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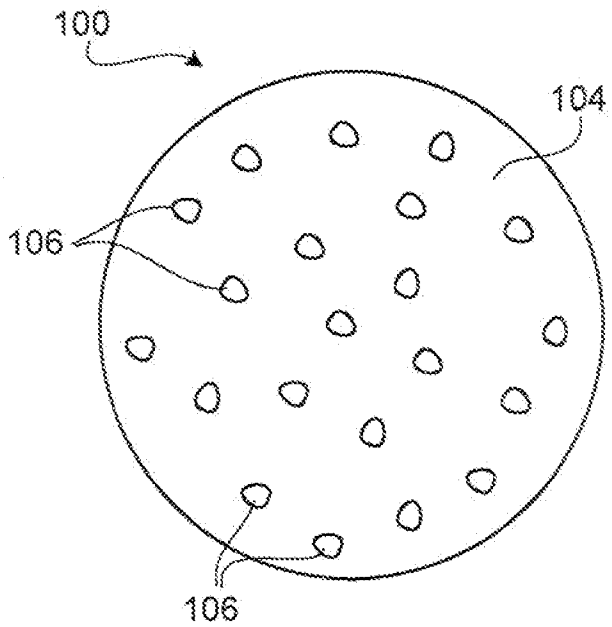
(54) Title: POLYMER PARTICLES INCLUDING COVALENTLY BONDED CHEMICAL SPECIES

(57) Abstract: Polymer particles including a covalently bonded chemical species, as well as related compositions and methods are disclosed.



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Polymer Particles Including Covalently Bonded Chemical Species

Cross-Reference to Related Application

This application claims priority under 35 U.S.C. §119 to USSN 60/822,545, filed August 16, 2006, the contents of which are hereby incorporated by reference.

Field

The disclosure relates to polymer particles including a covalently bonded chemical species, as well as related compositions and methods.

Background

Agents, such as therapeutic agents, can be delivered systemically, for example, by injection through the vascular system or oral ingestion, or they can be applied directly to a site where treatment is desired. In some cases, particles are used to deliver a therapeutic agent to a target site. Additionally or alternatively, particles may be used to perform embolization procedures and/or to perform radiotherapy procedures.

Summary

In one aspect, the invention features a particle that includes a polymer a chemical species covalently bonded to the polymer. The polymer includes vinyl alcohol monomer units, and the chemical species is selected from polymers, oligomers and monomers. The particle has a maximum dimension of 5,000 microns or less.

In another aspect, the invention features a particle that includes a polymer, a chemical species covalently bonded to the polymer and a therapeutic agent. The polymer includes at least five weight percent vinyl alcohol monomer units and at least five weight percent vinyl formal monomer units. The chemical species is selected from polymers, oligomers and monomers and the particle has a maximum dimension of 5,000 microns or less.

In a further aspect, the invention features a composition that includes a carrier fluid and a plurality of particles in the carrier fluid. At least some of the plurality of particles have a maximum dimension of 5,000 microns or less and include a polymer and a chemical species covalently bonded to the polymer. The polymer includes vinyl alcohol monomer units, and the chemical species is selected from polymers, oligomers and monomers.

In an additional aspect, the invention features a method that includes forming a particle that includes a polymer. The polymer has vinyl alcohol monomer units. The method also includes contacting the polymer with a chemical species selected from polymers, oligomers and monomers. The method further includes exposing the polymer and the chemical species to radiation to bond the chemical species to the polymer to form a particle having a maximum dimension of 5,000 microns or less and including the chemical species bonded to the polymer.

In another aspect, the invention features a method that includes forming a particle that has a polymer. The polymer includes at least five weight percent vinyl alcohol monomer units and at least five weight percent vinyl formal monomer units. The method also includes contacting the polymer with a chemical species selected from polymers, oligomers and monomers. The method further includes exposing the polymer and the chemical species to radiation to bond the chemical species to the polymer to form a particle with the chemical species bonded to the polymer. In addition, the method includes contacting a therapeutic agent with the particle. The particle has a maximum dimension of 5,000 microns or less.

Embodiments can include one or more of the following features.

The polymer can include at least five weight percent vinyl alcohol monomers.

The polymer can further include vinyl formal monomer units (e.g., at least five weight percent vinyl formal monomer units).

The polymer can further include vinyl acetate monomer units.

The polymer can include pores. For example, the chemical species can be at least partially disposed in the pores of the polymer.

The chemical species can be coated on a surface of the polymer.

The particle can further include a therapeutic agent. For example, the therapeutic agent can be preferentially associated with the chemical species.

The polymer can be cross-linked.

The chemical species comprises a polymer, such as, for example, polystyrene sulfonic acid, polyvinyl sulfonic acid, polydialkylamino alkyl (meth) acrylate, and/or any hydrophilic or hydrophobic polymer that alters the chemical character of the particle to change the way a therapeutic is preferentially absorbed and released.

The method can use, for example, radiation is selected from electron beam radiation, UV radiation and gamma radiation (e.g., UV radiation).

Exposing the polymer and the chemical species to radiation can cross-link the polymer. For example, it can cause chemical bonds to form between the polymer in the particle and the additional polymer (chemical species) added to modify the chemical character of the particle.

Embodiments can include one or more of the following advantages.

The chemical species (polymer, oligomer, monomer) can be used to manipulate in a desired fashion the release characteristics (e.g., timing, quantity) of one or more therapeutic agents. For example, the chemical species may be associated (e.g., ionically bonded) or associated with (e.g., via van der waals forces or by solubility of the therapeutic in) the chemical species with the therapeutic agent such that, for example, the therapeutic agent can be released by a particle as the environment in which the particle is present changes.

The particles can optionally be used to deliver therapeutic agents within a body lumen, alone or in combination with an embolization procedure.

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

Brief Description of the Drawings

FIG. 1A is side a side view of an embodiment of a particle.

FIG. 1B is a cross-sectional view of the particle of FIG. 1A taken along line 1B-1B.

FIG. 2A is a schematic illustrating an embodiment of a method of injecting a composition including particles into a vessel.

FIG. 2B is a greatly enlarged view of region 2B in FIG. 2A.

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

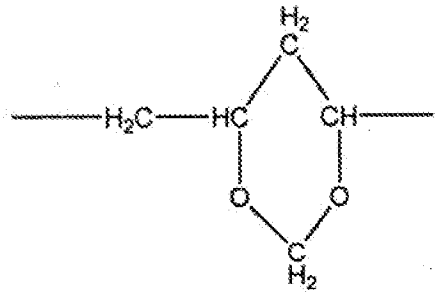
FIGS. 4A-4C are an illustration of an embodiment of a system and method for producing particles.

FIG. 5 is an illustration of an embodiment of a drop generator.

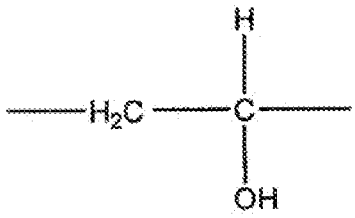
Detailed Description

FIGS. 1A and 1B show a particle 100 that can be used, for example, to in an embolization procedure. Particle 100 includes a cavity 102 surrounded by a matrix 104 including pores 106. The matrix 104 is formed of a matrix polymer. Particle 100 also includes a chemical species that is covalently bonded to the matrix polymer (e.g., covalently bonded to the outer surface of particle 100 and/or covalently bonded to the surface of one or more pores 104). The chemical species is one or more monomers, oligomers and/or polymers.

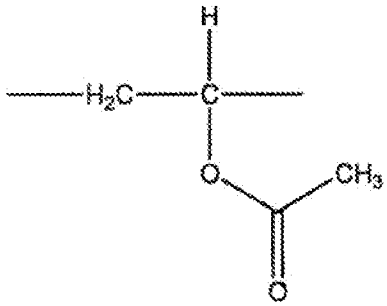
In general, the matrix polymer is formed of a biocompatible material. Examples include polymers that include vinyl alcohol monomers, vinyl formal monomers and/or vinyl acetate monomers. As referred to herein, a vinyl formal monomer unit has the following structure:



As referred to herein, a vinyl alcohol monomer unit has the following structure:

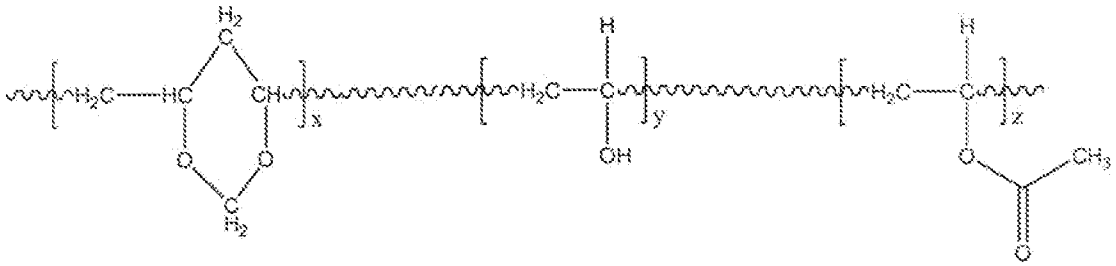


As referred to herein, a vinyl acetate monomer unit has the following structure:



In general, the monomer units can be arranged in a variety of different ways. As an example, in some embodiments, the polymer can include different monomer units that alternate with each other. For example, the polymer can include repeating blocks, each block including a vinyl formal monomer unit, a vinyl alcohol monomer unit, and a vinyl acetate monomer unit. As another example, in certain embodiments, the polymer can include blocks including multiple monomer units of the same type.

