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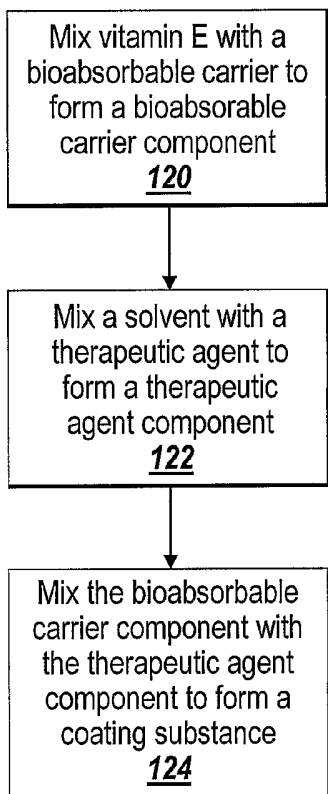
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[Continued on next page]

(54) Title: PRE-DRIED DRUG DELIVERY COATING FOR USE WITH A STENT



(57) Abstract: A method and apparatus for the provision of a coating for application to a medical device results in a medical device having a bio-absorbable coating. The coating includes a bio-absorbable carrier component. In addition to the bio-absorbable carrier component, a therapeutic agent component and solvent can also be provided. The solvent is removed from the coating before the coating is applied to the medical device. The coated medical device is implantable in a patient to effect controlled delivery of the coating, including the therapeutic agent, to the patient.

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## PRE-DRIED DRUG DELIVERY COATING FOR USE WITH A STENT

### Related Applications

5           This application claims priority to, and the benefit of, co-pending United States Provisional Application No. 60/613745, filed September 28, 2004, for all subject matter common to both applications. The disclosure of said provisional application is hereby incorporated herein by reference in its entirety. This application also relates to co-pending United States Patent Application No. 10/\_\_\_ (Attorney Docket No. ATA-426),  
10       filed concurrently with this application on September 28, 2005.

### FIELD OF THE INVENTION

15           The present invention relates to coatings suitable for application to medical devices for delivery of one or more biologically active agents, and more particularly to a bio-absorbable coating in which solvent is removed before the coating material is applied to the medical devices, and an apparatus and method for removing solvent from the coating material.

### BACKGROUND OF THE INVENTION

20           Therapeutic agents may be delivered to a targeted location in a human utilizing a number of different methods. For example, agents may be delivered nasally, transdermally, intravenously, orally, or via other conventional methods. Delivery may vary by release rate (i.e., quick release or slow release). Delivery may also vary as to  
25       how the drug is administered. Specifically, a drug may be administered locally to a targeted area, or administered systemically.

30           With systemic administration, the therapeutic agent is administered in one of a number of different ways including orally or intravenously to be systemically processed by the patient. However, there are drawbacks to systemic delivery of a therapeutic agent, one of which is that high concentrations of the therapeutic agent travels to all portions of the patient's body and can have undesired effects at areas not targeted for

treatment by the therapeutic agent. Furthermore, large doses of the therapeutic agent only amplify the undesired effects at non-target areas. As a result, the therapeutic dose required for a specific target location in a patient may have to be reduced when administered systemically to reduce complications from systemic toxicity.

5

An alternative to the systemic administration of a therapeutic agent is the use of a targeted local therapeutic agent delivery approach. With local delivery of a therapeutic agent, the therapeutic agent is administered using a medical device or apparatus, directly by hand, or sprayed on the tissue, at a selected targeted tissue location of the patient that requires treatment. The therapeutic agent emits, or is otherwise delivered, from the medical device apparatus, and/or carrier, and is applied to the targeted tissue location. The local delivery of a therapeutic agent enables a more concentrated and higher quantity of therapeutic agent to be delivered directly at the targeted tissue location, without having broader systemic side effects. With local delivery, the therapeutic agent that escapes the targeted tissue location dilutes as it travels to the remainder of the patient's body, substantially reducing or eliminating systemic side effects.

Local delivery is often carried out using a medical device as the delivery vehicle. One example of a medical device that is used as a delivery vehicle is a stent. Boston Scientific Corporation sells the Taxus® stent, which contains a polymeric coating for delivering Paclitaxel. Johnson & Johnson, Inc. sells the Cypher® stent which includes a polymeric coating for delivery of Sirolimus.

