution delivered by the drop generator, and the solution is processed as described above to form the particle. In certain embodiments in which a drop generator is used in the preparation of a particle, the ferromagnetic material(s) can be included in the gelling vessel so that the polymeric material is incorporated into the drop when the drop contacts the gelling agent. Combinations of these methods can be used.

In some embodiments (e.g., in which a particle is formed with or without the use of a droplet generator), the ferromagnetic material(s) can be added to a particle in a separate operation. For example, the ferromagnetic material(s) can be applied to the surface of a particle by compounding the matrix material with one or more of the coating materials and then applying the compounded coating material to the surface of the particle. In certain embodiments, the ferromagnetic material(s) can be placed in a particle (e.g., in one or more pores or cavities of the particle). In embodiments in which the ferromagnetic material is in liquid form (e.g., a contrast agent) prior to being incorporated into the particle, the ferromagnetic material can be incorporated into the particles by, for example, absorption. Combinations of these methods can be used. For example, in some embodiments, one material can be incorporated into a cavity in a particle, while another material (either the same as, or different from, the first material) can be absorbed through the surface of the particle.

In certain embodiments, one or more therapeutic agents can be incorporated into a particle as described above with respect to the ferromagnetic material(s). In some embodiments, a therapeutic agent can be included in a particle by forming a particle, and then soaking the particle in a liquid containing the therapeutic agent.

As noted above, the particles can be used in embolization procedures.

In some embodiments, multiple particles are combined with a carrier fluid (e.g., a saline solution, a contrast agent, or both) to form an embolic composition. Such embolic compositions

can be used in, for example, neural, pulmonary, and/or AAA (abdominal aortic aneurysm) applications. The compositions can be used in the treatment of, for example, fibroids, tumors, internal bleeding, arteriovenous malformations (AVMs), and/or hypervascular tumors. The compositions can be used as, for example, fillers for aneurysm sacs, AAA sac (Type II endoleaks), endoleak sealants, arterial sealants, and/or puncture sealants, and/or can be used to provide occlusion of other lumens such as fallopian tubes. Fibroids can include uterine fibroids which grow within the uterine wall (intramural type), on the outside of the uterus (subserosal type), inside the uterine cavity (submucosal type), between the layers of broad ligament supporting the uterus (interligamentous type), attached to another organ (parasitic type), or on a mushroom-like stalk (pedunculated type). Internal bleeding includes gastrointestinal, urinary, renal and varicose bleeding. AVMs are for example, abnormal collections of blood vessels, e.g. in the brain, which shunt blood from a high pressure artery to a low pressure vein, resulting in hypoxia and malnutrition of those regions from which the blood is diverted. In some embodiments, a composition containing the particles can be used to prophylactically treat a condition.

The magnitude of a dose of an embolic composition can vary based on the nature, location and severity of the condition to be treated, as well as the route of administration. A physician treating the condition, disease or disorder can determine an effective amount of embolic composition. An effective amount of embolic composition refers to the amount sufficient to result in amelioration of symptoms or a prolongation of survival of the subject. The embolic compositions can be administered as pharmaceutically acceptable compositions to a subject in any therapeutically acceptable dosage, including those administered to a subject intravenously, subcutaneously, percutaneously, intratrachealy, intramuscularly, intramucosaly, intracutaneously, intra-articularly, orally or parenterally.

An embolic composition can be prepared in calibrated concentrations of the particles for ease of delivery by the physician. Suspensions of the particles in saline solution can be prepared to remain stable (e.g., to not precipitate) over a duration of time. A suspension of the particles can be stable, for example, for from about one minute to about 20 minutes (e.g. from about one minute to about ten minutes, from about two minutes to about seven minutes, from about three minutes to about six minutes). The concentration of particles can be determined by adjusting the weight ratio of the particles to the physiological solution. If the weight ratio of the particles is

too small, then too much liquid could be injected into a blood vessel, possibly allowing the particles to stray into lateral vessels. In some embodiments, the physiological solution can contain from about 0.01 weight percent to about 15 weight percent of the particles. A composition can include a mixture of particles, such as particles including ferromagnetic material, and particles including radiopaque material.

Referring to FIGS. 7A and 7B, an embolic composition, including embolic particles 111 and a carrier fluid, is injected into a vessel through an instrument such as a catheter 150. Catheter 150 is connected to a syringe barrel 110 with a plunger 160. Catheter 150 is inserted, for example, into a femoral artery 120 of a subject. Catheter 150 delivers the embolic composition to, for example, occlude a uterine artery 130 leading to a fibroid 140. Fibroid 140 is located in the uterus of a female subject. The embolic composition is initially loaded into syringe 110. Plunger 160 of syringe 110 is then compressed to deliver the embolic composition through catheter 150 into a lumen 165 of uterine artery 130.

Referring particularly to FIG. 7B, which is an enlarged view of section 7B of FIG. 7A, uterine artery 130 is subdivided into smaller uterine vessels 170 (e.g., having a diameter of about two millimeters or less) which feed fibroid 140. The embolic particles 111 in the embolic composition partially or totally fill the lumen of uterine artery 130, either partially or completely occluding the lumen of the uterine artery 130 that feeds uterine fibroid 140.

In some embodiments, a magnetic source can be used to move or direct the particles to a treatment site (see discussion below). The magnetic source can be external to the subject's body, or can be used internally. In some cases, both an external magnetic source and an internal magnetic source can be used to move the particles. An example of an internal magnetic source is a magnetic catheter. Magnetic catheters are described in co-pending Published Patent Application No. US 2003/0187320 A1, published on October 2, 2003, and entitled "Magnetically Enhanced Injection Catheter", which is incorporated herein by reference. An example of an external magnetic source is a magnetic wand.