In some embodiments, the polymer can have the formula that is schematically represented below, in which x, y and z each are integers that are greater than zero. The individual monomer units that are shown can be directly attached to each other, and/or can include one or more other monomer units (e.g., vinyl formal monomer units, vinyl alcohol monomer units, vinyl acetate monomer units) between them:



vinyl formal monomer unit vinyl alcohol monomer unit vinyl acetate monomer unit

Optionally, formal lingaes can occur between PVA molecules giving crosslinks.

In some embodiments, the polymer can include at least five percent by weight (e.g., at least 15 percent by weight, at least 25 percent by weight, at least 35 percent by weight) vinyl alcohol monomer units, and/or at most 80 percent by weight (e.g., at most 50 percent by weight, at most 25 percent by weight, at most 10 percent by weight) vinyl

alcohol monomer units. The weight percent of a monomer unit in a polymer can be measured using solid-state NMR spectroscopy.

In some embodiments, the polymer can include at least five percent by weight (e.g., at least 25 percent by weight, at least 50 percent by weight, at least 75 percent by weight, at least 85 percent by weight) vinyl formal monomer units, and/or at most 90 percent by weight (e.g., at most 75 percent by weight, at most 50 percent by weight, at most 25 percent by weight) vinyl formal monomer units. As used herein, the weight percent of a monomer unit in a polymer is measured using solid-state NMR spectroscopy as described above.

In some embodiments, the polymer can include at least one percent by weight (e.g., at least two percent by weight, at least five percent by weight, at least 10 percent by weight, at least 15 percent by weight) vinyl acetate monomer units, and/or at most 20 percent by weight (e.g., at most 15 percent by weight, at most 10 percent by weight, at most five percent by weight) vinyl acetate monomer units. As used herein, the weight percent of a monomer unit in a polymer is measured using solid-state NMR spectroscopy as described above.

Alternatively or in addition, other polymers may also be used as a matrix polymer in particle 100. Examples of polymers 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. Polymers are described, for example, in Lanphere et al., U.S. Patent Application Publication No. US 2004/0096662 A1, published on May 20, 2004, and entitled "Embolization"; Song et al., U.S. Patent Application Serial No. 11/314,056, filed on December 21, 2005, and entitled "Block Copolymer Particles"; and Song et al., U.S. Patent Application Serial No. 11/314,557, filed on December 21, 2005, and entitled "Block Copolymer Particles", all of which are incorporated herein by reference.

Examples of monomers that can be covalently bonded to the matrix polymer(s) of particle 100 include monomers of the polymers disclosed above. As an example, if the matrix polymer is formed of formalized or unformalized PVA, styrene sulfonic acid can be covalently bonded to the matrix polymer. As another example, if the matrix polymer is formed of formalized or unformalized PVA, dimethylaminoethylacrylate can be covalently bonded to the matrix polymer. As a further example, if the matrix polymer is formed of formalized or unformalized PVA, styrene can be covalently bonded to the matrix polymer. As an additional example, if the matrix polymer is formed of formalized or unformalized PVA, acrylic acid can be covalently bonded to the matrix polymer.

Examples of oligomers that can be covalently bonded to the matrix polymer(s) of particle 100 include PEG acrylate oligomers, and low molecular weight versions of the polymers mentioned above. As an example, if the matrix polymer is formed of formalized or unformalized PVA, PLA can be covalently bonded to the matrix polymer. As another example, if the matrix polymer is formed of formalized or unformalized PVA, PEG can be covalently bonded to the matrix polymer.

Examples of polymers that can be covalently bonded to the matrix polymer(s) of particle 100 include the polymers disclosed above. As an example, if the matrix polymer is formed of formalized or unformalized PVA, a polystyrene (e.g., polystyrene sulfonic acid) can be covalently bonded to the matrix polymer. As another example, if the matrix polymer is formalized or unformalized PVA, polystyrene sulfonic can be covalently bonded to the matrix polymer. As another example, if the matrix polymer is formalized or unformalized PVA, polydimethylaminoethylacrylate can be covalently bonded to the matrix polymer. As a further example, if the matrix polymer is formalized or unformalized PVA, polyacrylic acid can be covalently bonded to the matrix polymer.

In general, the chemical species can be covalently bonded to the matrix polymer(s) using any desired method. The process can involve, for example, bringing them into contact. In some embodiments, this can be achieved by coating the matrix polymer with the chemical species. In certain embodiments, the chemical species can be diffused into the pores of the particle. Subsequently, the chemical species can be covalently bonded to the matrix polymer. For example, the chemical species and matrix polymer can be exposed to appropriate radiation (e.g., electron beam radiation, gamma

radiation). An exemplary dose range for gamma or electron beam radiation is a minimum of one Kgy. An exemplary dose range for UV radiation is 250 nm for 5 minutes. Exposure to radiation can, for example, cross-link the matrix polymer.

As an example, a gamma or an electron beam can be used to covalently bond polystyrene sulfonic acid to formalized or unformalized PVA. As another example, a gamma or an electron beam can be used to covalently bond polyacrylic acid to formalized or unformalized PVA. As a further example, a gamma or an electron beam can be used to covalently bond polydimethylaminoethylacrylate to formalized or unformalized PVA. As an additional example, a gamma or an electron beam can be used to covalently bond PEG acrylate oligomer to formalized or unformalized PVA.

Alternatively or in addition, a chemical species can be covalently bonded to a matrix polymer by reaction between a free radical initiator incorporated into the matrix polymer and one of more monomers exposed to such matrix.

In general, the maximum dimension of particle 100 is 5,000 microns or less (e.g., from two microns to 5,000 microns; from 10 microns to 5,000 microns; from 40 microns to 2,000 microns; from 100 microns to 700 microns; from 500 microns to 700 microns; from 100 microns to 500 microns; from 100 microns to 300 microns; from 300 microns to 500 microns; from 500 microns to 1,200 microns; from 500 microns to 700 microns; from 700 microns to 900 microns; from 900 microns to 1,200 microns; from 1,000 microns to 1,200 microns). In some embodiments, the maximum dimension of particle 100 is 5,000 microns or less (e.g., 4,500 microns or less, 4,000 microns or less, 3,500 microns or less, 3,000 microns or less, 2,500 microns or less; 2,000 microns or less; 1,500 microns or less; 1,200 microns or less; 1,150 microns or less; 1,100 microns or less; 1,050 microns or less; 1,000 microns or less; 900 microns or less; 700 microns or less; 500 microns or less; 400 microns or less; 300 microns or less; 100 microns or less; 50 microns or less; 10 microns or less; five microns or less) and/or one micron or more (e.g., five microns or more; 10 microns or more; 50 microns or more; 100 microns or more; 300 microns or more; 400 microns or more; 500 microns or more; 700 microns or more; 900 microns or more; 1,000 microns or more; 1,050 microns or more; 1,100 microns or more; 1,150 microns or more; 1,200 microns or more; 1,500 microns or more;

2,000 microns or more; 2,500 microns or more). In some embodiments, the maximum dimension of particle 100 is less than 100 microns (e.g., less than 50 microns).

In some embodiments, particle 100 can be substantially spherical. In certain embodiments, particle 100 can have a sphericity of 0.8 or more (e.g., 0.85 or more, 0.9 or more, 0.95 or more, 0.97 or more). Particle 100 can be, for example, manually compressed, essentially flattened, while wet to 50 percent or less of its original diameter and then, upon exposure to fluid, regain a sphericity of 0.8 or more (e.g., 0.85 or more, 0.9 or more, 0.95 or more, 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.

Multiple particles can be combined with a carrier fluid (e.g., a pharmaceutically acceptable carrier, such as a saline solution, a contrast agent, or both) to form a composition, which can then be delivered to a site and used to embolize the site. FIGS. 2A and 2B illustrate the use of a composition including particles to embolize a lumen of a subject. As shown, a composition including particles 100 and a carrier fluid is injected into a vessel through an instrument such as a catheter 250. Catheter 250 is connected to a syringe barrel 210 with a plunger 260. Catheter 250 is inserted, for example, into a femoral artery 220 of a subject. Catheter 250 delivers the composition to, for example, occlude a uterine artery 230 leading to a fibroid 240 located in the uterus of a female subject. The composition is initially loaded into syringe 210. Plunger 260 of syringe 210 is then compressed to deliver the composition through catheter 250 into a lumen 265 of uterine artery 230.

FIG. 2B, which is an enlarged view of section 2B of FIG. 2A, shows uterine artery 230, which is subdivided into smaller uterine vessels 270 (e.g., having a diameter of two millimeters or less) that feed fibroid 240. The particles 100 in the composition

partially or totally fill the lumen of uterine artery 230, either partially or completely occluding the lumen of the uterine artery 230 that feeds uterine fibroid 240.

Compositions including particles such as particles 100 can be delivered to various sites in the body, including, for example, sites having cancerous lesions, such as the breast, prostate, lung, thyroid, or ovaries. The 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 a 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 composition. An effective amount of embolic composition refers to the amount sufficient to result in amelioration of symptoms and/or a prolongation of survival of the subject, or the amount sufficient to prophylactically treat a subject. The 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.

A composition can include a mixture of particles (e.g., particles formed of polymers including different weight percents of vinyl alcohol monomer units, particles including different types of therapeutic agents), or can include particles that are all of the same type. In some embodiments, a composition can be prepared with a calibrated concentration of particles for ease of delivery by a physician. A physician can select a composition of a particular concentration based on, for example, the type of procedure to be performed. In certain embodiments, a physician can use a composition with a relatively high concentration of particles during one part of an embolization procedure, and a composition with a relatively low concentration of particles during another part of the embolization procedure.