Targeted local therapeutic agent delivery using a medical device can be further broken into two categories, namely, short term and long term. The short term delivery of a therapeutic agent occurs generally within a matter of seconds or minutes to a few days or weeks. The long term delivery of a therapeutic agent occurs generally within several weeks to a number of months. Typically, to achieve the long term delivery of a therapeutic agent, the therapeutic agent must be combined with a delivery agent, or otherwise formed with a physical impediment as a part of the medical device, to slow the release of the therapeutic agent.

US Patent Publication No. 2003/0204168 is directed to the local administration of drug combinations for the prevention and treatment of vascular disease. The publication discusses using intraluminal medical devices having drugs, agents, and/or compounds affixed thereto to treat and prevent disease and minimize biological reactions to the introduction of the medical device. The publication states that both bio-  
5 absorbable and biostable compositions have been reported as coatings for stents. They have been polymeric coatings that either encapsulate a pharmaceutical/therapeutic agent or drug, e.g. rapamycin, taxol etc., or bind such an agent to the surface, e.g. heparin-coated stents. These coatings are applied to the stent in a number of ways, including,  
10 though not limited to, dip, spray, or spin coating processes.

The publication goes on to state that although stents prevent at least a portion of the restenosis process, a combination of drugs, agents or compounds which prevents smooth muscle cell proliferation, reduces inflammation and reduces thrombosis or  
15 prevents smooth muscle cell proliferation by multiple mechanisms, reduces inflammation and reduces thrombosis combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis. The systemic use of drugs, agents or compounds in combination with the local delivery of the same or different drug/drug combinations may also provide a beneficial treatment option.

20 The invention subsequently described in the '168 publication relates to the provision of polymeric coatings comprising a polyfluoro copolymer and implantable medical devices, for example, stents coated with a film of the polymeric coating in amounts effective to reduce thrombosis and/or restenosis when such stents are used in,  
25 for example, angioplasty procedures. Blends of polyfluoro copolymers are also used to control the release rate of different agents or to provide a desirable balance of coating properties, i.e. elasticity, toughness, etc., and drug delivery characteristics, for example, release profile. Polyfluoro copolymers with different solubilities in solvents may be used to build up different polymer layers that may be used to deliver different drugs or  
30 to control the release profile of a drug.

The coatings and drugs, agents or compounds described are described as being useful in combination with any number of medical devices, and in particular, with

implantable medical devices such as stents and stent-grafts. Other devices such as vena cava filters and anastomosis devices may be used with coatings having drugs, agents, or compounds therein.

5 US Patent No. 6,358,556 is directed to a drug release stent coating. The patent describes processes for producing a relatively thin layer of biostable elastomeric material in which an amount of biologically active material is dispersed as a coating on the surfaces of a deployable stent. The coating is described as preferably being applied as a mixture, solution, or suspension of polymeric material and finely divided biologically  
10 active species dispersed in an organic vehicle or a solution or partial solution of such species in a solvent or vehicle for the polymer and/or biologically active species. Essentially the active material is dispersed in a carrier material that may be a polymer, a solvent, or both.

15 US Patent No. 6,299,604 is directed to a coated implantable medical device having a layer of bioactive material and a coated layer providing controlled release of the bioactive material. The patent discusses the idea that the degradation of an agent, a drug, or a bioactive material, applied to an implantable medical device may be avoided by covering the agent, drug, or bioactive material, with a porous layer of a  
20 biocompatible polymer that is applied without the use of solvents, catalysts, heat or other chemicals or techniques, which would otherwise be likely to degrade or damage the agent, drug or material. Those biocompatible polymers may be applied preferably by vapor deposition or plasma deposition, and may polymerize and cure merely upon condensation from the vapor phase, or may be photolytically polymerizable and are  
25 expected to be useful for this purpose. As such, this patent focuses on the use of polymers to act as drug delivery agents in providing a controlled release of a drug from an implanted medical device.