In certain embodiments , the particles can be used to enhance the effects of tissue heating procedures and/or tissue ablation procedures, which procedures are generally designed to damage or destroy tumor tissue. For example, the particles can be used to enhance the ablation of a tumor. First, an RF probe (e.g., a 3.5 centimeter coaxial LeVeen electrode, available from RadioTherapeutics, Mountain View, CA) having tines at one end can be inserted into the area of

the tumor. The particles can then be delivered to the area around the tines of the RF probe by, e.g., a catheter or a syringe. Thereafter, the tines can be deployed and the RF probe can be activated so that RF energy flows through the tines and interacts with and heats the particles, thereby heating and/or ablating body tissue. The body tissue that is heated and/or ablated can be immediately adjacent the particles and/or removed a distance from the particles. Various algorithms can be used when exposing the particles to RF energy. In some embodiments, the RF power source is initially set at a power level of 30 Watts, and the power is increased by 10 Watts every minute. In certain embodiments, the RF power source is initially set at a power level of 60 Watts, and the power is increased by 10 Watts every 30 seconds. The end of the procedure can be determined, for example, by the temperature of the ablated tissue and/or by the measured impedance of the RF power circuit. Without wishing to be bound by theory, it is believed that the presence of the ferromagnetic material(s) in the particles may enhance the burning of the tissue (which results in damage or destruction of the tissue) during heating. It is also believed that the presence of the embolic particles can assist in treating the tissue through heating. For example, it is believed that the embolic particles can reduce local blood flow, which can reduce the amount of heat that is removed via blood flow from the region near the tissue.

In some embodiments, heating the embolic particles (e.g., via exposure to RF energy) is used to release the therapeutic agent(s) from the particles. In general, the particles and/or tissue are heated to a temperature of at least about 40°C (e.g., at least about 50°C) and/or at most about 200°C (e.g., at most about 150°C, at most about 100°C, at most about 90°C). The heat can be used, for example, to break one or more chemical bonds to release the therapeutic agent(s). Alternatively or additionally, the heat can be used to provide sufficient energy to physically release the therapeutic agent(s) from the particles. As an example, heating the particles may expand the polymeric matrix to allow the therapeutic agent(s) to be released from the particles. Without wishing to be bound by theory, it is believed that heating the tissue to be treated, in conjunction with exposure of the tissue to the therapeutic agents, can enhance the therapeutic effect achieved relative to exposing the tissue to the same amount of therapeutic agent in the absence of tissue heating.

In certain embodiments, a magnetic field can be applied to the particles to affect the extent of conductivity. The magnetic field can be varied to adjust the conductivity of the particles (and, therefore, to adjust the extent of heating and ablation).

In some embodiments, the particles can be used in an agitation ablation process. In such a process, a magnetic field can be used to agitate the particles, such that the particles heat and/or physically deform the surrounding tissue, thereby ablating the surrounding tissue.

In some embodiments, among the particles delivered to a subject in an embolic composition, the majority (e.g., about 50 percent or more, about 60 percent or more, about 70 percent or more, about 80 percent or more, about 90 percent or more) of the particles have a diameter of about 3,000 microns or less (e.g., about 2,500 microns or less; about 2,000 microns or less; about 1,500 microns or less; about 1,200 microns or less; about 900 microns or less; about 700 microns or less; about 500 microns or less; about 400 microns or less; about 300 microns or less; about 100 microns or less) and/or about ten microns or more (e.g., about 100 microns or more; about 300 microns or more; about 400 microns or more; about 500 microns or more; about 700 microns or more; about 900 microns or more; about 1,200 microns or more; about 1,500 microns or more; about 2,000 microns or more; about 2,500 microns or more).

In certain embodiments, the particles delivered to a subject in an embolic composition have a mean diameter of about 3,000 microns or less (e.g., about 2,500 microns or less; about 2,000 microns or less; about 1,500 microns or less; about 1,200 microns or less; about 900 microns or less; about 700 microns or less; about 500 microns or less; about 400 microns or less; about 300 microns or less; about 100 microns or less) and/or about ten microns or more (e.g., about 100 microns or more; about 300 microns or more; about 400 microns or more; about 500 microns or more; about 700 microns or more; about 900 microns or more; about 1,200 microns or more; about 1,500 microns or more; about 2,000 microns or more; about 2,500 microns or more). Exemplary ranges for the mean diameter of particles delivered to a subject include from about 100 microns to about 300 microns; from about 300 microns to about 500 microns; from about 500 microns to about 700 microns; and from about 900 microns to about 1,200 microns. In general, the particles delivered to a subject in an embolic composition have a mean diameter in approximately the middle of the range of the diameters of the individual particles, and a variance of about 20 percent or less (e.g. about 15 percent or less, about ten percent or less).

In some embodiments, the mean size of the particles delivered to a subject in an embolic composition can vary depending upon the particular condition to be treated. As an example, in embodiments in which the particles in an embolic composition are used to treat a liver tumor, the particles delivered to the subject can have a mean diameter of about 500 microns or less (e.g.,

from about 100 microns to about 300 microns; from about 300 microns to about 500 microns). As another example, in embodiments in which the particles in an embolic composition are used to treat a uterine fibroid, the particles delivered to the subject in an embolic composition can have a mean diameter of about 1,200 microns or less (e.g., from about 500 microns to about 700 microns; from about 700 microns to about 900 microns; from about 900 microns to about 1,200 microns).

While certain embodiments have been described, the invention is not so limited.