Suspensions of particles in saline solution can be prepared to remain stable (e.g., to remain suspended in solution and not settle and/or float) over a desired period of time. A suspension of particles can be stable, for example, for from one minute to 20 minutes (e.g. from one minute to 10 minutes, from two minutes to seven minutes, from three minutes to six minutes).

In some embodiments, particles can be suspended in a physiological solution by matching the density of the solution to the density of the particles. In certain embodiments, the particles and/or the physiological solution can have a density of from one gram per cubic centimeter to 1.5 grams per cubic centimeter (e.g., from 1.2 grams per cubic centimeter to 1.4 grams per cubic centimeter, from 1.2 grams per cubic centimeter to 1.3 grams per cubic centimeter).

In certain embodiments, the carrier fluid of a composition can include a surfactant. The surfactant can help the particles to mix evenly in the carrier fluid and/or can decrease the likelihood of the occlusion of a delivery device (e.g., a catheter) by the particles. In certain embodiments, the surfactant can enhance delivery of the composition (e.g., by enhancing the wetting properties of the particles and facilitating the passage of the particles through a delivery device). In some embodiments, the surfactant can decrease the occurrence of air entrapment by the particles in a composition (e.g., by porous particles in a composition). Examples of liquid surfactants include Tween® 80 (available from Sigma-Aldrich) and Cremophor EL® (available from Sigma-Aldrich). An example of a powder surfactant is Pluronic® F127 NF (available from BASF). In

certain embodiments, a composition can include from 0.05 percent by weight to one percent by weight (e.g., 0.1 percent by weight, 0.5 percent by weight) of a surfactant. A surfactant can be added to the carrier fluid prior to mixing with the particles and/or can be added to the particles prior to mixing with the carrier fluid.

In some embodiments, among the particles delivered to a subject (e.g., in a composition), the majority (e.g., 50 percent or more, 60 percent or more, 70 percent or more, 80 percent or more, 90 percent or more) of the particles can have a maximum dimension of 5,000 microns or less (e.g., 4,500 microns or less, 4,000 microns or less, 3,500 microns or less, 3,000 microns or less, 2,500 microns or less; 2,000 microns or less; 1,500 microns or less; 1,200 microns or less; 1,150 microns or less; 1,100 microns or less; 1,050 microns or less; 1,000 microns or less; 900 microns or less; 700 microns or less; 500 microns or less; 400 microns or less; 300 microns or less; 100 microns or less; 50 microns or less; 10 microns or less; five microns or less) and/or one micron or more (e.g., five microns or more; 10 microns or more; 50 microns or more; 100 microns or more; 300 microns or more; 400 microns or more; 500 microns or more; 700 microns or more; 900 microns or more; 1,000 microns or more; 1,050 microns or more; 1,100 microns or more; 1,150 microns or more; 1,200 microns or more; 1,500 microns or more; 2,000 microns or more; 2,500 microns or more). In some embodiments, among the particles delivered to a subject, the majority of the particles can have a maximum dimension of less than 100 microns (e.g., less than 50 microns).

In certain embodiments, the particles delivered to a subject (e.g., in a composition) can have an arithmetic mean maximum dimension of 5,000 microns or less (e.g., 4,500 microns or less, 4,000 microns or less, 3,500 microns or less, 3,000 microns or less, 2,500 microns or less; 2,000 microns or less; 1,500 microns or less; 1,200 microns or less; 1,150 microns or less; 1,100 microns or less; 1,050 microns or less; 1,000 microns or less; 900 microns or less; 700 microns or less; 500 microns or less; 400 microns or less; 300 microns or less; 100 microns or less; 50 microns or less; 10 microns or less; five microns or less) and/or one micron or more (e.g., five microns or more; 10 microns or more; 50 microns or more; 100 microns or more; 300 microns or more; 400 microns or more; 500 microns or more; 700 microns or more; 900 microns or more; 1,000 microns or more; 1,050 microns or more; 1,100 microns or more; 1,150 microns or

more; 1,200 microns or more; 1,500 microns or more; 2,000 microns or more; 2,500 microns or more). In some embodiments, the particles delivered to a subject can have an arithmetic mean maximum dimension of less than 100 microns (e.g., less than 50 microns).

Exemplary ranges for the arithmetic mean maximum dimension of particles delivered to a subject include from 100 microns to 500 microns; from 100 microns to 300 microns; from 300 microns to 500 microns; from 500 microns to 700 microns; from 700 microns to 900 microns; from 900 microns to 1,200 microns; and from 1,000 microns to 1,200 microns. In general, the particles delivered to a subject (e.g., in a composition) can have an arithmetic mean maximum dimension in approximately the middle of the range of the diameters of the individual particles, and a variance of 20 percent or less (e.g. 15 percent or less, 10 percent or less).

In some embodiments, the arithmetic mean maximum dimension of the particles delivered to a subject (e.g., in a composition) can vary depending upon the particular condition to be treated. As an example, in certain embodiments in which the particles are used to embolize a liver tumor, the particles delivered to the subject can have an arithmetic mean maximum dimension of 500 microns or less (e.g., from 100 microns to 300 microns; from 300 microns to 500 microns). As another example, in some embodiments in which the particles are used to embolize a uterine fibroid, the particles delivered to the subject can have an arithmetic mean maximum dimension of 1,200 microns or less (e.g., from 500 microns to 700 microns; from 700 microns to 900 microns; from 900 microns to 1,200 microns). As an additional example, in certain embodiments in which the particles are used to treat a neural condition (e.g., a brain tumor) and/or head trauma (e.g., bleeding in the head), the particles delivered to the subject can have an arithmetic mean maximum dimension of less than 100 microns (e.g., less than 50 microns). As a further example, in some embodiments in which the particles are used to treat a lung condition, the particles delivered to the subject can have an arithmetic mean maximum dimension of less than 100 microns (e.g., less than 50 microns). As another example, in certain embodiments in which the particles are used to treat thyroid cancer, the particles can have an arithmetic maximum dimension of 1,200 microns or less (e.g., from 1,000 microns to 1,200 microns). As an additional example,

in some embodiments in which the particles are used only for therapeutic agent delivery, the particles can have an arithmetic mean maximum dimension of less than 100 microns (e.g., less than 50 microns, less than 10 microns, less than five microns).

The arithmetic mean maximum dimension of a group of particles can be determined using a Beckman Coulter RapidVUE Image Analyzer version 2.06 (Beckman Coulter, Miami, FL), described above. The arithmetic mean maximum dimension of a group of particles (e.g., in a composition) can be determined by dividing the sum of the diameters of all of the particles in the group by the number of particles in the group.

In some embodiments, particle 100 can have pores. For example, the polymer can form a matrix in which the pores are present. Additionally or alternatively, particle 100 can have one or more cavities. For example, particle 100 can be formed so that the polymer surrounds one or more cavities.

A pore has a maximum dimension of at least 0.01 micron (e.g., at least 0.05 micron, at least 0.1 micron, at least 0.5 micron, at least one micron, at least five microns, at least 10 microns, at least 15 microns, at least 20 microns, at least 25 microns, at least 30 microns, at least 35 microns, at least 50 microns, at least 100 microns, at least 150 microns, at least 200 microns, at least 250 microns), and/or at most 300 microns (e.g., at most 250 microns, at most 200 microns, at most 150 microns, at most 100 microns, at most 50 microns, at most 35 microns, at most 30 microns, at most 25 microns, at most 20 microns, at most 15 microns, at most 10 microns, at most five microns, at most one micron, at most 0.5 micron, at most 0.1 micron, at most 0.05 micron).

A cavity has a maximum dimension of at least one micron (e.g., a least five microns, at least 10 microns, at least 25 microns, at least 50 microns, at least 100 microns, at least 250 microns, at least 500 microns, at least 750 microns) and/or at most 1,000 microns (e.g., at most 750 microns, at most 500 microns, at most 250 microns, at most 100 microns, at most 50 microns, at most 25 microns, at most 10 microns, at most five microns). In some embodiments (e.g., when the particle is used to deliver a therapeutic agent within a body lumen, independent of whether embolization is desired), the particle can also include a therapeutic agent. In some embodiments, the therapeutic agent can be present on the surface of the particle and/or in the pores of the particles.

Optionally, the therapeutic agent can be bonded to or associated with the chemical species and/or matrix polymer. Examples of such bonding include ionic bonding, covalent bonding, van der waals bonding or solubility between the therapeutic and the chemical species.