US Publication No. 2003/0004564 is directed to a drug delivery platform. The  
30 publication describes compositions and methods for a stent based drug delivery system. The stent comprises a matrix, where the matrix has entrapped a pharmaceutical agent of interest. The matrix, for example microspheres, etc. resides within a channel formed on one or both of the abluminal or adluminal surfaces of the stent, and allows for release,

usually sustained release, of the entrapped agent. The stent and matrix is encased with a gel covalently bound to the stent surface and optionally also covalently bound to the matrix, which prevents loss of the matrix during transport and implantation of the stent, and which affects the release of the biologically active agent, through degradation and diffusion characteristics. The matrix is described as a biodegradable, bioerodible, or biocompatible non-biodegradable matrix comprising a biologically active agent that is placed within the channels of the stent surface. The matrix may be of any geometry including fibers, sheets, films, microspheres, circular discs, plaques and the like. The gel is selected to be a polymeric compound that will fill the spaces between the matrix and the channel, that can be covalently bound to the stent surface and optionally covalently bound to the matrix, and that provides a porous protective barrier between the matrix and the environment, for example during storage, implantation, flow conditions, etc. The gel may contribute to the control of drug release through its characteristics of degradation and diffusion.

15

US Patent No. 4,952,419 is directed to a method of making antimicrobial coated implant devices. The reference discusses the desire to have better retention of coatings on the implant surface during mechanized implant packaging operations. The solution presented involves the use of a silicone fluid in contact with the surface of the implant and an antimicrobial agent in contact with the silicone fluid. There is no discussion of any therapeutic benefit inherent in the silicone fluid itself, and there is no suggestion that other oils can be utilized to control the delivery of the antimicrobial agent

The above-described references fail to teach or suggest the use of bio-absorbable fats or oils in any form as the drug delivery platform. In each instance, the drug delivery platform includes the use of a form of polymeric material, or silicone material, with a solvent additive. The polymeric material serves as either a base upon which a drug coating is applied, a substance mixed in with the drug to form the coating, or a top coating applied over a previously applied drug coating to control the release of the drug.

30

PCT application publication No. WO 00/62830 is directed to a system and method for coating medical devices using air suspension. The technique involves suspending a medical device in an air stream and introducing a coating material into the

air stream such that the coating material is dispersed therein and coats the medical device. The publication discusses applying the coating to a number of different medical devices formed of a number of different materials. The publication further suggests that the coating materials can be comprised of therapeutic agents alone or in combination with solvents, and that the coating may provide for controlled release, which includes long-term or sustained release. As stated in the publication, a list of coating materials other than therapeutic agents include polymeric materials, sugars, waxes, and fats applied alone or in combination with therapeutic agents, and monomers that are cross-linked or polymerized. The publication goes on to discuss the use of a drug matrix formed of a polymer structure, which can be used to control the release rate of drugs combined with the polymer.

Although the '830 publication attempts to discuss every possible combination of delivery coating in combination with every drug or therapeutic agent that may have some utility in targeted delivery applications, there is no realization of the difficulty of using an oil for the controlled release of a therapeutic agent in a long term application. A list of potential delivery vehicles identifies waxes and fats, however there is no indication that such vehicles can be utilized for anything other than a short term drug delivery. A later discussion of controlled long term release of a drug mentions only the use of polymers to control the release.

US Patent No. 6,117,911 is directed to the use of compounds and different therapies for the prevention of vascular and non-vascular pathologies. The '911 patent discusses the possibility of using many different types of delivery methods for a therapeutic agent or agents to prevent various vascular and non-vascular pathologies. One such approach is described as providing a method of preventing or treating a mammal having, or at risk of developing, atherosclerosis, including administering an amount of a combination of aspirin or an aspirinate and at least one omega-3 fatty acid, wherein said amount of omega-3 fatty acid is effective to maintain or increase the level of TGF-beta so as to provide a synergistic effect with a therapeutic compound to inhibit or reduce vessel lumen diameter dimension. As such, the patent discusses some of the therapeutic benefits of primarily systemic administration of omega-3 fatty acids to affect TGF-beta levels when a therapeutic agent is combined with aspirin or aspirinate. That

is, the dose or concentration of omega-3-fatty acid required to increase the level of TGF-beta is significantly greater, requiring long term systemic delivery.

5 PCT Application Publication No. WO 03/028622 is directed to a method of delivering drugs to a tissue using drug coated medical devices. The drug coated medical device is brought into contact with the target tissue or circulation and the drugs are quickly released onto the area surrounding the device in a short period of time after contact is made. The release of the drug may occur over a period of 30 seconds, 1 minute or 3 minutes. In one embodiment described in the publication, the carrier of the drug is a liposome. Other particles described as potential drug carriers include lipids, 10 sugars, carbohydrates, proteins, and the like. The publication describes these carriers as having properties appropriate for a quick short term release of a drug combined with the carriers.