As an example, while embodiments have been described in which one or more of the polymers (e.g., polyvinyl alcohol) of the polymeric matrix is crosslinked as the particles are formed, in some embodiments, one or more (e.g., all) of the polymers of the polymeric matrix may not be crosslinked during the particle formation process. For example, in certain embodiments in which a polymeric matrix includes polyvinyl alcohol, the polyvinyl alcohol may not be crosslinked during the particle formation process. The particles that are formed as a result of such a particle formation process can have a gel polymeric matrix. In some embodiments in which a fluid ferromagnetic material is incorporated into the solution that contains the material of the polymeric matrix and the gelling precursor (and that is used in the particle formation process), one or more of the polymers of the polymeric matrix may not be crosslinked during the process of making the particle.

As another example, a particle can be prepared (e.g., for use in an embolic composition) without removal of the gelling precursor (e.g. alginate). Such particles can be prepared, for example, using a drop generator as described above, but without removing the gelling precursor from the particle after cross-linking.

As an additional example, in some embodiments one or more particles is/are substantially nonspherical. In some embodiments, particles can be shaped (e.g., molded, compressed, punched, and/or agglomerated with other particles) at different points in the particle manufacturing process. In some embodiments (e.g., where the matrix polymer is a polyvinyl alcohol and the gelling precursor is sodium alginate), after contacting the particles with the gelling agent but before cross-linking, the particles can be physically deformed into a specific shape and/or size. After shaping, the matrix polymer (e.g., polyvinyl alcohol) can be cross-linked, optionally followed by substantial removal of the gelling precursor (e.g., alginate). While substantially spherical particles are preferred, non-spherical particles can be manufactured and

formed by controlling, for example, drop formation conditions. In some embodiments, nonspherical particles can be formed by post-processing the particles (e.g., by cutting or dicing into other shapes). Particle shaping is described, for example, in co-pending Published Patent Application No. US 2003/0203985 A1, published on October 30, 2003, and entitled "Forming a Chemically Cross-Linked Particle of a Desired Shape and Diameter", which is incorporated herein by reference.

As a further example, in some embodiments the particles can be used for tissue bulking. As an example, the particles can be placed (e.g., injected) into tissue adjacent to a body passageway. The particles can narrow the passageway, thereby providing bulk and allowing the tissue to constrict the passageway more easily. The particles can be placed in the tissue according to a number of different methods, for example, percutaneously, laparoscopically, and/or through a catheter. In certain embodiments, a cavity can be formed in the tissue, and the particles can be placed in the cavity. Particle tissue bulking can be used to treat, for example, intrinsic sphincteric deficiency (ISD), vesicoureteral reflux, gastroesophageal reflux disease (GERD), and/or vocal cord paralysis (e.g., to restore glottic competence in cases of paralytic dysphonia). In some embodiments, particle tissue bulking can be used to treat urinary incontinence and/or fecal incontinence. The particles can be used as a graft material or a filler to fill and/or to smooth out soft tissue defects, such as for reconstructive or cosmetic applications (e.g., surgery). Examples of soft tissue defect applications include cleft lips, scars (e.g., depressed scars from chicken pox or acne scars), indentations resulting from liposuction, wrinkles (e.g., glabella frown wrinkles), and soft tissue augmentation of thin lips. Tissue bulking is described, for example, in co-pending Published Patent Application No. US 2003/0233150 A1, published on December 18, 2003, and entitled "Tissue Treatment", which is incorporated herein by reference.

As another example, in certain embodiments a particle can have a cavity (a portion that is substantially devoid of a matrix material such as a matrix polymer) that has a diameter of at least about 50 microns (e.g., at least about 100 microns, at least about 150 microns). In some embodiments, such a cavity can contain one or more ferromagnetic materials. In such embodiments, the ferromagnetic material(s) can be nonhomogeneously distributed in the particle.

As a further example, in some embodiments one or more ferromagnetic materials can be located at the surface of the particle. In such embodiments, the interior of the particle can be

substantially devoid the ferromagnetic material(s), or the interior of the particle can further include the ferromagnetic radiopaque material(s).

As another example, in some embodiments a particle can further contain one or more radiopaque materials (e.g., distributed as noted above with respect to the ferromagnetic material(s)). As used herein, a radiopaque material refers to a material having a density of about ten grams per cubic centimeter or greater (e.g., about 25 grams per cubic centimeter or greater, about 50 grams per cubic centimeter or greater). A radiopaque material can be, for example, a metal (e.g., tungsten, tantalum, platinum, palladium, lead, gold, titanium, silver), a metal alloy (e.g., stainless steel, an alloy of tungsten, an alloy of tantalum, an alloy of platinum, an alloy of palladium, an alloy of lead, an alloy of gold, an alloy of titanium, an alloy of silver), a metal oxide (e.g., titanium dioxide, zirconium oxide, aluminum oxide), bismuth subcarbonate, or barium sulfate. In some embodiments, a radiopaque material is a radiopaque contrast agent. Examples of radiopaque contrast agents include Omnipaque™, Renocal®, iodiamide meglumine, diatrizoate meglumine, ipodate calcium, ipodate sodium, iodamide sodium, iothalamate sodium, iopamidol, and metrizamide. Radiopaque contrast agents are commercially available from, for example, Bracco Diagnostic. In embodiments in which a particle includes one or more radiopaque materials, the particle can exhibit enhanced visibility under X-ray fluoroscopy, such as when the particle is in a subject (see discussion below). In some embodiments, X-ray fluoroscopy can be performed without the use of a radiopaque contrast agent.