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; proteins; gene therapies; nucleic acids with and without carrier vectors (e.g., recombinant nucleic acids, DNA (e.g., naked DNA), cDNA, RNA, genomic DNA, cDNA or RNA in a non-infectious vector or in a viral vector which may have attached peptide targeting sequences, antisense nucleic acids (RNA, DNA)); oligonucleotides; gene/vector systems (e.g., anything that allows for the uptake and expression of nucleic acids); DNA chimeras (e.g., DNA chimeras which include gene sequences and encoding for ferry proteins such as membrane translocating sequences ("MTS") and herpes simplex virus-1 ("VP22")); compacting agents (e.g., DNA compacting agents); viruses; polymers; hyaluronic acid; proteins (e.g., enzymes such as ribozymes, asparaginase); immunologic species; nonsteroidal anti-inflammatory medications; oral contraceptives; progestins; gonadotrophin-releasing hormone agonists; chemotherapeutic agents; and radioactive species (e.g., radioisotopes, radioactive molecules). Examples of radioactive species include yttrium (^{90}Y), holmium (^{166}Ho), phosphorus (^{32}P), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212}Bi or ^{213}Bi),), samarium (^{153}Sm), iridium (^{192}Ir), rhodium (^{105}Rh), iodine (^{131}I or ^{125}I), indium (^{111}In), technetium (^{99}Tc), phosphorus (^{32}P), sulfur (^{35}S), carbon (^{14}C), tritium (^{3}H), chromium (^{51}Cr), chlorine (^{36}Cl), cobalt (^{57}Co or ^{58}Co), iron (^{59}Fe), selenium (^{75}Se), and/or gallium (^{67}Ga). In some embodiments, yttrium (^{90}Y), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212}Bi or ^{213}Bi), holmium (^{166}Ho), samarium (^{153}Sm), iridium (^{192}Ir), and/or rhodium (^{105}Rh) can be used as therapeutic agents. In certain embodiments, yttrium (^{90}Y), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212}Bi or ^{213}Bi), holmium (^{166}Ho), samarium (^{153}Sm), iridium (^{192}Ir), rhodium (^{105}Rh), iodine (^{131}I or ^{125}I),

indium (^{111}In), technetium (^{99}Tc), phosphorus (^{32}P), carbon (^{14}C), and/or tritium (^{3}H) can be used as a radioactive label (e.g., for use in diagnostics). In some embodiments, a radioactive species can be a radioactive molecule that includes antibodies containing one or more radioisotopes, for example, a radiolabeled antibody. Radioisotopes that can be bound to antibodies include, for example, iodine (^{131}I or ^{125}I), yttrium (^{90}Y), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212}Bi or ^{213}Bi), indium (^{111}In), technetium (^{99}Tc), phosphorus (^{32}P), rhodium (^{105}Rh), sulfur (^{35}S), carbon (^{14}C), tritium (^{3}H), chromium (^{51}Cr), chlorine (^{36}Cl), cobalt (^{57}Co or ^{58}Co), iron (^{59}Fe), selenium (^{75}Se), and/or gallium (^{67}Ga). Examples of antibodies include monoclonal and polyclonal antibodies including RS7, Mov18, MN-14 IgG, CC49, COL-1, mAB A33, NP-4 F(ab´)2 anti-CEA, anti-PSMA, ChL6, m-170, or antibodies to CD20, CD74 or CD52 antigens. Examples of radioisotope/antibody pairs include m-170 MAB with ^{90}Y. Examples of commercially available radioisotope/antibody pairs include Zevalin™ (IDEC pharmaceuticals, San Diego, CA) and Bexxar™ (Corixa corporation, Seattle, WA). Further examples of radioisotope/antibody pairs can be found in J. Nucl. Med. 2003, Apr: 44(4): 632-40.

Non-limiting examples of therapeutic agents include anti-thrombogenic agents; thrombogenic agents; agents that promote clotting; agents that inhibit clotting; antioxidants; angiogenic and anti-angiogenic agents and factors; anti-proliferative agents (e.g., agents capable of blocking smooth muscle cell proliferation, such as rapamycin); calcium entry blockers (e.g., verapamil, diltiazem, nifedipine); targeting factors (e.g., polysaccharides, carbohydrates); agents that can stick to the vasculature (e.g., charged moieties) (e.g., gelatin, chitosn, collagen, polymers containg bioactive groups like RGD peptides); and survival genes which protect against cell death (e.g., anti-apoptotic Bcl-2 family factors and Akt kinase).

Examples of 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, acetyl salicylic acid, sulfasalazine and mesalamine; antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, cisplatin, methotrexate, 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 factors or peptides; vascular cell growth promoters such as growth factors, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors (e.g., PDGF inhibitor-Trapidil), 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.

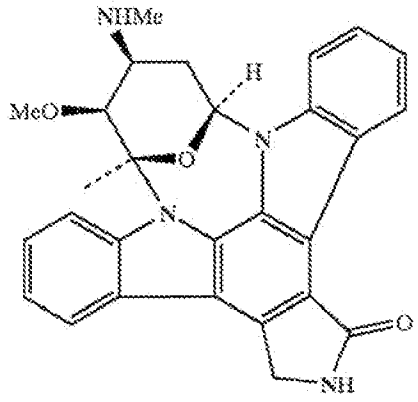
Examples of genetic therapeutic agents include: anti-sense DNA and RNA; DNA coding for anti-sense RNA, tRNA or rRNA to replace defective or deficient endogenous molecules, angiogenic factors including growth factors such as acidic and basic fibroblast growth factors, vascular endothelial growth factor, 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 additionally, 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; and non-viral vectors such as lipids, liposomes and cationic lipids.

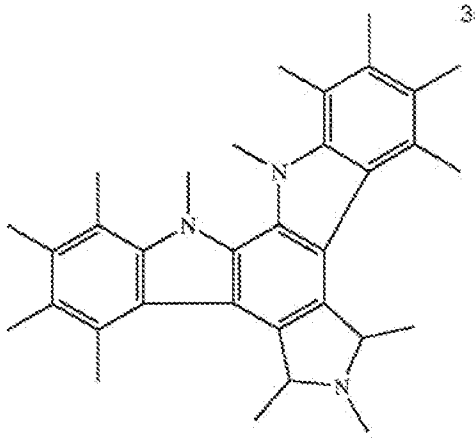
Cells include cells of human origin (autologous or allogeneic), including stem cells, or from an animal source (xenogeneic), which can be genetically engineered if desired to deliver proteins of interest.

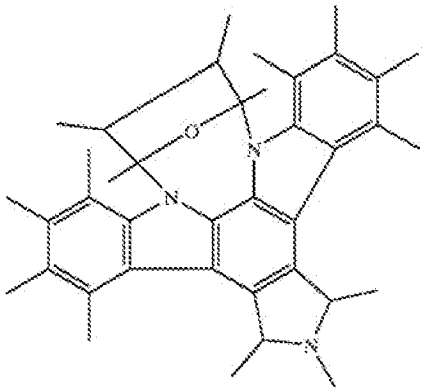
Several of the above and numerous additional therapeutic agents are disclosed in Kunz et al., U.S. Patent No. 5,733,925, which is incorporated herein by reference. Therapeutic agents disclosed in this patent include the following:

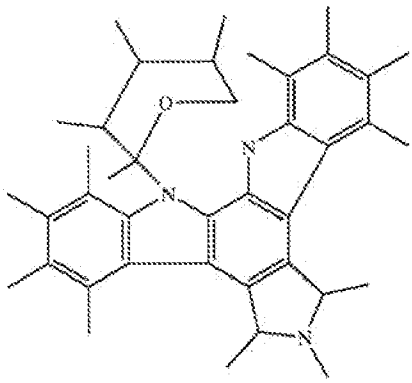
"Cytostatic agents" (i.e., agents that prevent or delay cell division in proliferating cells, for example, by inhibiting replication of DNA or by inhibiting spindle fiber formation). Representative examples of cytostatic agents include modified toxins, methotrexate, adriamycin, radionuclides (e.g., such 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 include one or more of the following: calcium-channel blockers, including benzothiazapines (e.g., diltiazem, clentiazem); dihydropyridines (e.g., nifedipine, amlodipine, nicardapine); phenylalkylamines (e.g., verapamil); serotonin pathway modulators, including 5-HT antagonists (e.g., ketanserin, naftidrofuryl) and 5-HT uptake inhibitors (e.g., fluoxetine); cyclic nucleotide pathway agents, including phosphodiesterase inhibitors (e.g., cilostazole, dipyridamole), adenylate/guanylate cyclase stimulants (e.g., forskolin), and adenosine analogs; catecholamine modulators, including α-antagonists (e.g., prazosin, bunazosine), β-antagonists (e.g., propranolol), and α/β-antagonists (e.g., labetalol, carvedilol); endothelin receptor antagonists; nitric oxide donors/releasing molecules, including organic nitrates/nitrites (e.g., nitroglycerin, isosorbide dinitrate, amyl nitrite), inorganic nitroso compounds (e.g., sodium nitroprusside), sydnonimines (e.g., molsidomine, linsidomine), nonoates (e.g., diazenium diolates, NO adducts of alkanediamines), S-nitroso compounds, including low molecular weight compounds (e.g., S-nitroso derivatives of captopril, glutathione and N-acetyl penicillamine) and 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, and L-arginine; ACE inhibitors (e.g., cilazapril, fosinopril, enalapril); ATII-receptor antagonists (e.g., saralasin, losartin); platelet adhesion inhibitors (e.g., albumin, polyethylene oxide);

platelet aggregation inhibitors, including aspirin and thienopyridine (ticlopidine, clopidogrel) and GP IIb/IIIa inhibitors (e.g., abciximab, epitifibatide, tirofiban, intergrilin); coagulation pathway modulators, including heparinoids (e.g., heparin, low molecular weight heparin, dextran sulfate, β-cyclodextrin tetradecasulfate), thrombin inhibitors (e.g., hirudin, hirulog, PPACK (D-phe-L-propyl-L-arg-chloromethylketone), argatroban), Fxa inhibitors (e.g., antistatin, TAP (tick anticoagulant peptide)), vitamin K inhibitors (e.g., warfarin), and activated protein C; cyclooxygenase pathway inhibitors (e.g., aspirin, ibuprofen, flurbiprofen, indomethacin, sulfinpyrazone); natural and synthetic corticosteroids (e.g., dexamethasone, prednisolone, methprednisolone, hydrocortisone); lipoxygenase pathway inhibitors (e.g., nordihydroguairetic acid, 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; prostacyclins and prostacyclin analogs (e.g., ciprostene, epoprostenol, carbacyclin, iloprost, beraprost); macrophage activation preventers (e.g., bisphosphonates); HMG-CoA reductase inhibitors (e.g., lovastatin, pravastatin, fluvastatin, simvastatin, cerivastatin); fish oils and omega-3-fatty acids; free-radical scavengers/antioxidants (e.g., probucol, vitamins C and E, ebselen, retinoic acid (e.g., trans-retinoic acid), SOD mimics); agents affecting various growth factors including FGF pathway agents (e.g., bFGF antibodies, chimeric fusion proteins), PDGF receptor antagonists (e.g., trapidil), IGF pathway agents (e.g., 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 (e.g., EGF antibodies, receptor antagonists, chimeric fusion proteins), TNF-α pathway agents (e.g., thalidomide and analogs thereof), thromboxane A2 (TXA2) pathway modulators (e.g., sulotroban, vapiprost, dazoxiben, ridogrel), protein tyrosine kinase inhibitors (e.g., tyrphostin, genistein, and quinoxaline derivatives); MMP pathway inhibitors (e.g., marimastat, ilomastat, metastat), and cell motility inhibitors (e.g., cytochalasin B); antiproliferative/antineoplastic agents including antimetabolites such as purine analogs (e.g., 6-mercaptopurine), pyrimidine analogs (e.g., cytarabine and 5-fluorouracil) and methotrexate, nitrogen mustards, alkyl sulfonates, ethylenimines, antibiotics (e.g., daunorubicin, doxorubicin, daunomycin, bleomycin, mitomycin, penicillins,