15 PCT application publication No. WO 02/100455 is directed to ozonated medical devices and methods of using ozone to prevent complications from indwelling medical devices. The application discusses having the ozone in gel or liquid form to coat the medical device. The ozone can be dissolved in olive oil, or other types of oil, to form a gel containing ozone bubbles, and the gel applied to the medical device as a coating. 20 The application later asserts a preference for the gel or other coating formulation to be composed so that the ozone is released over time. However, there is no indication in the application as to how a slow controlled release of ozone can be affected. There is no enablement to a long term controlled release of ozone from the olive oil gel, however, there is mention of use of biocompatible polymers to form the coating that holds and 25 releases the ozone. Other drugs are also suggested for combination with the ozone for delivery to a targeted location. The application later describes different application methods for the coating, including casting, spraying, painting, dipping, sponging, atomizing, smearing, impregnating, and spreading.

30 US Patent No. 5,509,899 is directed to a medical device having a lubricious coating. In the background section of this patent, it states that catheters have been rendered lubricious by coating them with a layer of silicone, glycerin, or olive oil in the past. It further states that such coatings are not necessarily satisfactory in all cases

because they tend to run off and lose the initial lubricity rather rapidly and they can also lack abrasion resistance. Hydrophilic coatings have also been disclosed such as polyvinyl pyrrolidone with polyurethane interpolymers or hydrophilic polymer blends of thermoplastic polyurethane and polyvinyl pyrrolidone. Accordingly, the invention in the  
5 '899 patent is described as providing a biocompatible surface for a device which can impede blocking or sticking of two polymer surfaces when the surfaces are placed in tight intimate contact with each other such as is the case when the balloon is wrapped for storage or when a surface of one device will contact a surface of another device. The description goes on to describe numerous polymeric substances.

10

European Patent Application No. EP 1 273 314 is directed to a stent having a biologically and physiologically active substance loaded onto the stent in a stable manner. The biologically and physiologically active substance is gradually released over a prolonged period of time with no rapid short term release. In order to achieve the  
15 long term controlled release, the application describes placing a layer of the biologically and physiologically active substance on the surface of the stent, and placing a polymer layer on top of the biologically and physiologically active substance layer. The polymer layer acts to slow the release of the biologically and physiologically active substance. There is no discussion of an alternative to the polymer substance forming the polymer  
20 layer for controlling the release of the biologically and physiologically active substance. There are instances discussed when the biologically and physiologically active substance has insufficient adhesion characteristics to adhere to the stent. In such instances, the application describes using an additional substance mixed with the biologically and physiologically active substance to increase its adhesion properties. In the case of a fat  
25 soluble substance, the recommendation is the use of a low molecular weight fatty acid having a molecular weight of up to 1000, such as fish oil, vegetable oil, or a fat-soluble vitamin such as vitamin A or vitamin E. The application always requires use of the additional polymer coating to create the long term controlled release of the biologically and physiologically active substance.

30

A paper entitled "Evaluation of the Biocompatibility and Drug Delivery Capabilities of Biological Oil Based Stent Coatings", by Shengqiao Li of the Katholieke Universiteit Leuven, discusses the use of biological oils as a coating for delivering drugs

after being applied to stents. Three different coatings were discussed, a glue coating (cod liver oil mixed with 100% ethanol at a 1:1 ratio), a vitamin E coating (97% vitamin E oil solution mixed with 100% ethanol at a 1:1 ratio), and a glue + vitamin E coating (cod liver oil and 97% vitamin E oil solution mixed with 100% ethanol at a 1:1 ratio).

5 Bare stents and polymer coated stents, along with stents having each of the above coatings, were implanted into test subjects, and analyzed over a four week period. At the end of the period, it was observed that the bare stents and polymer coated stents resulted in some minor inflammation of the tissue. The main finding of the study was that the glue coatings have a good biocompatibility with coronary arteries, and that the  
10 glue coating does not affect the degree of inflammation, thrombosis, and neointimal proliferation after endovascular stenting compared with the conventional stenting approach. A further hypothesis asserted was that the oil coating provided lubrication to the stent, thus decreasing the injury to the vascular wall.

