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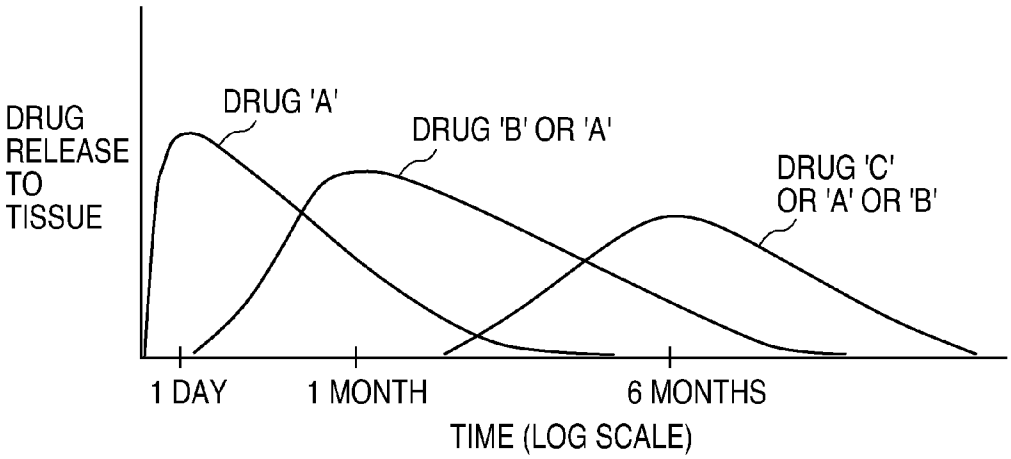

FIG. 2

(57) Abstract: Medical devices comprising nanobeads encapsulating one or more bioactive agents and methods of use thereof are provided.

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NANOBEAD RELEASING MEDICAL DEVICES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is generally related to nanoparticle releasing medical devices, such as drug delivery vascular stents.

Description of the State of the Art

Stents are used not only as a mechanical intervention of vascular conditions but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents which have been applied in PTCA (Percutaneous Transluminal Coronary Angioplasty) procedures include stents illustrated in U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No. 4,886,062 issued to Wiktor.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects on the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results.

In many patients, especially diabetic patients, stentable lesions are focal manifestations of widespread vascular disease. The advent of drug eluting stents has brought relief from restenosis of the treated lesion, but leaves progression of regional vascular disease unaddressed.

The embodiments described below address the above-identified problems.

SUMMARY

In some embodiments, provided herein is a medical device comprising a coating. The coating comprises nanobeads embedded in a slurry. The coating provides for a customizable controlled release of a bioactive agent or agents encapsulated in the nanobeads. The slurry can include a polymer or a non-polymer material. In some embodiments, the slurry comprises a material that can be one of ceramic materials, bioglass, polymer, and combinations thereof. The medical device can be any drug delivery device, some examples of which are stent.

In some embodiments, the nanobeads can include a first plurality of nanobeads that encapsulate a first bioactive agent and a second plurality of nanobeads that encapsulate a second bioactive agent. The first plurality of nanobeads and the second plurality of nanobeads can be embedded in the same layer of coating or in different layers of coating, e.g., a first layer comprising the first plurality of nanobeads, and a second layer comprising the second plurality of nanobeads. In some embodiments, the nanobeads can comprise a third plurality of nanobeads that encapsulate a third bioactive agent. The first plurality of nanobeads, the second plurality of nanobeads, and third plurality of nanobeads that encapsulate a third bioactive agent can be embedded in the same layer of slurry coating or in different layers of slurry coating, e.g., a first layer comprising the first plurality of nanobeads, a second layer comprising the second plurality of nanobeads, and a

third layer comprising the third bioactive agent. In some embodiments, the first bioactive agent, the second bioactive agent, and/or the third bioactive agent are the same or different.

In some embodiments, the nanobeads can include more than three pluralities of nanobeads incorporating more than three bioactive agents included in more than three different layers, the first layer including the first plurality of nanobeads, the second layer including the second plurality of nanobeads, the third layer including the third plurality of nanobeads, the fourth layer including the fourth plurality of nanobeads, etc. These agents can be the same or different.

The bioactive agents can be any diagnostic, therapeutic, or prophylactic agent. Some examples of the bioactive agents are paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, 40-epi-(N1-tetrazolyl)-rapamycin (ABT-578), TAFA-93, biolimus-7, biolimus-9, clobetasol, pimecrolimus, imatinib mesylate, midostaurin, prodrugs thereof, co-drugs thereof, or combinations thereof.