As an additional example, in some embodiments a particle can further include one or more MRI-visible materials (e.g., distributed as noted above with respect to the ferromagnetic material(s)). As used herein, a MRI-visible material refers to a material that has a magnetic susceptibility of at most about one or less (e.g., at most about 0.5 or less; at most about zero or less) when measured at 25°C. An MRI-visible material can be, for example, a non-ferrous metal-alloy containing paramagnetic elements (e.g., dysprosium or gadolinium) such as terbium-dysprosium, dysprosium, and gadolinium; a non-ferrous metallic band coated with an oxide or a carbide layer of dysprosium or gadolinium (e.g., Dy_2O_3 or Gd_2O_3); a non-ferrous metal (e.g., copper, silver, platinum, or gold) coated with a layer of superparamagnetic material, such as nanocrystalline Fe_3O_4, $CoFe_2O_4$, $MnFe_2O_4$, or $MgFe_2O_4$; or nanocrystalline particles of the transition metal oxides (e.g., oxides of Fe, Co, Ni). In some embodiments, the ferromagnetic material contained within the particle can also serve as an MRI-visible material if the

ferromagnetic material is present in a sufficiently low concentration. For example, if the ferromagnetic material 14 is a bioerodible material, the ferromagnetic material 14 may interfere with MRI-visibility when used in the body in a high concentration and/or a condensed form (e.g., when used in a particle), but, as the ferromagnetic material is bioeroded and dispersed throughout the body or excreted from the body, its interference with MRI-visibility can decrease. In some embodiments, an MRI-visible material can be an MRI contrast agent. Examples of MRI contrast agents include superparamagnetic iron oxides (e.g., ferumoxides, ferucarbotran, ferumoxsil, ferumoxtran (e.g., ferumoxtran-10), PEG-feron, ferucarbotran); gadopentetate dimeglumine; gadoterate meglumine; gadodiamide; gadoteridol; gadoversetamide; gadobutrol; gadobenate dimeglumine; mangafodipir trisodium; gadoxetic acid; gadobenate dimeglumine; macromolecular Gd-DOTA derivate; gadobenate dimeglumine; gadopentetate dimeglumine; ferric ammonium citrate; manganese chloride; manganese-loaded zeolite; ferristene; perfluoro-octylbromide; and barium sulfate. MRI contrast agents are described, for example, in U.S. Patent Application Serial No. 10/390,202, filed on March 17, 2003, and entitled "Medical Devices", which is incorporated herein by reference. In embodiments in which an MRI-visible material is contained within the particle, the particle can exhibit enhanced visibility using MRI, such as when the particle is in a subject (see discussion below). In some embodiments, MRI can be performed without the use of an MRI contrast agent.

As a further example, in certain embodiments one or more ferromagnetic materials, one or more MRI-visible materials and/or one or more radiopaque materials can be attached to the surface of a particle (e.g., via a chemical linker).

As another example, in some embodiments, the particles can be linked together to form particle chains. For example, the particles can be connected to each other by links that are formed of one or more of the same material(s) as the particles, or of one or more different material(s) from the particles. In certain embodiments, a nozzle/gel droplet generator system can be used to form particle chains. For example, the vibration frequency of the nozzle can be selected to cause the nozzle to form particle chains. Particle chains and methods of making particle chains are described, for example, in U.S. Patent Application No. 10/830,195, filed on April 22, 2004, and entitled "Embolization", which is incorporated herein by reference.

As an additional example, in some embodiments, a particle can contain one or more surface preferential materials. Surface preferential materials are described, for example, in U.S.

Patent Application No. 10/791,552, filed on March 2, 2004, and entitled "Embolization", which is incorporated herein by reference.

As another example, in certain embodiments, a particle can include one or more shape memory materials. Such materials can be capable of being configured to remember (e.g., to change to) a predetermined configuration or shape. In some embodiments, particles that include one or more shape memory materials can be selectively transitioned from a first state to a second state. For example, a heating device provided in the interior of a delivery catheter can be used to cause a particle including a shape memory material to transition from a first state to a second state. Shape memory materials and particles that include shape memory materials are described in, for example, in co-pending Published Patent Application No. US 2004/0091543 A1, published on May 13, 2004, and entitled "Embolic Compositions", and U.S. Patent Application No. 10/791,103, filed March 2, 2004, and entitled "Embolic Compositions", both of which are incorporated herein by reference.

Other embodiments are in the claims.

WHAT IS CLAIMED IS:

1. A method, comprising:

providing a particle having a diameter of from about ten microns to about 3,000 microns, the particle comprising a polymeric matrix, a ferromagnetic material and a therapeutic agent; and

heating the particle to release the therapeutic agent from the particle.

2. The method of claim 1, wherein the method includes heating the particle to a temperature of at least about 40°C.

3. The method of claim 2, wherein the method includes heating the particle to a temperature of at most about 200°C.

4. The method of claim 1, wherein the method includes heating the particle to a temperature of at most about 200°C.

5. The method of claim 1, wherein the ferromagnetic material is selected from the group consisting of transition metals, metal alloys, and metal oxides.

6. The method of claim 1, wherein the ferromagnetic material is in the shape of at least one article selected from the group consisting of particles, fibers, flakes, and powders.

7. The method of claim 1, wherein the polymeric matrix comprises at least one polymer selected from the group consisting of polyvinyl alcohols, polyacrylic acids, polymethacrylic acids, poly vinyl sulfonates, carboxymethyl celluloses, hydroxyethyl celluloses, substituted celluloses, polyacrylamides, polyethylene glycols, polyamides, polyureas, polyurethanes, polyesters, polyethers, polystyrenes, polysaccharides, polylactic acids, polyethylenes, polymethylmethacrylates, polycaprolactones, polyglycolic acids, and poly(lactic-co-glycolic) acids.

8. The method of claim 1, further comprising, before heating the particle, disposing the particle in a body lumen.

9. The method of claim 1, further comprising:

providing a plurality of particles, each of the particles having a diameter of from about ten microns to about 3,000 microns, and each of the particles comprising a polymer matrix, a ferromagnetic material and a therapeutic agent; and

heating at least some of the plurality of particles to release the therapeutic agent from the particle.