15 The study went on to analyze the drug loading capacity of biological oil based stent coatings. Balloon mounted bare stents were dip-coated in a biological oil solution with the maximal solublizable amount of different drugs (a separate drug for each trial), and compared with polymer coated, drug loaded, stents. According to the release rate curves, there was a clear indication that drug release was fast in the first 24 hours with  
20 more than 20% of the drug released, for the oil based coatings. The release rate after the first 24 hours was much slower, and continued for a period up to about six weeks.

Another aspect of the study looked at the efficacy of drug loaded biological stents to decrease inflammation and neointimal hyperplasia in a porcine coronary stent  
25 model. In this part of the study, glue or modified glue (biological oil) coated stainless steel stents were loaded with different drugs. The result was that the characteristics of the particular drug loaded onto the stent were the major factor to the reduction of restenosis, and the biological oil did not have a major impact on either causing or reducing inflammation.

30

A further comment indicated that in the studies comparison was made between biological oil based drug loaded stents and bare stents to find differences in inflammation, injury, and hyperplasia. Inflammation, injury, and neointimal hyperplasia

resulted in in-stent area stenosis. Any anti-inflammation observed was the result of the particular drug loaded on the stent, regardless of biological oil, or polymer, coating.

PCT Application Publication No. WO 03/039612 is directed to an intraluminal  
5 device with a coating containing a therapeutic agent. The publication describes coating  
an intraluminal device with a therapeutic agent comprised of a matrix that sticks to the  
intraluminal device. The matrix is formed of a bio-compatible oil or fat, and can further  
include alpha-tocopherol. The publication further indicates that an oil or fat adheres  
sufficiently strongly to the intraluminal device so that most of the coating remains on the  
10 intraluminal device when it is inserted in a body lumen. The publication further states  
that the oil or fat slows the release of the therapeutic agent, and also acts as an anti-  
inflammatory and a lubricant. The publication goes on to indicate that the oil or fat can  
be chemically modified, such as by the process of hydrogenation, to increase their  
melting point. Alternatively, synthetic oils could be manufactured as well. The oil or  
15 fat is further noted to contain fatty acids.

The '612 publication provides additional detail concerning the preferred oil or  
fat. It states that a lower melting point is preferable, and a melting point of 0°C related  
to the oils utilized in experiments. The lower melting point provides a fat in the form of  
20 an oil rather than a wax or solid. It is further stated that oils at room temperature can be  
hydrogenated to provide a more stable coating and an increased melting point, or the oils  
can be mixed with a solvent such as ethanol. Preferences were discussed for the use of  
oils rather than waxes or solids, and the operations performed on the fat or oil as  
described can be detrimental to the therapeutic characteristics of some oils, especially  
25 polyunsaturated oils containing omega-3 fatty acids.

US Publication No. 2003/0083740 similarly discusses the use of certain oils as a  
matrix for delivery of drugs. More specifically, this publication is directed to a method  
for forming liquid coatings for medical devices such as stents and angioplasty balloons.  
30 The liquid coatings can be made from biodegradable materials in liquid, low melting  
solid, or wax forms, which preferably degrade in the body without producing potentially  
harmful fragments. These fragments occur with harder coatings that fracture and break  
off after implantation. The liquid coatings may also contain biologically active

components, such as drugs, which are released from the coatings through diffusion from the coatings and the degradation of the coatings.

5 Some of this second group of references do refer to the use of oils as a drug delivery platform. However, there is no realization of the difficulty of using an oil for the controlled release of a therapeutic agent in a long term application. There is further no indication that the coatings described in the above references are bio-absorbable, while also providing a controlled release of biologically active components, such as drugs. For controlled release of a drug, the above references require use of a polymer  
10 based coating either containing the drug or applied over the drug on the medical device.

What is desired is a bio-absorbable delivery agent having non-inflammatory characteristics that is able to be prepared in combination with at least one therapeutic agent for the delivery of that therapeutic agent to body tissue in a long term controlled  
15 release manner.

#### SUMMARY OF THE INVENTION

20 There is a need for a bio-absorbable coating for application to an implantable medical device for therapeutic purposes. There is also a need for solvent in the coating material to be removed before the coating material is applied to the medical device. In particular, there is a need for accelerating the removal rate of solvent from the coating material. The present invention is directed toward further solutions to address this need.