The medical device described herein can be used to treat, prevent or ameliorate a medical condition in a patient by implanting in the patient the medical device and causing nanobeads in the medical device to release from the medical device so as to release the bioactive agent(s) to treat, prevent, or ameliorate the medical condition. Some examples of medical conditions or disorders that can be treated, prevented, or ameliorated by the medical device described herein include, but are not limited to, atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication, anastomotic proliferation for vein and

artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows two examples of a coating including nanobeads of the present invention;

Figure 2 shows a release profile of drug A, drug B, and drug C from a coating including the nanobeads of the present invention.

DETAILED DESCRIPTION

In some embodiments, provided herein is a medical device comprising a coating. The coating comprises nanobeads embedded in a slurry. The coating provides for a customizable controlled release of a bioactive agent or agents encapsulated in the nanobeads. The slurry can include a polymer or a non-polymer material. In some embodiments, the slurry comprises a material that can be one of ceramic materials, bioglass, polymer, and combinations thereof. The medical device can be any drug delivery device, some examples of which are stent.

In some embodiments, the nanobeads can include a first plurality of nanobeads that encapsulate a first bioactive agent and a second plurality of nanobeads that encapsulate a second bioactive agent. The first plurality of nanobeads and the second plurality of nanobeads can be embedded in the same layer of coating or in different layers of coating, e.g., a first layer comprising the first plurality of nanobeads, and a second layer comprising the second plurality of nanobeads. In some embodiments, the nanobeads can comprise a third plurality of nanobeads that encapsulate a third bioactive agent. The first plurality of nanobeads, the second plurality of nanobeads, and third plurality of nanobeads that encapsulate a third bioactive agent can be embedded in the same layer of slurry coating or in different layers of slurry coating, e.g., a first layer comprising the first plurality of nanobeads, a second layer comprising the second plurality of nanobeads, and a

third layer comprising the third bioactive agent. In some embodiments, the first bioactive agent, the second bioactive agent, and/or the third bioactive agent are the same or different.

In some embodiments, the nanobeads can include more than three pluralities of nanobeads incorporating more than three bioactive agents included in more than three different layers, the first layer including the first plurality of nanobeads, the second layer including the second plurality of nanobeads, the third layer including the third plurality of nanobeads, the fourth layer including the fourth plurality of nanobeads, etc. These agents can be the same or different.

The bioactive agents can be any diagnostic, therapeutic, or prophylactic agent. Some examples of the bioactive agents are paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, 40-epi-(N1-tetrazolyl)-rapamycin (ABT-578), TAFA-93, biolimus-7, biolimus-9, clobetasol, pimecrolimus, imatinib mesylate, midostaurin, prodrugs thereof, co-drugs thereof, or combinations thereof.

The medical device described herein can be used to treat, prevent or ameliorate a medical condition in a patient by implanting in the patient the medical device and causing nanobeads in the medical device to release from the medical device so as to release the bioactive agent(s) to treat, prevent, or ameliorate the medical condition. Some examples of medical conditions or disorders that can be treated, prevented, or ameliorated by the medical device described herein include, but are not limited to, atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication, anastomotic proliferation for vein and

artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, and combinations thereof.

As used herein, the term "naonparticles" and "nanobeads" can be used interchangeably. The term "nanocapsules" refers to nanoparticles having a shell encapsulating a bioactive agent. The term "matrix nanoparticles" refers to nanoparticles that do not have a shell where a bioactive agent(s) is dispersed in the matrix of the nanoparticles.

The nanobeads generally have a size a size in the range from about 1 nm to over 1000 nm, e.g., about 5 nm, about 10 nm, about 20 nm, about 50 nm, about 80 nm, about 90 nm, about 95 nm, about 100 nm, about 200 nm, about 500 nm, about 800 nm, about 900 nm, about 1000 nm or about 1500 nm. In some embodiments, the nanobeads can have a size from about 10 nm to about 1000 nm, from about 20 nm to aobut 500 nm, or from about 50 nm to about 200 nm.