cephalosporins, ciprofalxin, vancomycins, aminoglycosides, quinolones, polymyxins, erythromycins, tertacyclines, chloramphenicols, clindamycins, linomycins, sulfonamides, and their homologs, analogs, fragments, derivatives, and pharmaceutical salts), nitrosoureas (e.g., carmustine, lomustine) and cisplatin, agents affecting microtubule dynamics (e.g., vinblastine, vincristine, colchicine, paclitaxel, epothilone), caspase activators, proteasome inhibitors, angiogenesis inhibitors (e.g., endostatin, angiostatin and squalamine), and rapamycin, cerivastatin, flavopiridol and suramin; matrix deposition/organization pathway inhibitors (e.g., halofuginone or other quinazolinone derivatives, tranilast); endothelialization facilitators (e.g., VEGF and RGD peptide); and blood rheology modulators (e.g., pentoxifylline).

Other examples of therapeutic agents include anti-tumor agents, such as docetaxel, alkylating agents (e.g., mechlorethamine, chlorambucil, cyclophosphamide, melphalan, ifosfamide), plant alkaloids (e.g., etoposide), inorganic ions (e.g., cisplatin), biological response modifiers (e.g., interferon), and hormones (e.g., tamoxifen, flutamide), as well as their homologs, analogs, fragments, derivatives, and pharmaceutical salts.

Additional examples of therapeutic agents include organic-soluble therapeutic agents, such as mithramycin, cyclosporine, and plicamycin. Further examples of therapeutic agents include pharmaceutically active compounds, anti-sense genes, viral, liposomes and cationic polymers (e.g., selected based on the application), biologically active solutes (e.g., heparin), prostaglandins, prostcyclins, L-arginine, nitric oxide (NO) donors (e.g., lisidomine, molsidomine, NO-protein adducts, NO-polysaccharide adducts, polymeric or oligomeric NO adducts or chemical complexes), enoxaparin, Warafin sodium, dicumarol, interferons, interleukins, chymase inhibitors (e.g., Tranilast), ACE inhibitors (e.g., Enalapril), serotonin antagonists, 5-HT uptake inhibitors, and beta blockers, and other antitumor and/or chemotherapy drugs, such as BiCNU, busulfan, carboplatinum, cisplatinum, cytoxan, DTIC, fludarabine, mitoxantrone, velban, VP-16, herceptin, leustatin, navelbine, rituxan, and taxotere.

In some embodiments, a therapeutic agent can be hydrophilic. An example of a hydrophilic therapeutic agent is doxorubicin hydrochloride. In certain embodiments, a therapeutic agent can be hydrophobic. Examples of hydrophobic therapeutic agents

include paclitaxel, cisplatin, tamoxifen, and doxorubicin base. In some embodiments, a therapeutic agent can be lipophilic. Examples of lipophilic therapeutic agents include paclitaxel, other taxane derivative, dexamethasone, other steroid based therapeutics.

Therapeutic agents are described, for example, in DiMatteo et al., U.S. Patent Application Publication No. US 2004/0076582 A1, published on April 22, 2004, and entitled "Agent Delivery Particle"; Schwarz et al., U.S. Patent No. 6,368,658; Buiser et al., U.S. Patent Application Serial No. 11/311,617, filed on December 19, 2005, and entitled "Coils"; and Song, U.S. Patent Application Serial No. 11/355,301, filed on February 15, 2006, and entitled "Block Copolymer Particles", all of which are incorporated herein by reference. In certain embodiments, in addition to or as an alternative to including therapeutic agents, particle 100 can include one or more radiopaque materials, materials that are visible by magnetic resonance imaging (MRI-visible materials), ferromagnetic materials, and/or contrast agents (e.g., ultrasound contrast agents). These materials can, for example, be bonded to the chemical species (monomer(s), oligomers(s), polymer(s)). Radiopaque materials, MRI-visible materials, ferromagnetic materials, and contrast agents are described, for example, in Rioux et al., U.S. Patent Application Publication No. US 2004/0101564 A1, published on May 27, 2004, and entitled "Embolization", which is incorporated herein by reference.

In certain embodiments, a particle can also include a coating. For example, FIG. 3 shows a particle 300 having a matrix 104, pores 106 and, and a coating 310. Coating 310 can, for example, be formed of a polymer (e.g., alginate) that is different from the polymer in matrix 304. Coating 310 can, for example, regulate release of therapeutic agent from particle 300, and/or provide protection to the interior region of particle 300 (e.g., during delivery of particle 300 to a target site). In certain embodiments, coating 310 can be formed of a bioerodible and/or bioabsorbable material that can erode and/or be absorbed as particle 300 is delivered to a target site. This can, for example, allow the interior region of particle 300 to deliver a therapeutic agent to the target site once particle 300 has reached the target site. A bioerodible material can be, for example, a polysaccharide (e.g., alginate); a polysaccharide derivative; an inorganic, ionic salt; a water soluble polymer (e.g., polyvinyl alcohol, such as polyvinyl alcohol that has not been cross-linked); biodegradable poly DL-lactide-poly ethylene glycol (PELA); a

hydrogel (e.g., polyacrylic acid, hyaluronic acid, gelatin, carboxymethyl cellulose); a polyethylene glycol (PEG); chitosan; a polyester (e.g., a polycaprolactone); a poly(ortho ester); a polyanhydride; a poly(lactic-co-glycolic) acid (e.g., a poly(d-lactic-co-glycolic) acid); a poly(lactic acid) (PLA); a poly(glycolic acid) (PGA); or a combination thereof. In some embodiments, coating 310 can be formed of a swellable material, such as a hydrogel (e.g., polyacrylamide co-acrylic acid). The swellable material can be made to swell by, for example, changes in pH, temperature, and/or salt. In certain embodiments in which particle 300 is used in an embolization procedure, coating 310 can swell at a target site, thereby enhancing occlusion of the target site by particle 300.

In some embodiments, the coating can be porous. The coating can, for example, be formed of one or more of the above-disclosed polymers.

In certain embodiments, a particle can include a coating that includes one or more therapeutic agents (e.g., a relatively high concentration of one or more therapeutic agents). One or more of the therapeutic agents can also be loaded into the interior region of the particle. Thus, the surface of the particle can release an initial dosage of therapeutic agent, after which the interior region of the particle can provide a burst release of therapeutic agent. The therapeutic agent on the surface of the particle can be the same as or different from the therapeutic agent in the interior region of the particle. The therapeutic agent on the surface of the particle can be applied to the particle by, for example, exposing the particle to a high concentration solution of the therapeutic agent.

In some embodiments, a therapeutic agent coated particle can include another coating over the surface of the therapeutic agent (e.g., a bioerodible 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. In certain embodiments, the coating can be applied by dipping and/or spraying the particle. The bioerodible polymer can be a polysaccharide (e.g., alginate). In some embodiments, the coating can be an inorganic, ionic salt. Other examples of bioerodible coating materials include polysaccharide derivatives, 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, hyaluronic acid,

gelatin, carboxymethyl cellulose), polyethylene glycols (PEG), chitosan, polyesters (e.g., polycaprolactones), poly(ortho esters), polyanhydrides, poly(lactic acids) (PLA), polyglycolic acids (PGA), poly(lactic-co-glycolic) acids (e.g., poly(d-lactic-co-glycolic) acids), and combinations thereof. 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., a bioerodible coating) can be applied to the particle surface in embodiments in which a high concentration of therapeutic agent has not been applied to the particle surface. Coatings are described, for example, in DiMatteo et al., U.S. Patent Application Publication No. US 2004/0076582 A1, published on April 22, 2004, and entitled "Agent Delivery Particle", which is incorporated herein by reference.

In general, an emulsion process, such as a single-emulsion process, can be performed with or without a droplet generator. As an example, in processes that do not involve a droplet generator, a solution of polymer in a water immiscible organic solvent can be added to an aqueous solution containing a surfactant, and small partices can be spontaneously formed. As another example, FIGS. 4A-4C show a single-emulsion process that can be used, for example, to make particles having vinyl alcohol monomer units and vinyl formal monomer units. As shown in FIGS. 4A-4C, a drop generator 500 (e.g., a pipette, a needle) forms drops 510 of an organic solution including an organic solvent, a therapeutic agent, and a polymer including vinyl alcohol monomer units and vinyl formal monomer units. Examples of organic solvents include glacial acetic acid, N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO). In certain embodiments, the organic solvent can be an aprotic polar solvent (e.g., DMF), which can dissolve both polar therapeutic agents and some non-polar therapeutic agents. In some embodiments, the organic solution can include at least about five weight percent and/or at most about 100 weight percent of the organic solvent. In general, as the concentration of the polymer in the organic solution increases, the sizes and/or masses of the particles that are formed from the organic solution can also increase. Typically, as the volume of organic solvent in the organic solution that is used to form drops 510 decreases, the rate at which particles form can increase. Generally, the rate of particle formation can increase as the volume of organic solvent that is used decreases.