25 In accordance with one embodiment of the present invention, a coated medical device includes a coating having a bio-absorbable carrier component, the bio-absorbable carrier component being at least partially formed of a cellular uptake inhibitor and a cellular uptake enhancer. The coating further includes a solubilized or dispersed therapeutic agent and solvent. The solvent is removed from the coating before the  
30 coating is applied to the medical device. The coated medical device may be in some cases implantable in a patient to effect controlled delivery of the therapeutic agent to the patient. The controlled delivery is at least partially characterized by total and relative

amounts of the cellular uptake inhibitor and cellular uptake enhancer in the bio-absorbable carrier component.

5 In accordance with aspects of the present invention, the bio-absorbable carrier component contains lipids. The bio-absorbable carrier component can be a naturally occurring oil, such as fish oil. The bio-absorbable carrier component can be modified from its naturally occurring state to a state of increased viscosity in the form of a cross-linked gel. The bio-absorbable carrier component can contain omega-3 fatty acids.

10 It should be noted that as utilized herein, the term fish oil fatty acid includes but is not limited to omega-3 fatty acid, fish oil fatty acid, free fatty acid, esters of fatty acids, triglycerides, or a combination thereof. The fish oil fatty acid includes one or more of arachidic acid, gadoleic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid or derivatives, analogs and pharmaceutically acceptable salts  
15 thereof. Furthermore, as utilized herein, the term free fatty acid includes but is not limited to one or more of butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, vaccenic acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, behenic acid, erucic acid, lignoceric acid, analogs and pharmaceutically acceptable salts thereof.

20 It should be noted that the term cross-linked gel, as utilized herein with reference to the present invention, refers to a gel that is non-polymeric and is derived from an oil composition comprising molecules covalently cross-linked into a three-dimensional network by one or more of ester, ether, peroxide, and carbon-carbon bonds in a  
25 substantially random configuration. In various preferred embodiments, the oil composition comprises a fatty acid molecule, a glyceride, and combinations thereof.

In accordance with further aspects of the present invention the therapeutic agent component mixes with the bio-absorbable carrier component. The therapeutic agent  
30 component can include an agent selected from the group consisting of antioxidants, anti-inflammatory agents, anti-coagulant agents, drugs to alter lipid metabolism, anti-proliferatives, anti-neoplastics, tissue growth stimulants, functional protein/factor delivery agents, anti-infective agents, imaging agents, anesthetic agents,

chemotherapeutic agents, tissue absorption enhancers, anti-adhesion agents, germicides, antiseptics, proteoglycans, GAG's, gene delivery (polynucleotides), antifibrotics, analgesics, prodrugs, polysaccharides (e.g., heparin), anti-migratory agents, pro-healing agents, and ECM/protein production inhibitors. The therapeutic agent component can  
5 alternatively take the form of an agent selected from the group consisting of cerivastatin, cilostazol, fluvastatin, lovastatin, paclitaxel, pravastatin, rapamycin, and simvastatin. The coating can be bio-absorbable, inhibit restenosis, and/or be non-polymeric.

In accordance with further aspects of the present invention, the solvent can be  
10 Ethanol, N-Methyl-2-Pyrrolidone (NMP), or some other solvent compatible with the coating, therapeutic agent, and intended use. The coating can further include a compatibilizer, such as vitamin E or its derivatives, which also acts as a stabilizer and/or preservative, therapeutic agent, antioxidant, thickener, or tactifier.

It should be noted that as utilized herein to describe the present invention, the  
15 term vitamin E and the term alpha-tocopherol, are intended to refer to the same or substantially similar substance, such that they are interchangeable and the use of one includes an implicit reference to both. Further included in association with the term vitamin E are such variations including but not limited to one or more of alpha-  
20 tocopherol, beta-tocopherol, delta-tocopherol, gamma-tocopherol, alpha-tocotrienol, beta-tocotrienol, delta-tocotrienol, gamma-tocotrienol, alpha-tocopherol acetate, beta-tocopherol acetate, gamma-tocopherol acetate, delta-tocopherol acetate, alpha-tocotrienol acetate, beta-tocotrienol acetate, delta-tocotrienol acetate, gamma-tocotrienol acetate, alpha-tocopherol succinate, beta-tocopherol succinate, gamma-tocopherol  
25 succinate, delta-tocopherol succinate, alpha-tocotrienol succinate, beta-tocotrienol succinate, delta-tocotrienol succinate, gamma-tocotrienol succinate, mixed tocopherols, vitamin E TPGS, derivatives, analogs and pharmaceutically acceptable salts thereof. It should also be noted that other antioxidants may be used as a substitute to fulfill the functions of Vitamin E in this coating.