The coating provides for controlled release of the drug(s) through use of different physical and chemical features of the encapsulating matrix or membrane. Once a medical device to which the nanoparticles are coated onto is deployed, the membrane of nanobeads encapsulating a bioactive agent can open up, releasing the drug(s) at controlled intervals and/or levels. Use of different physical and chemical features of the encapsulating membrane(s) / macromolecules / polymers / gels (e.g., microscopic spheres) and drug(s) (e.g., varying-thickness nanoencapsulating membranes, nanoencapsulating membranes of different chemical or physical character, or some combination of these features) leads to modulation of release profile of the bioactive agent in the nanobeads.

The nanobeads can provide a variety of delivery profiles of a bioactive agent. For instance, in some embodiments, the nanobeads can have a layered construct including different layers of spheres such that the outermost spheres have the least (or most) thick

membranes (or their equivalent in terms of physical or chemical character) and the innermost spheres might have the greatest (or least) membrane thickness (or equivalent), with intermediate layers such that the overall effect is to provide for a controlled or graduated release of a drug or drugs in terms of time and intensity of the drug and different drugs with different properties (chemical physical and biological) in nanobeads of each layer to target different layers of arterial tissue.

Figure 1 shows an embodiment of the present invention, which is a coating design on a stent that includes the nanobeads described herein. The coating includes a slurry having drug A nanobeads and drug B nanobeads. The porosity and slurry to nanobead ratio can be varied to change drug total content and drug/s release rate characteristics.

Figure 2 shows the release profile of drug A, drug B and drug C from a coating of the present invention that includes nanobeads of drug A, drug B, and drug C. The curve for Drug A provides an initial drug dose to prevent initial inflammation from the trauma to the vessel during stenting. Drug B as indicated by its curve can be introduced at a later date to continue the healing process. Drug C as indicated by its curve can be introduced to stop "late loss" or restenosis that occurs after say 6months or 1 or 2 years. In some embodiments, an alternative approach can be to use drug A on 3 curves or one tailored curve. The number of drugs and the curve shape can be designed specifically for the individual patient, taking into account diabetes, age, gender and other factors.

In some embodiments, an initial burst release of drug(s) from nanobeads can be caused by the pressure onto the nanobeads, e.g., pressure from a stent or a balloon delivery device, with a more graduated response to follow that is not pressure dependent.

In some embodiments, the nanobeads described herein can be used in lieu of or in combination with available coating systems for drug delivery stents. In some embodiments, the nanobeads can be used as non-stent delivery systems.

To facilitate the release of nanobeads from the vessel wall, in some embodiments, a patient can ingest or have delivered into the bloodstream a small molecule drug, chemical agent or catalyst to Activate/facilitate release of a drug or biopharmaceuticals that are in nanobeads, thus allowing the physician to externally control and very the rate of delivery from the nanobeads of the drug or biopharmaceuticals into the vessel wall. The doctor will thus be able to change the rate of release based upon the evolving assessment of the patient The mechanism for activating the nanobeads contents could be by allowing the external agent to react with the slurry, the nonobead material or the nonobead contents in such a way that the properties were changed to allow the drug to release. In another embodiment the oral or blood stream delivered drug or other substance would itself have a therapeutic effect. In still another embodiment the oral or blood stream delivered drug or other substance together with the nonobead contents would provide a therapeutic effect different than the individual effect of each alone. In this way the combined effect could provide a much broader and varied therapy. Such small molecule drug, chemical agent or catalyst can be anything that facilitates the release of nanobeads from a module including such nanobeads. For example, a small molecule drug, chemical agent or catalyst can be membrane disruptive or can change the aciditity/basicity or enzyme activity surrounding the module. Administration of the small molecule drug, chemical agent or catalyst can therefore cause the nanobeads to be released from the module in the vessel wall.

In some embodiments, a magnetic material(s) (compound or element) can be included in nanobeads. This can allow an electromagnetic source located external to the vascular system to provide for the release of these nanobeads and to direct where they concentrate in the vascular system. Magnetic materials can be any biocompatible magnetic material. Some examples are materials containing iron, platinum elements or compounds. In some embodiments, magnetic materials can be made biocompatible by

using a biocompatible coating (e.g., a coating formed of a biocompatible polymeric or non-polymeric material).

Methods of forming nanobead delivery systems

In some embodiments, to effect a sustained delivery of the nanobeads, the nanobeads containing a drug can be chemically bonded to a drug delivery system. In some embodiments, the nanobeads can be embedded in a slurry. Such slurry can be, e.g., a biodurable, biodegradable or bioabsorbable material, such as polymer, ceramic, or bioglass.