10. The method of claim 1, wherein heating the embolic particle comprises exposing the embolic particle to RF radiation.

11. The method of claim 1, wherein the particle is disposed in a body lumen, and heating the particle heats body tissue adjacent the particle.

12. A method, comprising:

disposing a particle in a body lumen, the particle having a diameter of from about ten microns to about 3,000 microns, and the particle comprising a polymeric matrix and a ferromagnetic material; and

heating the particle to heat body tissue.

13. The method of claim 12, wherein the method includes heating the particle to a temperature of at least about 40°C.

14. The method of claim 13, wherein the method includes heating the particle to a temperature of at most about 200°C.

15. The method of claim 12, wherein the method includes heating the particle to a temperature of at most about 200°C.

16. The method of claim 12, wherein the ferromagnetic material is selected from the group consisting of transition metals, metal alloys, and metal oxides.

17. The method of claim 12, wherein the ferromagnetic material is in the shape of at least one article selected from the group consisting of particles, fibers, flakes, and powders.

18. The method of claim 12, wherein the polymeric matrix comprises at least one polymer selected from the group consisting of polyvinyl alcohols, polyacrylic acids, polymethacrylic acids, poly vinyl sulfonates, carboxymethyl celluloses, hydroxyethyl celluloses, substituted celluloses, polyacrylamides, polyethylene glycols, polyamides, polyureas, polyurethanes, polyesters, polyethers, polystyrenes, polysaccharides, polylactic acids, polyethylenes, polymethylmethacrylates, polycaprolactones, polyglycolic acids, and poly(lactic-co-glycolic) acids.

19. The method of claim 12, further comprising:

disposing a plurality of particles in the body lumen, each of the particles having a diameter of from about ten microns to about 3,000 microns, and each of the particles comprising a polymeric matrix and a ferromagnetic material; and

heating at least some of the plurality of particles to release the therapeutic agent from the particle.

20. The method of claim 12, wherein heating the embolic particle comprises exposing the embolic particle to RF radiation.

21. The method of claim 12, wherein the particle further comprises a therapeutic agent.

22. The method of claim 12, wherein the body tissue is adjacent the particle.

23. A particle comprising:

a polymeric matrix; and

a ferromagnetic material contained within the polymeric matrix,

wherein the particle has a first density of pores in an interior region and a second density of pores at a surface region, the first density being different from the second density.

24. The particle of claim 23, wherein a density of the ferromagnetic material in the interior region of the particle is greater than a density of the ferromagnetic material at the surface region of the particle.

25. The particle of claim 24, wherein there is substantially no ferromagnetic material at the surface region.

26. The particle of claim 23, wherein the particle further comprises a therapeutic agent contained within the polymeric matrix.

27. The particle of claim 23, further comprising a coating surrounding the polymeric matrix, the coating comprising a therapeutic agent.

28. The particle of claim 23, wherein the particle further comprises a third region between the interior region and the surface region, the third region having a third density of pores less than the first density and less than the second density.

29. The method of claim 23, wherein the polymeric matrix comprises at least one polymer selected from the group consisting of polyvinyl alcohols, polyacrylic acids, polymethacrylic acids, poly vinyl sulfonates, carboxymethyl celluloses, hydroxyethyl celluloses, substituted celluloses, polyacrylamides, polyethylene glycols, polyamides, polyureas, polyurethanes, polyesters, polyethers, polystyrenes, polysaccharides, polylactic acids, polyethylenes, polymethylmethacrylates, polycaprolactones, polyglycolic acids, and poly(lactic-co-glycolic) acids.

30. The method of claim 23, wherein the ferromagnetic material is selected from the group consisting of transition metals, metal alloys, and metal oxides.

31. A particle comprising:

a gel polymeric matrix; and

a ferromagnetic material homogeneously distributed in the gel polymer.

32. The particle of claim 31, wherein the particle includes an interior region and an exterior region surrounding the interior region, and a density of the ferromagnetic material in the interior region is greater than a density of the ferromagnetic material in the exterior region.

33. The particle of claim 32, wherein there is substantially no ferromagnetic material in the exterior region.

34. The particle of claim 33, further comprising a therapeutic agent contained in the gel polymeric matrix.

35. The particle of claim 34, wherein there is substantially no therapeutic agent in the exterior region.

36. The particle of claim 32, further comprising a coating surrounding the gel polymeric matrix, the coating containing a therapeutic agent.

37. The particle of claim 31, further comprising a therapeutic agent contained in the gel polymeric matrix.

38. The particle of claim 31, further comprising a coating surrounding the gel polymeric matrix, the coating containing a therapeutic agent.

39. The particle of claim 31, wherein the particle includes an interior region that is substantially devoid of the gel polymeric matrix.

40. The particle of claim 39, wherein the particle includes a first region of the gel polymeric matrix and a second region of the gel polymeric matrix, the second region of the gel polymeric matrix surrounding the first region of the gel polymeric matrix, a density of the ferromagnetic material in the first region being greater than a density of the ferromagnetic material in the second region.