30

In accordance with further aspects of the present invention, the medical device can be a stent. The stent can be formed of a metal. The stent can further be formed of a

substance selected from the group consisting of stainless steel, Nitinol alloy, nickel alloy, titanium alloy, cobalt-chromium alloy, ceramics, plastics, and polymers.

5 In accordance with further aspects of the present invention, the surface of the medical device can be provided with a surface preparation prior to the application of the coating comprising the bio-absorbable carrier component. The pre-treatment, or preparation of the surface, improves coating conformability and consistency and enhances the adhesion of the coating comprising the bio-absorbable carrier component. The pre-treatment can be bio-absorbable, and can contain lipids. The pre-treatment can be a naturally occurring oil, such as fish oil, and can be modified from its naturally occurring state to state of increased viscosity in the form of a cross-linked gel. The pre-treatment can contain omega-3 fatty acids. The pre-treatment can contain a drug.

15 In accordance with another embodiment of the present invention, a method of making a coated medical device includes providing the medical device. A coating is also provided having a bio-absorbable carrier component, the bio-absorbable carrier component being at least partially formed of a cellular uptake inhibitor and a cellular uptake enhancer. The coating further includes a solubilized or dispersed therapeutic agent and solvent. After the solvent is removed from the coating, the coating is applied to the medical device. The coated medical device is implantable in a patient to effect controlled delivery of the therapeutic agent to the patient. The controlled delivery is at least partially characterized by total and relative amounts of the cellular uptake inhibitor and cellular uptake enhancer in the bio-absorbable carrier component.

25 In accordance with aspects of the present invention, the bio-absorbable carrier component can contain lipids, and can be naturally occurring oil, such as fish oil.

In accordance with aspects of the present invention, the method can further include modifying the bio-absorbable carrier component from its naturally occurring state to a state of increased viscosity in the form of a cross-linked gel. The bio-absorbable carrier component can contain omega-3 fatty acids.

30

In accordance with further aspects of the present invention, the solvent can be Ethanol, NMP, or another solvent compatible with the coating and the therapeutic component. The solvent can be a solvent or mixture of solvents and include solvents that are generally acceptable for pharmaceutical use. Suitable solvents include, for example: alcohols and polyols, such as C<sub>2</sub>-C<sub>6</sub> alkanols, 2-ethoxyethanol, ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, and polypropylene glycol; amides, such as 2-pyrrolidone, 2-piperidone, 2-caprolactam, N-alkylpyrrolidone, N-methyl-2-pyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide; esters, such as ethyl acetate, methyl acetate, butyl acetate, ethylene glycol diethyl ether, ethylene glycol dimethyl ether, propylene glycol dimethyl ether, ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl cutyrate, tracetin, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solvents, such as water, dimethylsulfoxide, benzyl benzoate, ethyl lactate, acetone, methylethyl ketone, dimethylsulfone, tetrahydrofuran, decylmethylsulfoxide, N,N-diethyl-m-toulamide or 1-dodecylazacycloheptan-2-one, hexane, chloroform, dichloromethane. The solvent can be removed with vacuum or heat.

The method can further provide a compatibilizer, such as vitamin E or its derivatives, which also acts as a stabilizer and preservative during formation of the coating.

The medical device coating using the method can be a stent. The stent can be formed of a metal, or other substance such as stainless steel, Nitinol alloy, nickel alloy, titanium alloy, cobalt-chromium alloy, ceramics, plastics, and polymers.

In accordance with further aspects of the present invention, the method can further include providing a surface preparation or pre-treatment on the surface of the medical device prior to application of the coating comprising the bio-absorbable carrier component, wherein the pre-treatment improves the coating consistency and

conformability and enhances the adhesion of the coating comprising the bio-absorbable carrier component. The pre-treatment can be bio-absorbable, contain lipids, and/or take the form of a naturally occurring oil, such as fish oil. The pre-treatment can be modified from its natural state to a state of increased viscosity in the form of a cross-linked gel.

5 The pre-treatment can contain a therapeutic agent. The pre-treatment can contain reactive oils.

In accordance with further aspects of the present invention, the step of applying the coating can include at least one of spraying the coating substance on the medical  
10 device, brushing the coating substance on the medical device, swabbing the coating substance on the medical device, painting the coating substance on the medical device, wiping the coating substance on the medical device, printing the coating substance on the medical device, and electrostatically applying the coating substance to the medical device, with or without an applicator.