In some embodiments, chemically attaching the nanobeads to the delivery system can be achieved by coupling the functional groups on the surface of nanobeads and the delivery system. In some embodiments, chemically attaching the nanobeads to the delivery system can be achieved by grafting, e.g., by causing groups on the surface of the nanobeads to bind to the surface of the delivery system. In some embodiments, chemically attaching the nanobeads to the delivery system can be achieved by modification of surface of the nanobeads or the delivery system by attaching silane or siloxane groups to the surface of the nanobeads or the delivery system and then causing the nanobeads to be attached to delivery system via the silane or siloxane groups. The attaching methods are well established in the art (see, e.g., Greg T. Hermanson, "Bioconjugate Techniques", Academic Pree, Elsevier, 1996; J. Biomed. Mater. Res., 60, 472; Langmuer, 18 (2002) 4090; Appl. Polym. Sci., 22,643-664; Macromolecules 34, 7236; J. Ame. Chem. Soc. (2003), 125, 1788; J. Biomed. Mater. Res. (2003), 65A, 196; Macromolecules 26, 5698; Advanced Drug Delivery Reviews, 43, (2002) 3-12, 457-458; J. Polymer Sci. A, Polymer Chem, 28, 219 (1990); Nature, 378, 472 (1995); Nature 411, 59 (2001); Bioconj Chem.. 14, 517 (2003); Trans Amer. Soc. Artif Inst Organs, 18, 10 (1972); US Patent # 4,424,311; J, Adhes. Sci. Technol. 7, 1065-1076 (1993); Biomaterila 23 (2002)

2043-2056; J. Ame. Chem. Soc., vol 115, No. 23m 1993, 10715; J Polymer Sci., Symposium No. 51, 135-153 (1975); Angew. Chem.., Int. Ed., 2006, 45, 2-20; Anticancer drugs, 16, 243-254; J.Contr.Res., 61, 137 (1999); Macromol Symposia, 172, 49 (2001); Biomaterial, 24, 4495 (2003); Macromoecules (2001) 34, 8657; Macromol Biosci (2004) 4, 192.

Nanobeads can be readily formed according to methods established in the art. Some examples of forming nanobeads are described in Seshadri and Sivasubramanian, Drug Delivery Technology, 7(3):39-46 (2007). Some other methods are described in the references described above.

Biocompatible polymers

Any biocompatible polymers can be included in the nanobeads described above and/or a coating including the nanobeads. The biocompatible polymer can be biodegradable (either bioerodable or bioabsorbable or both) or nondegradable, and can be hydrophilic or hydrophobic.

Representative biocompatible polymers include, but are not limited to, poly(ester amide), polyhydroxyalkanoates (PHA), poly(3-hydroxyalkanoates) such as poly(3-hydroxypropanoate), poly(3-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxyhexanoate), poly(3-hydroxyheptanoate) and poly(3-hydroxyoctanoate), poly(4-hydroxyalkanaote) such as poly(4-hydroxybutyrate), poly(4-hydroxyvalerate), poly(4-hydroxyhexanote), poly(4-hydroxyheptanoate), poly(4-hydroxyoctanoate) and copolymers including any of the 3-hydroxyalkanoate or 4-hydroxyalkanoate monomers described herein or blends thereof, poly(D,L-lactide), poly(L-lactide), polyglycolide, poly(D,L-lactide-co-glycolide), poly(L-lactide-co-glycolide), polycaprolactone, poly(lactide-co-caprolactone), poly(glycolide-co-caprolactone), poly(dioxanone), poly(ortho esters), poly(anhydrides), poly(tyrosine carbonates) and derivatives thereof, poly(tyrosine ester)

and derivatives thereof, poly(imino carbonates), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), polycyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyphosphazenes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride, polyvinyl ethers, such as polyvinyl methyl ether, polyvinylidene halides, such as polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate, copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers, polyamides, such as Nylon 66 and polycaprolactam, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, poly(glyceryl sebacate), poly(propylene fumarate), poly(n-butyl methacrylate), poly(sec-butyl methacrylate), poly(isobutyl methacrylate), poly(tert-butyl methacrylate), poly(n-propyl methacrylate), poly(isopropyl methacrylate), poly(ethyl methacrylate), poly(methyl methacrylate), epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, polyethers such as poly(ethylene glycol) (PEG), copoly(ether-esters) (e.g. poly(ethylene oxide-co-lactic acid) (PEO/PLA)), polyalkylene oxides such as poly(ethylene oxide), poly(propylene oxide), poly(ether ester), polyalkylene oxalates, phosphoryl choline, choline, poly(aspirin), polymers and co-polymers of hydroxyl bearing monomers such as 2-hydroxyethyl methacrylate (HEMA), hydroxypropyl methacrylate (HPMA), hydroxypropylmethacrylamide, PEG acrylate (PEGA), PEG methacrylate, 2-methacryloyloxyethylphosphorylcholine (MPC) and *n*-vinyl pyrrolidone (VP), carboxylic acid bearing monomers such as methacrylic acid (MA),