Without wishing to be bound by theory, it is believed that this occurs because the organic solvent can evaporate from drops 510 more quickly during the particle formation process.

After they are formed, drops 510 fall from drop generator 500 into a vessel 520 that contains an aqueous solution including water (e.g., from about 50 milliliters to about 100 milliliters of water) and a surfactant. Examples of surfactants include lauryl sulfate, polyvinyl alcohols, poly(vinyl pyrrolidone) (PVP), and polysorbates (e.g., Tween® 20, Tween® 80). The concentration of the surfactant in the aqueous solution can be at least about 0.1 percent w/v, and/or at most about 20 percent w/v. For example, in some embodiments, the solution can include about one percent w/v lauryl sulfate. Generally, as the concentration of the surfactant in the aqueous solution increases, the sphericity of the particles that are produced from the drop generation process, and the rate of formation of the particles during the particle formation process, can also increase. In some embodiments, the aqueous solution can be at a temperature of at least about freezing temperature and/or at most about 100°C. Typically, as the temperature of the aqueous solution increases, the rate at which particles (e.g., relatively rigid particles) form can also increase.

As FIG. 4B shows, after drops 510 have fallen into vessel 520, the solution is mixed (e.g., homogenized) using a stirrer 530. In some embodiments, the solution can be mixed for a period of at least about one minute and/or at most about 24 hours. In certain embodiments, mixing can occur at a temperature of at least about freezing temperature and/or at most about 100°C. The mixing results in a suspension 540 including particles 100 suspended in the solvent (FIG. 4C).

After particles 100 have been formed, they are separated from the solvent by, for example, filtration (e.g., through a drop funnel, filter paper, and/or a wire mesh), centrifuging followed by removal of the supernatant, and/or decanting. Thereafter, particles 100 are dried (e.g., by evaporation, by vacuum drying, by air drying). In some embodiments, combinations of drying methods can be used. In certain embodiments, after being formed, particles 100 can be stored in a carrier fluid, such as saline. In some embodiments, particles 100 can be stored in deionized water. Examples of such processes are disclosed, for example, in U.S. Patent Application **[Attorney Docket: 01194-495001]** which is hereby incorporated by reference.

While pipettes and needles have been described as examples of drop generators that can be used in a particle formation process, in some embodiments, other types of drop generators or drop generator systems can be used in a particle formation process. For example, FIG. 5 shows a drop generator system 601 that includes a flow controller 600, a viscosity controller 605, a drop generator 610, and a vessel 620. Flow controller 600 delivers a solution (e.g., a solution including a solvent, a therapeutic agent, and a polymer including vinyl formal monomer units) to viscosity controller 605, which heats the solution to reduce its viscosity prior to delivery to drop generator 610. The solution then passes through an orifice in a nozzle in drop generator 610, resulting in the formation of drops of the solution. The drops are then directed into vessel 620, which contains, for example, an aqueous solution including a surfactant such as polyvinyl alcohol (PVA). Drop generators are described, for example, in Lanphere et al., U.S. Patent Application Publication No. US 2004/0096662 A1, published on May 20, 2004, and entitled "Embolization", and in DiCarlo et al., U.S. Patent Application Serial No. 11/111,511, filed on April 21, 2005, and entitled "Particles", both of which are incorporated herein by reference.

While certain embodiments have been described, other embodiments are possible.

As another example, in some embodiments, 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 Bourne et al., U.S. Patent Application Publication No. US 2003/0233150 A1, published on December 18, 2003, and entitled "Tissue Treatment", which is incorporated herein by reference.

As an additional example, in certain embodiments, particles can be used to treat trauma and/or to fill wounds. In some embodiments, the particles can include one or more bactericidal agents and/or bacteriostatic agents.

As a further example, while compositions including particles suspended in at least one carrier fluid have been described, in certain embodiments, particles may not be suspended in any carrier fluid. For example, particles alone can be contained within a syringe, and can be injected from the syringe into tissue during a tissue ablation procedure and/or a tissue bulking procedure.

As an additional example, in some embodiments, particles having different shapes, sizes, physical properties, and/or chemical properties can be used together in a procedure (e.g., an embolization procedure). The different particles can be delivered into the body of a subject in a predetermined sequence or simultaneously. In certain embodiments, mixtures of different particles can be delivered using a multi-lumen catheter and/or syringe. In some embodiments, particles having different shapes and/or sizes can be capable of interacting synergistically (e.g., by engaging or interlocking) to form a well-packed occlusion, thereby enhancing embolization. Particles with different shapes, sizes, physical properties, and/or chemical properties, and methods of embolization using such particles are described, for example, in Bell et al., U.S. Patent Application Publication No. US 2004/0091543 A1, published on May 13, 2004, and entitled "Embolic Compositions", and in DiCarlo et al., U.S. Patent Application Publication No. US 2005/0095428 A1, published on May 5, 2005, and entitled "Embolic Compositions", both of which are incorporated herein by reference.

As a further example, in some embodiments in which a particle including a polymer is used for embolization, the particle can also include (e.g., encapsulate) one or more embolic agents, such as a sclerosing agent (e.g., ethanol), a liquid embolic agent

(e.g., n-butyl-cyanoacrylate), and/or a fibrin agent. The other embolic agent(s) can enhance the restriction of blood flow at a target site.

As another example, in some embodiments, a treatment site can be occluded by using particles in conjunction with other occlusive devices. For example, particles can be used in conjunction with coils. Coils are described, for example, in Elliott et al., U.S. Patent Application Serial No. 11/000,741, filed on December 1, 2004, and entitled "Embolic Coils", and in Buiser et al., U.S. Patent Application Serial No. 11/311,617, filed on December 19, 2005, and entitled "Coils", both of which are incorporated herein by reference. In certain embodiments, particles can be used in conjunction with one or more gels. Gels are described, for example, in Richard et al., U.S. Patent Application Publication No. US 2006/0045900 A1, published on March 2, 2006, and entitled "Embolization", which is incorporated herein by reference. Additional examples of materials that can be used in conjunction with particles to treat a target site in a body of a subject include gel foams, glues, oils, and alcohol.

As a further example, while particles including a polymer have been described, in some embodiments, other types of medical devices and/or therapeutic agent delivery devices can include such a polymer. For example, in some embodiments, a coil can include a polymer as described above. In certain embodiments, the coil can be formed by flowing a stream of the polymer into an aqueous solution, and stopping the flow of the polymer stream once a coil of the desired length has been formed. Coils are described, for example, in Elliott et al., U.S. Patent Application Serial No. 11/000,741, filed on December 1, 2004, and entitled "Embolic Coils", and in Buiser et al., U.S. Patent Application Serial No. 11/311,617, filed on December 19, 2005, and entitled "Coils", both of which are incorporated herein by reference. In certain embodiments, sponges (e.g., for use as a hemostatic agent and/or in reducing trauma) can include a polymer as described above. In some embodiments, coils and/or sponges can be used as bulking agents and/or tissue support agents in reconstructive surgeries (e.g., to treat trauma and/or congenital defects).

Other embodiments are in the claims.

Claims

1. A particle, comprising:

a polymer comprising vinyl alcohol monomer units; and

a chemical species covalently bonded to the polymer,

wherein the chemical species is selected from the group consisting of polymers, oligomers and monomers, and the particle has a maximum dimension of 5,000 microns or less.

2. The particle of claim 1, wherein the polymer comprises at least five weight percent vinyl alcohol monomers.

3. The particle of claim 1, wherein the polymer further comprises vinyl formal monomer units.

4. The particle of claim 3, wherein the polymer comprises at least five weight percent vinyl formal monomer units.

5. The particle of claim 1, wherein the polymer further comprises vinyl acetate monomer units.

6. The particle of claim 5, wherein the polymer further comprises vinyl formal monomer units.

7. The particle of claim 1, wherein the polymer includes pores.

8. The particle of claim 7, wherein the chemical species is at least partially disposed in the pores of the polymer.

9. The particle of claim 1, wherein the chemical species is coated on a surface of the polymer.

10. The particle of claim 9, wherein the particle includes pores.

11. The particle of claim 1, wherein the particle further comprises a therapeutic agent.

12. The particle of claim 11, wherein the therapeutic agent is bonded to the chemical species.

13. The particle of claim 1, wherein the polymer is cross-linked.

14. The particle of claim 1, wherein the chemical species comprises a polymer.

15. The particle of claim 14, wherein the polymer is selected from the group consisting of polystyrene sulfonic acid, polyvinylsulfonic acid, polyacrylic acid and polydimethylaminoethyl acrylate.

16. A particle, comprising:

a polymer comprising at least five weight percent vinyl alcohol monomer units and at least five weight percent vinyl formal monomer units;

a chemical species covalently bonded to the polymer; and

a therapeutic agent,

wherein:

the chemical species is selected from the group consisting of polymers, oligomers and monomers; and

the particle has a maximum dimension of 5,000 microns or less.

17. The particle of claim 16, wherein the therapeutic agent is bonded to the chemical species.

18. A composition, comprising:

a carrier fluid; and

a plurality of particles in the carrier fluid,

wherein:

at least some of the plurality of particles have a maximum dimension of 5,000 microns or less and comprise a polymer comprising vinyl alcohol monomer units and a chemical species covalently bonded to the polymer; and

the chemical species is selected from the group consisting of polymers, oligomers and monomers.