41. The particle of claim 40, wherein there is substantially no ferromagnetic material in the second region.

42. The particle of claim 31, wherein the gel polymeric matrix comprises alginate or polyvinyl alcohol.

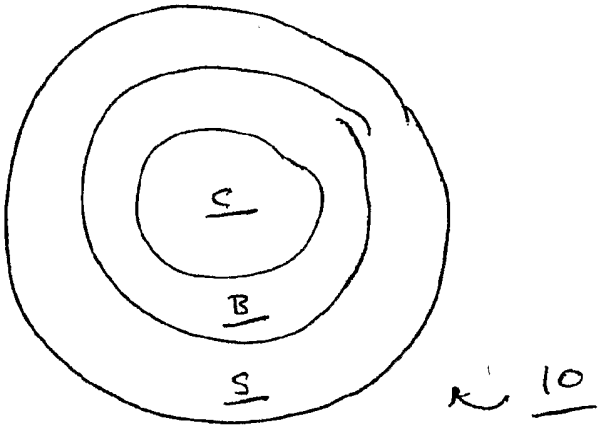


Fig. 1

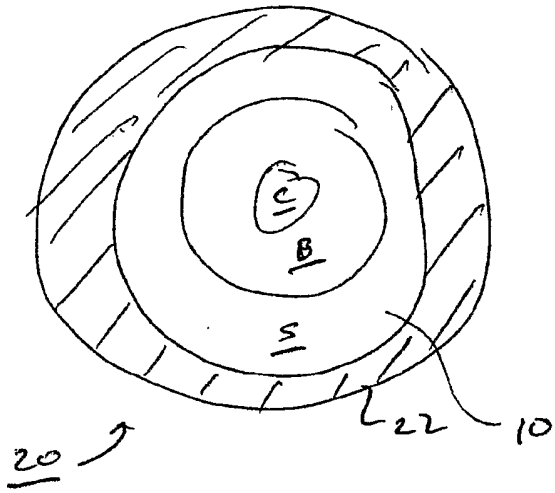


Fig. 2

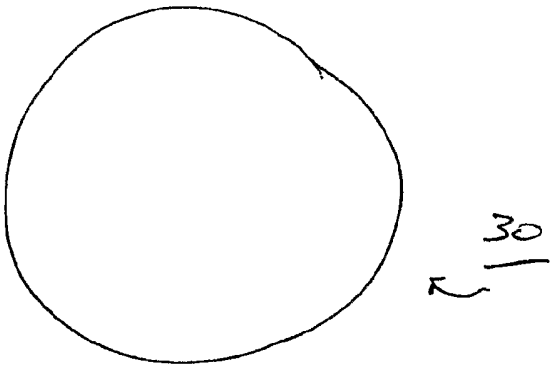


Fig. 3

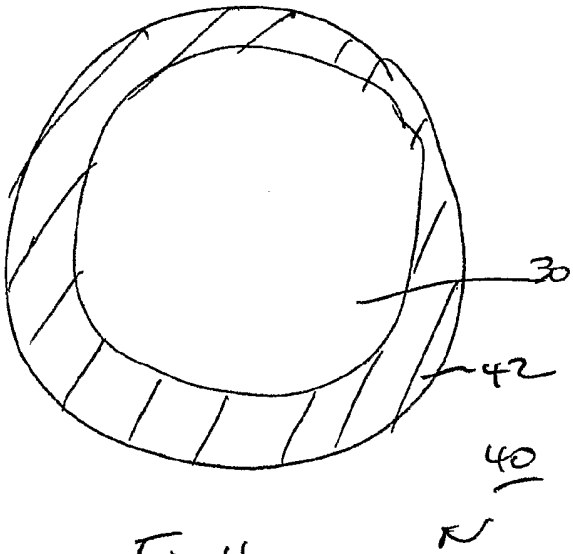


Fig. 4

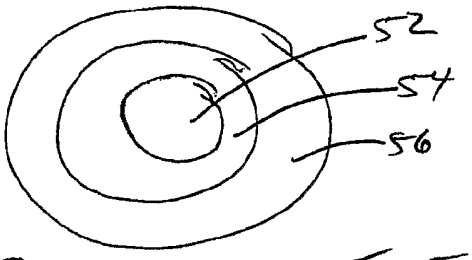
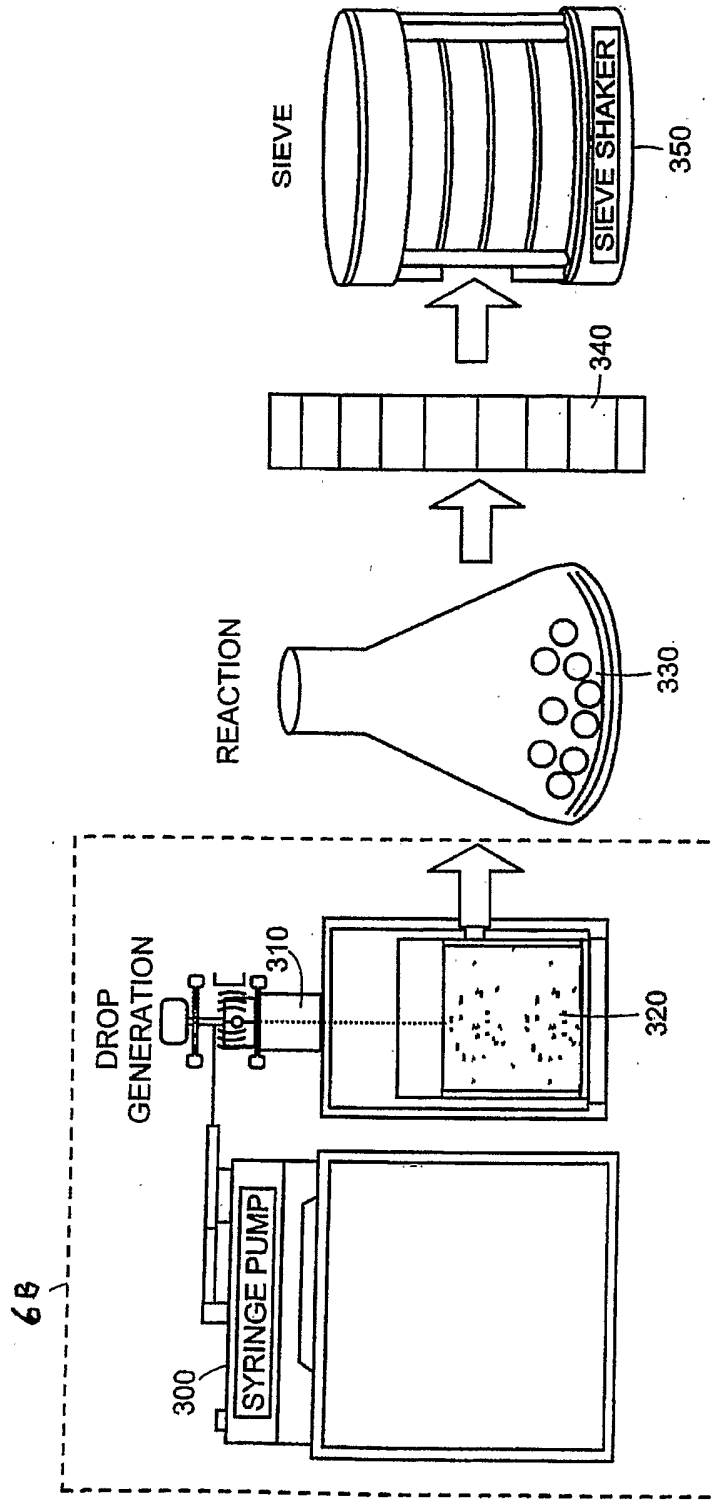