acrylic acid (AA), alkoxymethacrylate, alkoxyacrylate, and 3-trimethylsilylpropyl methacrylate (TMSPMA), poly(styrene-isoprene-styrene)-PEG (SIS-PEG), polystyrene-PEG, polyisobutylene-PEG, polycaprolactone-PEG (PCL-PEG), PLA-PEG, poly(methyl methacrylate)-PEG (PMMA-PEG), polydimethylsiloxane-co-PEG (PDMS-PEG), poly(vinylidene fluoride)-PEG (PVDF-PEG), PLURONIC™ surfactants (polypropylene oxide-co-polyethylene glycol), poly(tetramethylene glycol), hydroxy functional poly(vinyl pyrrolidone), biomolecules such as collagen, chitosan, alginate, fibrin, fibrinogen, cellulose, starch, dextran, dextrin, hyaluronic acid, fragments and derivatives of hyaluronic acid, heparin, fragments and derivatives of heparin, glycosamino glycan (GAG), GAG derivatives, polysaccharide, elastin, or combinations thereof. In some embodiments, the nanoparticles can exclude any one of the aforementioned polymers.

As used herein, the terms poly(D,L-lactide), poly(L-lactide), poly(D,L-lactide-co-glycolide), and poly(L-lactide-co-glycolide) can be used interchangeably with the terms poly(D,L-lactic acid), poly(L-lactic acid), poly(D,L-lactic acid-co-glycolic acid), or poly(L-lactic acid-co-glycolic acid), respectively.

In some embodiments, the nanobeads described herein or a slurry including the nanobeads can further include a biobeneficial material. The biobeneficial material can be a polymeric material or non-polymeric material. The biobeneficial material is preferably non-toxic, non-antigenic and non-immunogenic. A biobeneficial material is one which enhances the biocompatibility of the particles or device by being non-fouling, hemocompatible, actively non-thrombogenic, or anti-inflammatory, all without depending on the release of a pharmaceutically active agent.

Bioactive Agents

The bioactive agents encapsulated in the nanobeads described herein can be any bioactive agent, which is a therapeutic, prophylactic, or diagnostic agent. These agents

can have anti-proliferative or anti-inflammatory properties or can have other properties such as antineoplastic, antiplatelet, anti-coagulant, anti-fibrin, antithrombonic, antimitotic, antibiotic, antiallergic, and antioxidant. The agents can be cystostatic agents, agents that promote the healing of the endothelium such as NO releasing or generating agents, agents that attract endothelial progenitor cells, or agents that promote the attachment, migration and proliferation of endothelial cells (e.g., natriuretic peptide such as CNP, ANP or BNP peptide or an RGD or cRGD peptide), while quenching smooth muscle cell proliferation. Examples of suitable therapeutic and prophylactic agents include synthetic inorganic and organic compounds, proteins and peptides, polysaccharides and other sugars, lipids, and DNA and RNA nucleic acid sequences having therapeutic, prophylactic or diagnostic activities. Some other examples of the bioactive agent include antibodies, receptor ligands, enzymes, adhesion peptides, blood clotting factors, inhibitors or clot dissolving agents such as streptokinase and tissue plasminogen activator, antigens for immunization, hormones and growth factors, oligonucleotides such as antisense oligonucleotides and ribozymes and retroviral vectors for use in gene therapy. Examples of anti-proliferative agents include rapamycin and its functional or structural derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), and its functional or structural derivatives, paclitaxel and its functional and structural derivatives. Examples of rapamycin derivatives include 40-epi-(N1-tetrazolyl)-rapamycin (ABT-578), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin. Examples of paclitaxel derivatives include docetaxel. Examples of antineoplastics and/or antimitotics include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include

sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, thrombin inhibitors such as Angiomax (Biogen, Inc., Cambridge, Mass.), calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), nitric oxide or nitric oxide donors, super oxide dismutases, super oxide dismutase mimetic, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), estradiol, anticancer agents, dietary supplements such as various vitamins, and a combination thereof. Examples of anti-inflammatory agents including steroidal and non-steroidal anti-inflammatory agents include tacrolimus, dexamethasone, clobetasol, or combinations thereof. Examples of cytostatic substances include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, NJ). An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, pimecrolimus, imatinib mesylate, midostaurin, bioactive RGD, and genetically engineered endothelial cells. The foregoing substances can also be used in the form of prodrugs or co-drugs thereof. The foregoing substances also include metabolites thereof and/or prodrugs of the metabolites. The

foregoing substances are listed by way of example and are not meant to be limiting. Other active agents which are currently available or that may be developed in the future are equally applicable.

The dosage or concentration of the bioactive agent required to produce a favorable therapeutic effect should be less than the level at which the bioactive agent produces toxic effects and greater than the level at which non-therapeutic results are obtained. The dosage or concentration of the bioactive agent can depend upon factors such as the particular circumstances of the patient, the nature of the trauma, the nature of the therapy desired, the time over which the ingredient administered resides at the vascular site, and if other active agents are employed, the nature and type of the substance or combination of substances.

In some embodiments, the dose will be tailored to the specific anatomy for treatment. Some of these areas are arteries of coronary, cerebral. carotid, renal, iliac, popliteal, tibial, etc. Therapeutic effective dosages can be determined empirically, for example by infusing vessels from suitable animal model systems and using immunohistochemical, fluorescent or electron microscopy methods to detect the agent and its effects, or by conducting suitable in vitro studies. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art. In addition patient state of health, diabetes type of anatomy, type of lesion, severity of lesion and other indicators can be used to determine dose and elution profile.

The bioactive agents described herein can have different release profiles, e.g., fast release (e.g., release of about 50% of the agent within 24 hours), sustained release (e.g., release of about 50% of the agent over a period of days or months), or pulse release profile. In some embodiments, the sustained release profile can be a zero order release.

Examples of Implantable Device

As used herein, an implantable device may be any suitable medical substrate that can be implanted in a human or veterinary patient. Examples of such implantable devices include self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), heart valve prostheses, cerebrospinal fluid shunts, pacemaker electrodes, catheters, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Abbott Vascular, Santa Clara, CA), anastomotic devices and connectors, orthopedic implants such as screws, spinal implants, electro-stimulatory devices. The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), high nitrogen stainless steel, e.g., BIODUR 108, cobalt chrome alloy L-605, "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biodurable (biostable) polymers could also be used with the embodiments of the present invention.

Method of Use

In accordance with embodiments of the invention, the nanoparticles can be released from a medical device (e.g., stent) during delivery and (in the case of a stent) expansion of the device, or thereafter, and released at a desired rate and for a predetermined duration of time at the site of implantation.

Preferably, the medical device is a stent. The stent described herein is useful for a variety of medical procedures, including, by way of example, treatment of obstructions

caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above-described coating is particularly useful for treating diseased regions of blood vessels caused by lipid deposition, monocyte or macrophage infiltration, or dysfunctional endothelium or a combination thereof, or occluded regions of blood vessels caused by abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries and veins.

Representative examples of sites include the iliac, renal, carotid and coronary arteries.

For implantation of a stent, an angiogram is first performed to determine the appropriate positioning for stent therapy. An angiogram is typically accomplished by injecting a radiopaque contrasting agent through a catheter inserted into an artery or vein as an x-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein, and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above-described features may then be mechanically expanded or released to self expand at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

The nanobeads can be used with a stent as described above.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the

appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

We claim:

1. A medical device comprising a coating, the coating comprises nanobeads embedded in a slurry, wherein the coating provides for a controlled release of a bioactive agent or agents encapsulated in the nanobeads.

2. The medical device of claim 1, wherein the slurry of a material is selected from the group consisting of ceramic materials, bioglass, polymer, and combinations thereof,

3. The medical device of claim 1, wherein the nanobeads comprise a first plurality of nanobeads that encapsulate a first bioactive agent and a second plurality of nanobeads that encapsulate a second bioactive agent.

4. The medical device of claim 1, wherein the coating comprises:

a first layer comprising the first plurality of nanobeads, and

a second layer comprising the second plurality of nanobeads.

5. The medical device of claim 3, wherein the coating comprises:

a first layer comprising the first plurality of nanobeads, and

a second layer comprising the second plurality of nanobeads.