19. The composition of claim 18, wherein the polymer includes pores, and the chemical species is at least partially disposed in the pores of the polymer.

20. The composition of claim 18, wherein the chemical species is coated on a surface of the polymer.

21. The composition of claim 18, wherein the particle further comprises a therapeutic agent.

22. The composition of claim 22, wherein the therapeutic agent is bonded to the chemical species.

23. A method, comprising:

forming a particle comprising a polymer comprising vinyl alcohol monomer units;

contacting the polymer with a chemical species selected from the group consisting of polymers, oligomers and monomers; and

exposing the polymer and the chemical species to radiation to bond the chemical species to the polymer to form a particle comprising the chemical species bonded to the polymer,

wherein the particle comprising the chemical species bonded to the polymer has a maximum dimension of 5,000 microns or less.

24. The method of claim 23, wherein the particle has pores, and the chemical species is disposed in the pores of the polymer.

25. The method of claim 23, wherein the chemical species is coated on a surface of the polymer.

26. The method of claim 23, further comprising contacting a therapeutic agent with the particle comprising the chemical species bonded to the polymer.

27. The method of claim 26, wherein the therapeutic agent is bonded to the chemical species.

28. The method of claim 23, wherein the radiation is selected from the group consisting of electron beam radiation and gamma radiation.

29. The method of claim 23, wherein the exposing the polymer and the chemical species to radiation cross-links the polymer.

30. A method, comprising:

forming a particle comprising a polymer comprising at least five weight percent vinyl alcohol monomer units and at least five weight percent vinyl formal monomer units;

contacting the polymer with a chemical species selected from the group consisting of polymers, oligomers and monomers;

exposing the polymer and the chemical species to radiation to bond the chemical species to the polymer to form a particle comprising the chemical species bonded to the polymer; and

contacting a therapeutic agent with the particle comprising the chemical species bonded to the polymer,

wherein the particle comprising the chemical species bonded to the polymer has a maximum dimension of 5,000 microns or less.