Fig. 5


SIEVE
SIEVE SHAKER
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340
REACTION
330
DROP
GENERATION
310
320
SYRINGE PUMP
300
6B

FIG. 6A

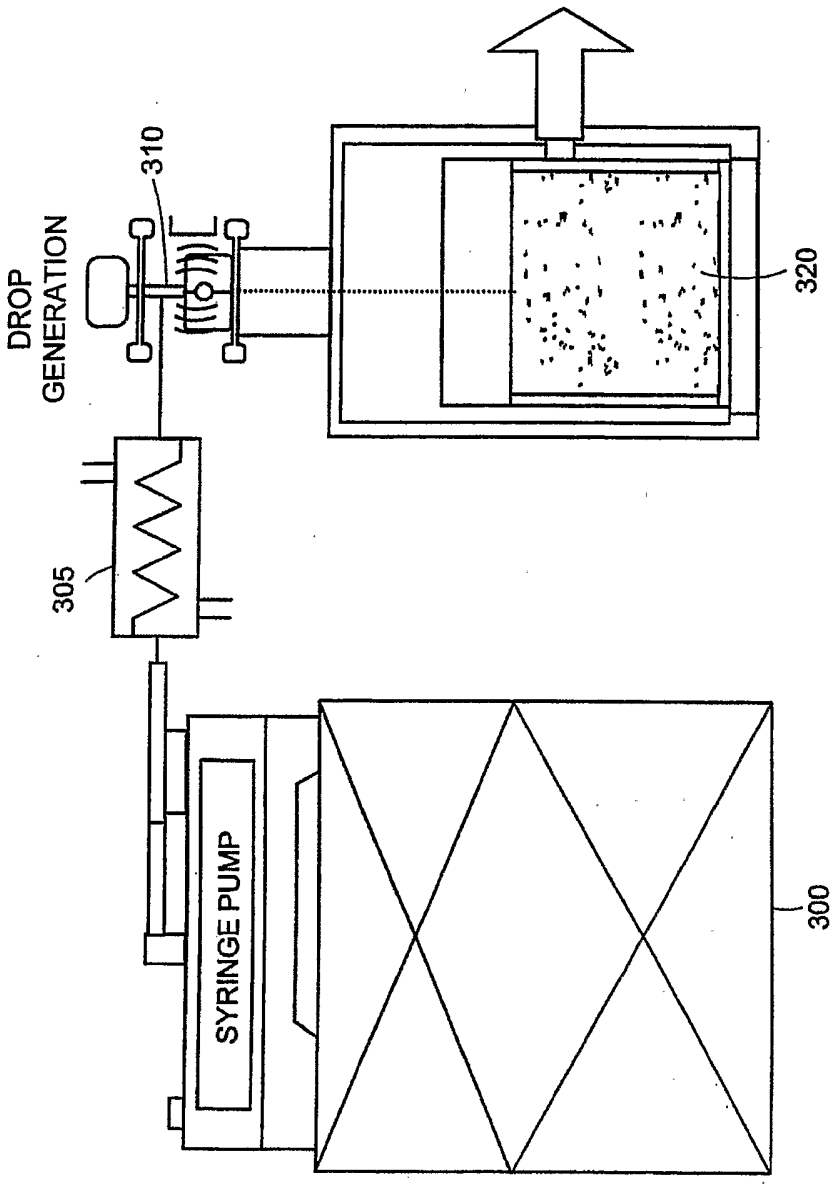


FIG. 6B

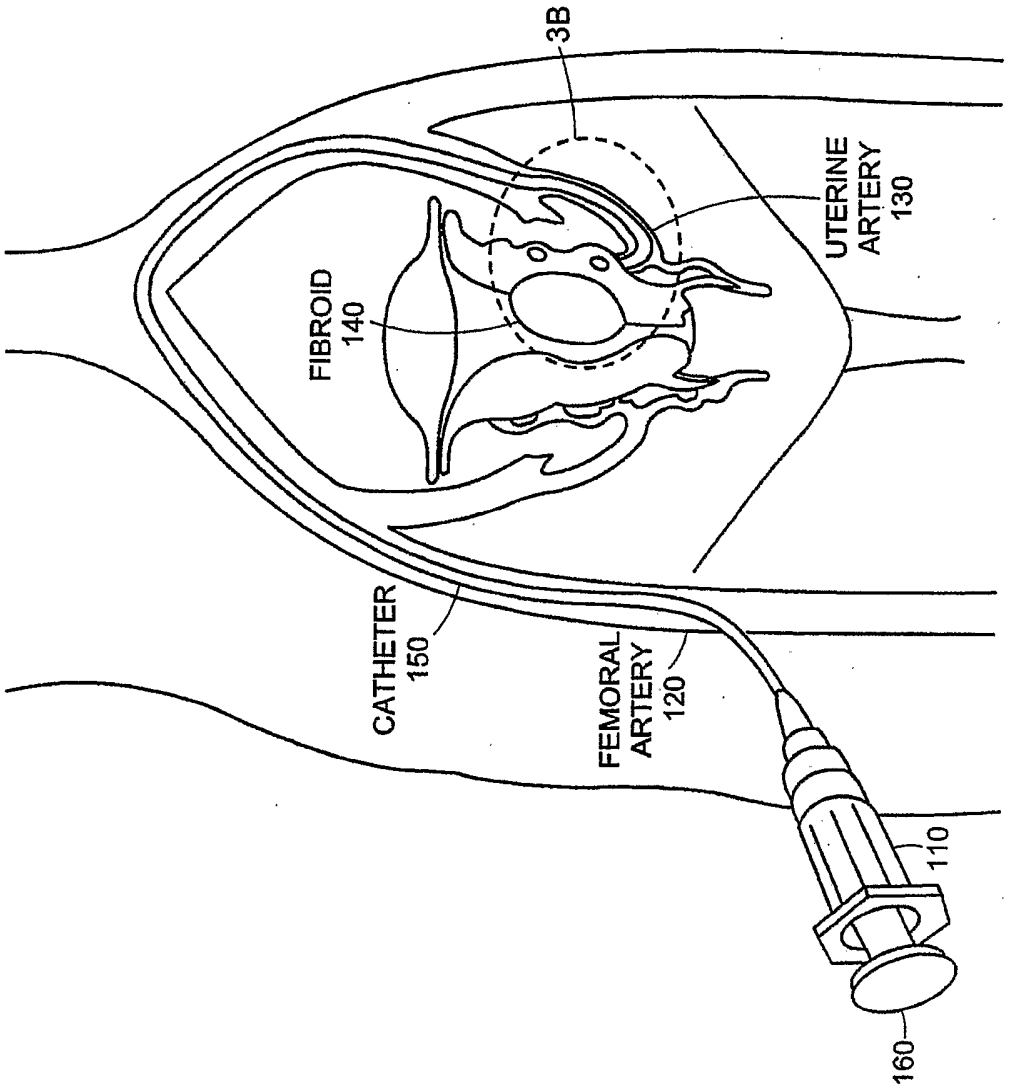
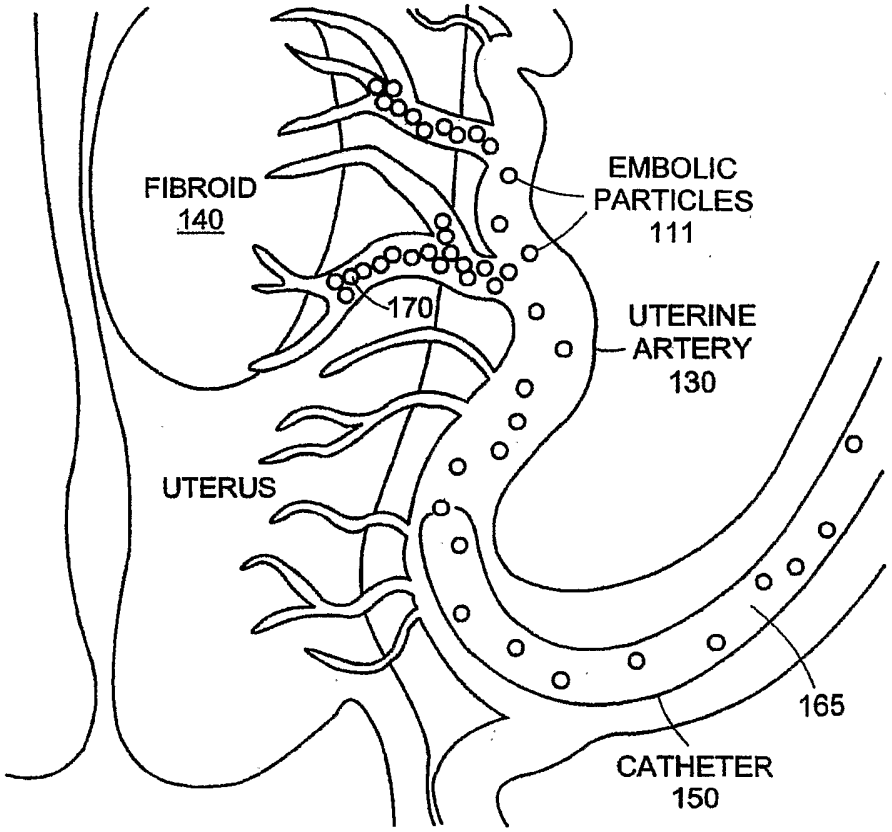

3B
UTERINE ARTERY 130
FIBROID 140
CATHETER 150
FEMORAL ARTERY 120
110
160

FIG. 7A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EMBOLIC
PARTICLES
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UTERINE
ARTERY
130
UTERUS
165
CATHETER
150

FIG. 7B