6. The medical device of claim 3, wherein the nanobeads further comprises a third plurality of nanobeads that encapsulate a third bioactive agent.

7. The medical device of claim 6, wherein the coating comprises:

a first layer comprising the first plurality of nanobeads,

a second layer comprising the second plurality of nanobeads, and

a third layer comprising the third plurality of nanobeads.

8. The medical device of claim 1, wherein the nanobeads comprise more than three pluralities of nanobeads,

wherein each plurality of nanobeads incorporates a bioactive agent that is the same or different from a bioactive agent included in another plurality of nanobeads.

9. The medical device of claim 8, wherein the coating comprises more than three different layers of coating, and

wherein each plurality of nanobeads is included in each layer of the more than three different layers of coating.

10. The medical device of claim 4, wherein the first bioactive agent and the second bioactive agent are the same or different.

11. The medical device of claim 5, wherein the first bioactive agent and the second bioactive agent are the same or different.

12. The medical device of claim 7, wherein the first bioactive agent, the second bioactive agent, and the third bioactive agent are the same or different.

13. The medical device of claim 1, wherein the slurry comprises a polymer.

14. The medical device of claim 10, wherein the first bioactive agent and the second bioactive agent are independently selected from the group consisting of paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, 40-epi-(N1-tetrazolyl)-rapamycin (ABT-578), TAFA-93, biolimus-7, biolimus-9, clobetasol, pimecrolimus, imatinib mesylate, midostaurin, prodrugs thereof, co-drugs thereof, and a combination thereof.

15. The medical device of claim 11, wherein the first bioactive agent and the second bioactive agent are independently selected from the group consisting of paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide dismutases, super oxide dismutases

mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, 40-epi-(N1-tetrazolyl)-rapamycin (ABT-578), TAFA-93, biolimus-7, biolimus-9, clobetasol, pimecrolimus, imatinib mesylate, midostaurin, prodrugs thereof, co-drugs thereof, and a combination thereof.

16. The medical device of claim 12, wherein the first bioactive agent, the second bioactive agent, and the third bioactive agent are independently selected from the group consisting of paclitaxel, docetaxel, estradiol, nitric oxide donors, super oxide dismutases, super oxide dismutases mimics, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO), tacrolimus, dexamethasone, rapamycin, rapamycin derivatives, 40-*O*-(2-hydroxy)ethyl-rapamycin (everolimus), 40-*O*-(3-hydroxy)propyl-rapamycin, 40-*O*-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-*O*-tetrazole-rapamycin, 40-epi-(N1-tetrazolyl)-rapamycin (ABT-578), TAFA-93, biolimus-7, biolimus-9, clobetasol, pimecrolimus, imatinib mesylate, midostaurin, prodrugs thereof, co-drugs thereof, and a combination thereof.

17. The medical device of claim 1, which is a stent.

18. The medical device of claim 1, wherein the nanobeads are chemically attached to the surface of the medical device.

19. The medical device of claim 1, wherein the nanobeads comprise a magnetic material which optionally includes a biocompatible coating.

20. The medical device of claim 19, wherein the nanobeads are capable of being directed to a target site by an external magnetic source.

21. The medical device of claim 7, wherein:

(a) the first layer comprising the first plurality of nanobeads further comprises a slurry,

(b) the second layer comprising the second plurality of nanobeads further comprises a slurry,

(c) the third layer comprising the third plurality of nanobeads further comprises a slurry, or

(d) any combination of (a)-(c).

22. The medical device of claim 9, wherein the each layer of the more than three different layers of coating further comprises a slurry.

23. The medical device of claim 21, wherein the slurry comprises a polymer.

24. The medical device of claim 22, wherein the slurry comprises a polymer.

25. A method of treating a disorder in a patient comprising implanting in the patient the medical device of claim 1 and causing the nanobeads to release from the medical device of claim 1,

wherein the disorder is selected from the group consisting of atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication, anastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, and combinations thereof.

26. A method of treating a disorder in a patient comprising implanting in the patient the medical device of claim 17, and causing the nanobeads to release from the medical device of claim 17,

wherein the disorder is selected from the group consisting of atherosclerosis, thrombosis, restenosis, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication, anastomotic proliferation for vein

and artificial grafts, bile duct obstruction, ureter obstruction, tumor obstruction, and combinations thereof.