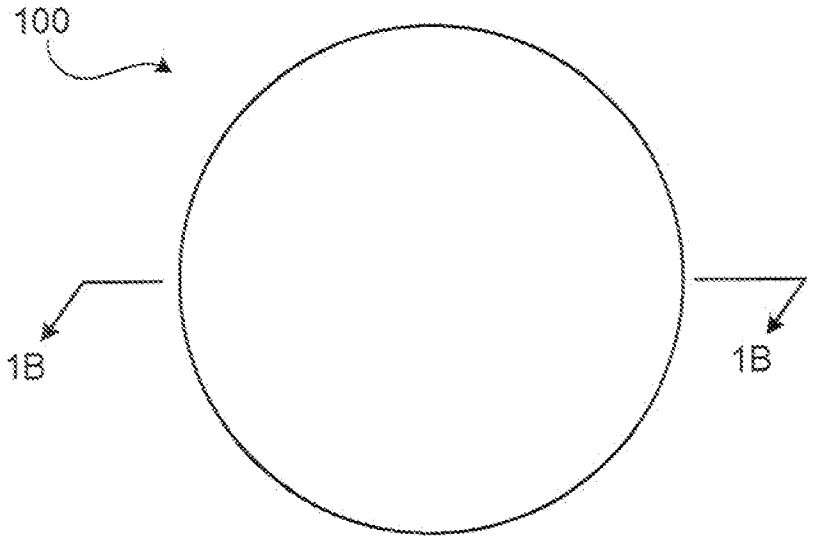


FIG. 1A

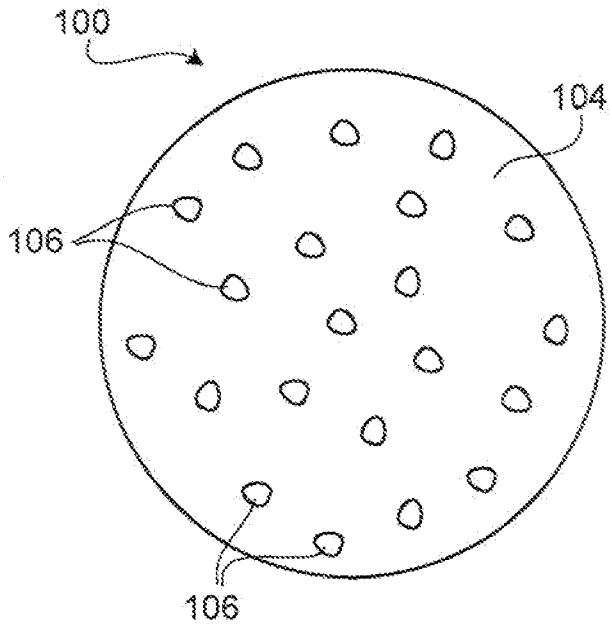


FIG. 1B

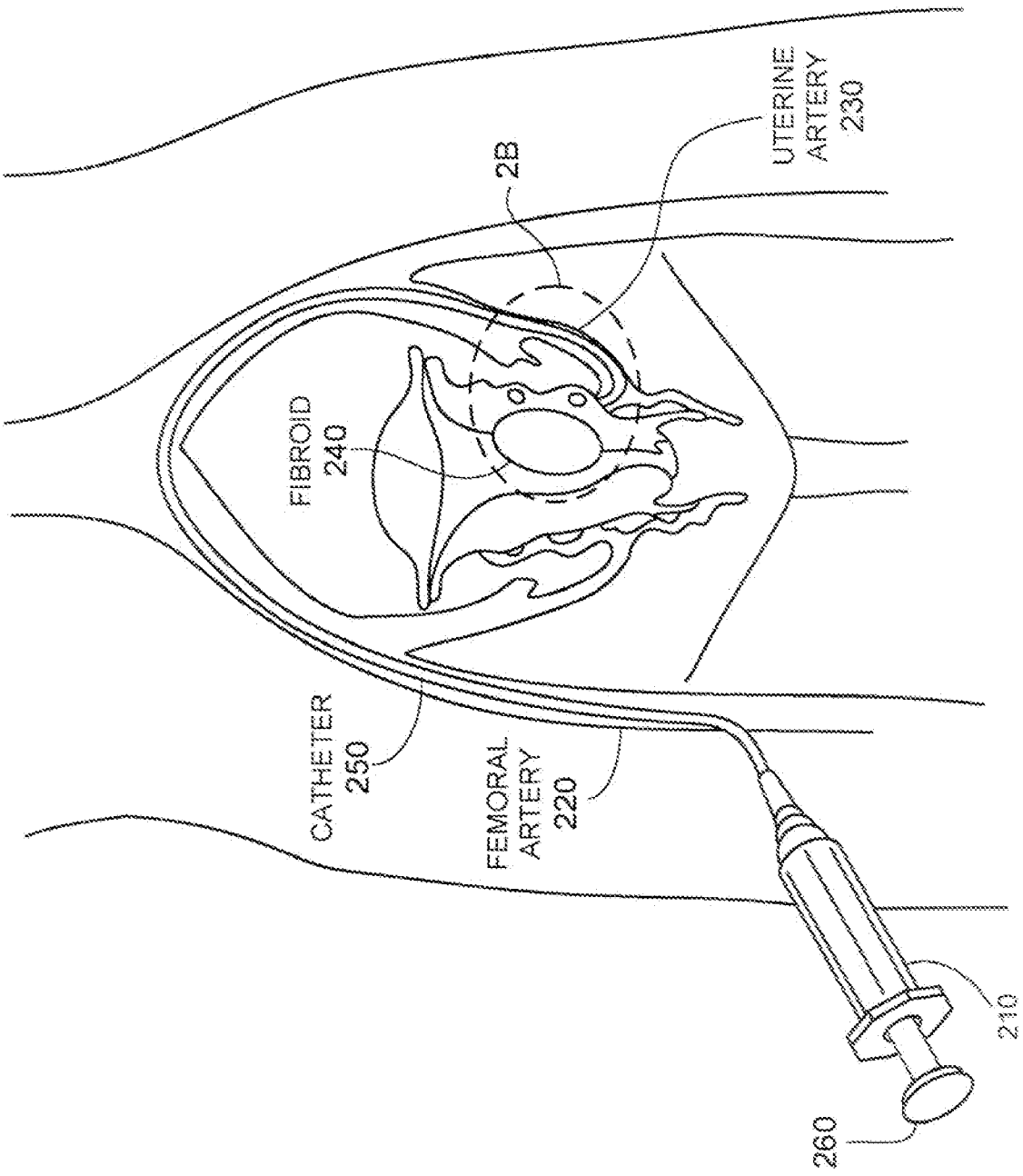

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FIG. 2A

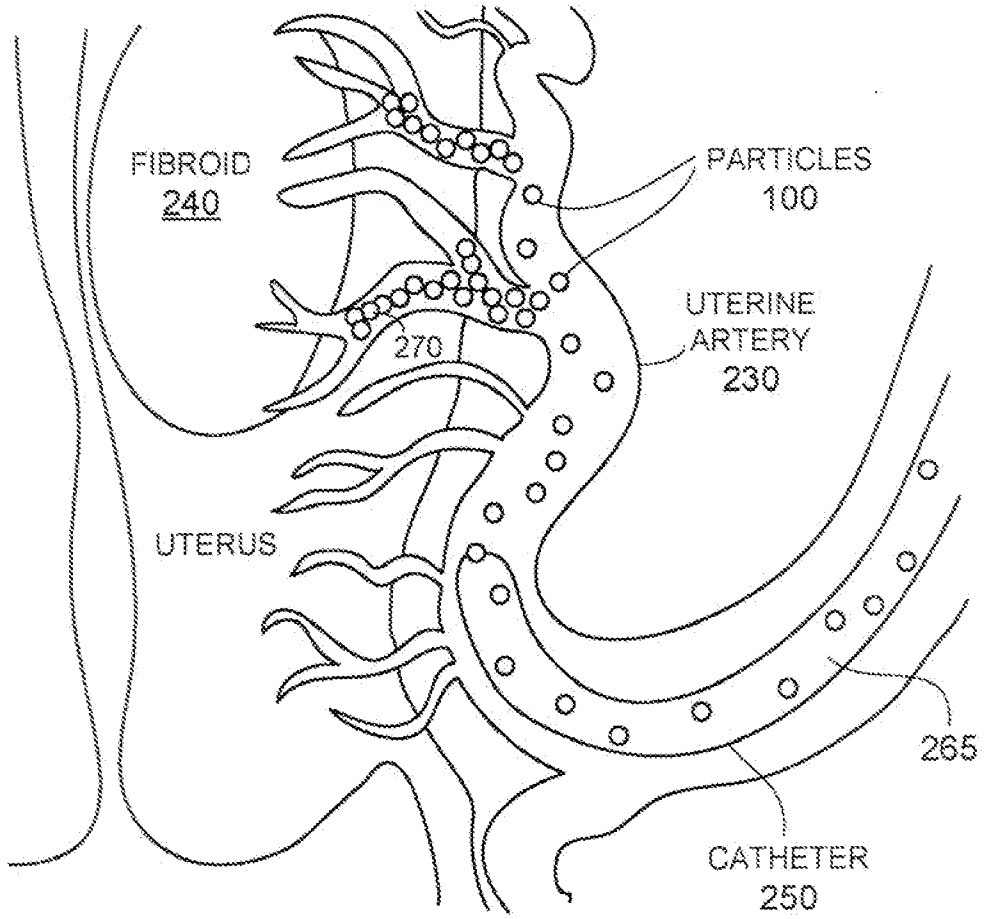
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FIG. 2B

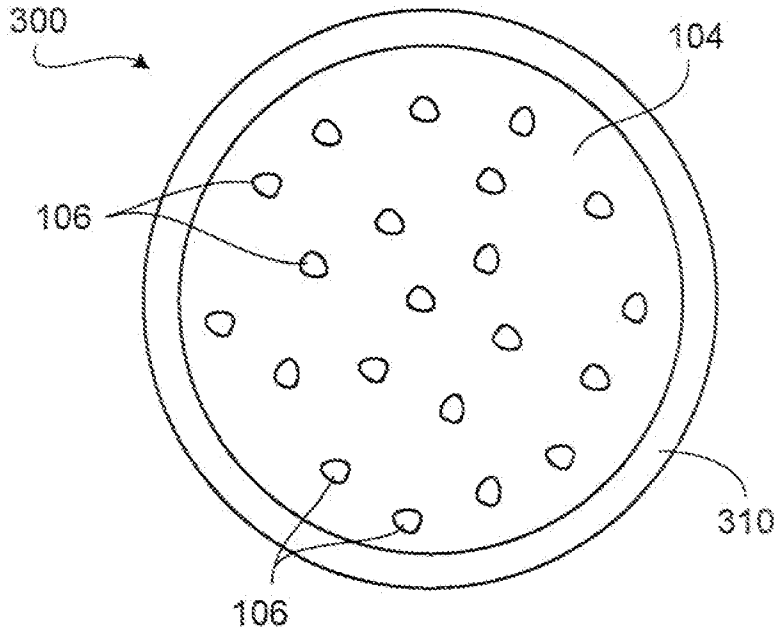

FIG. 3

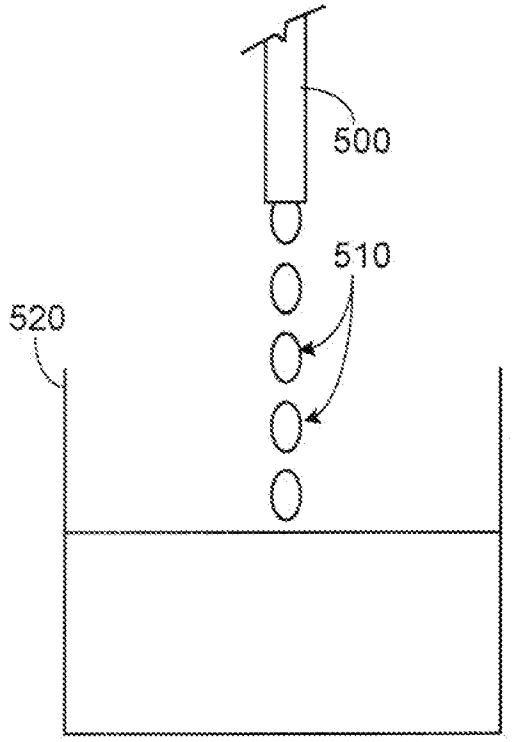

FIG. 4A

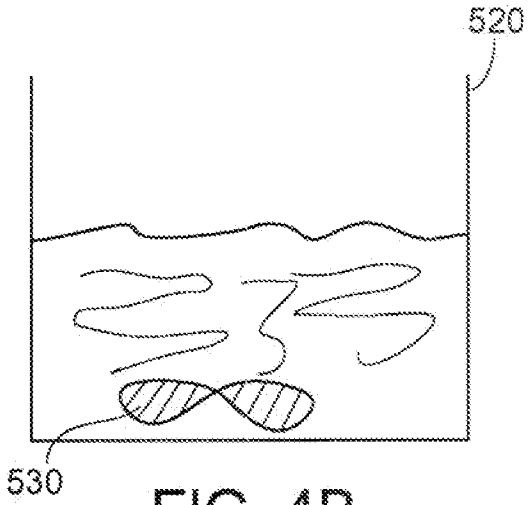

FIG. 4B

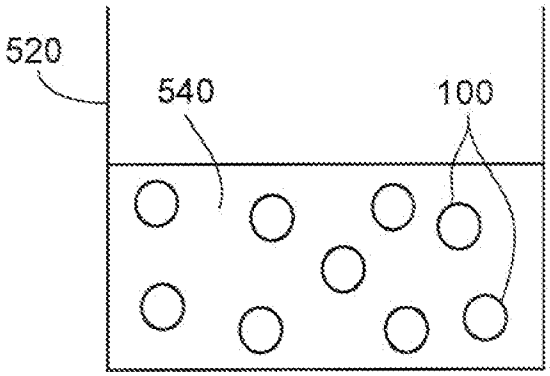

FIG. 4C

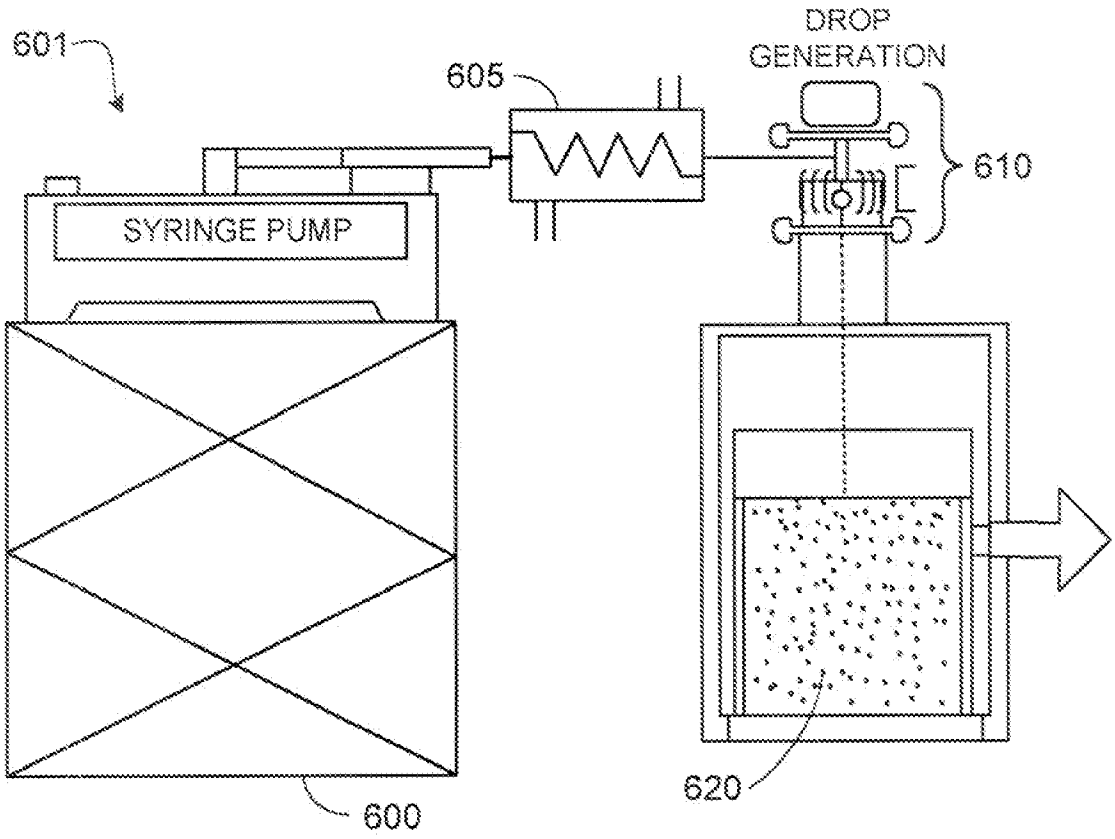

FIG. 5