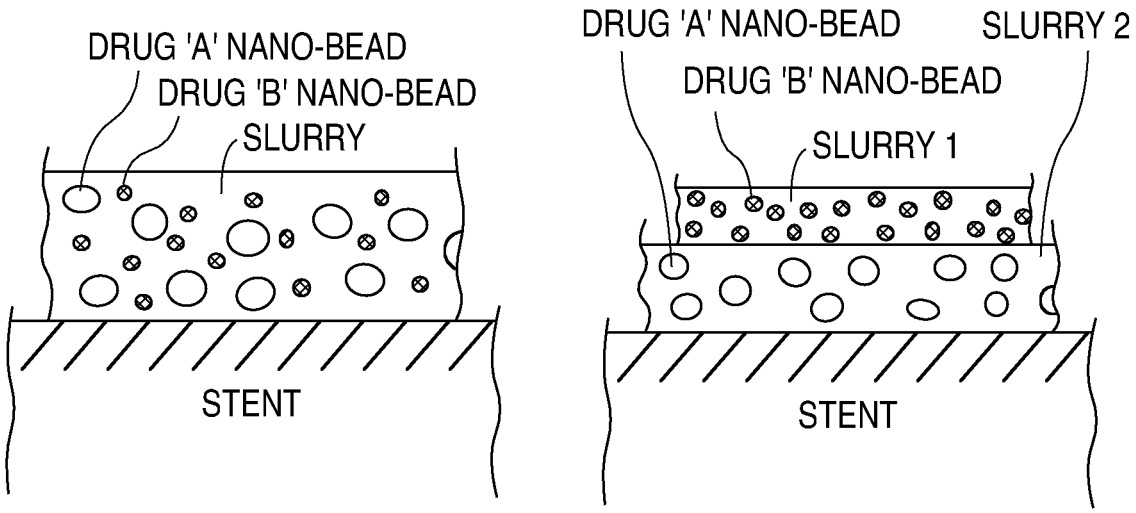
DRUG 'A' NANO-BEAD
DRUG 'B' NANO-BEAD
SLURRY
STENT
DRUG 'A' NANO-BEAD
SLURRY 2
DRUG 'B' NANO-BEAD
SLURRY 1
STENT

FIG. 1

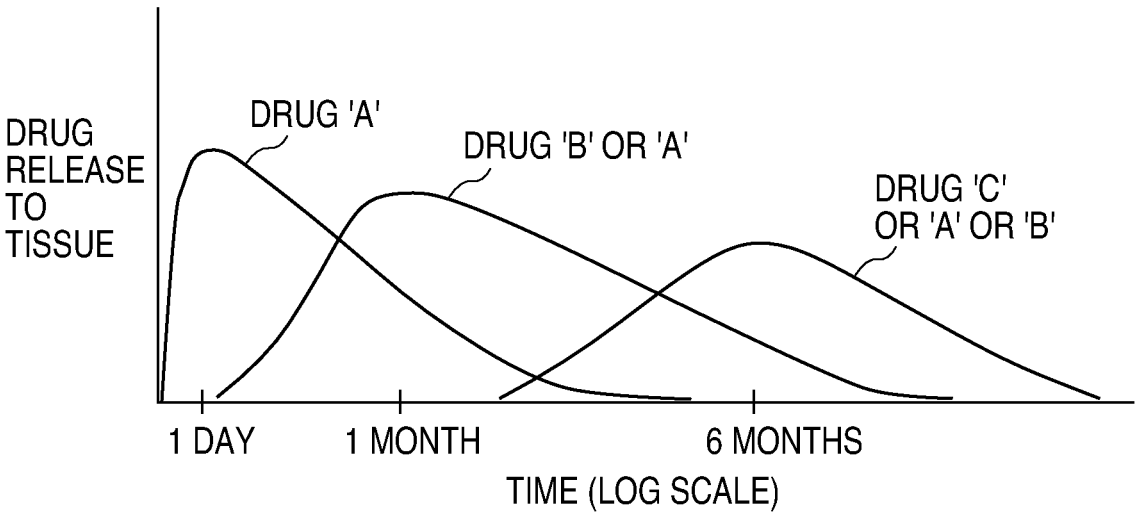
DRUG RELEASE TO TISSUE
DRUG 'A'
DRUG 'B' OR 'A'
DRUG 'C' OR 'A' OR 'B'
1 DAY
1 MONTH
6 MONTHS
TIME (LOG SCALE)

FIG. 2