15

The method can further include curing the coating on the medical device. Curing can involve applying at least one of heat, UV light, chemical cross-linker, or reactive gas to cure the coating. Curing with respect to the present invention generally refers to thickening, hardening, or drying of a material brought about by heat, UV, or chemical  
20 means.

In addition, methods can be used to enhance the curing process. These methods include, for example, the addition of other reactive oils, such as linseed oil, and the application of reactive gasses, such as oxygen, fluorine, methane or propylene, plasma  
25 treatment, and pressure in the presence of reactive gasses and the like.

The method can further include sterilizing the coating and the medical device. Sterilization can involve use of at least one of ethylene oxide, gamma radiation, e-beam, steam, gas plasma, and vaporized hydrogen peroxide (VHP). It should be noted that  
30 those listed herein are merely examples of sterilization processes and other sterilization processes can also be applied that result in a sterilization of the coated medical device, preferably without having a detrimental effect on the coating.

In accordance with another embodiment of the present invention, an apparatus is provided for drying a coating material applied to a medical device. The term "drying" is used to refer to removing solvent from the coating material in the description of the present invention. The apparatus includes a device for providing an environment in which the coating material can be dried. For example, the device can provide a vacuum or heat to dry the coating material. It should be noted that the use of vacuum and/or heat is illustrative and the coating material can be dried using other methods in different embodiments. For example, the coating material can be dried while blowing air or an inert gas over the surface of the coating material either in an oven or on a bench.

The apparatus can also include a mechanism for agitating, mixing, stirring or otherwise replenishing the surface of coating substance to increase the rate of solvent evaporation. The mechanism accelerates the transfer of solvent to the surrounding environment. For example, the apparatus can include a rotating fixture containing the coating material. By rotating the fixture, it can continuously disturb and refresh the surface of the coating material in the fixture, and hence increase the drying rate of the coating material in the fixture.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

The aforementioned features and advantages, and other features and aspects of the present invention, will become better understood with regard to the following description and accompanying drawings, wherein:

**FIG. 1** is a diagrammatic illustration of a medical device, according to one embodiment of the present invention;

**FIG. 2** is a cross-sectional view of the medical device in accordance with one aspect of the present invention;

**FIG. 3** is a cross-sectional view of the medical device in accordance with another aspect of the present invention;

**FIG. 4** is a flow chart illustrating a method of making the coated medical device of the present invention, in accordance with one embodiment of the present invention;

**FIG. 5** is a flow chart illustrating a variation of the method of **FIG. 4**, in accordance with one embodiment of the present invention;

**FIG. 6A** is a flow chart illustrating another variation of the method of **FIG. 4**, in accordance with one embodiment of the present invention;

**FIG. 6B** shows an exemplary apparatus for drying the solvent from the coating substance in accordance with one embodiment of the present invention;

5 **FIG. 6C** shows another exemplary apparatus for drying the solvent from the coating substance in accordance with one embodiment of the present invention;

**FIG. 7** is a flow chart illustrating another variation of the method of **FIG. 4**, in accordance with one embodiment of the present invention; and

10 **FIG. 8** is a diagrammatic illustration of a coated medical device in accordance with one embodiment of the present invention.

### DETAILED DESCRIPTION

An illustrative embodiment of the present invention relates to the provision of a coating on an implantable medical device. The coating includes a bio-absorbable carrier component. In addition to the bio-absorbable carrier component, a therapeutic agent component can also be provided. The coated medical device is implantable in a patient to effect controlled delivery of the coating to the patient. In particular, the illustrative embodiment provides an apparatus and method for removing solvent from the coating before the coating is applied to the medical device.

As utilized herein, the term "bio-absorbable" generally refers to having the property or characteristic of being able to penetrate the tissue of a patient's body. In certain embodiments of the present invention bio-absorption occurs through a lipophilic mechanism. The bio-absorbable substance is soluble in the phospholipid bi-layer of cells of body tissue, and therefore impacts how the bio-absorbable substance penetrates into the cells.

It should be noted that a bio-absorbable substance is different from a biodegradable substance. Biodegradable is generally defined as capable of being decomposed by biological agents, or capable of being broken down by microorganisms or biological processes, in a manner that does not result in cellular uptake of the biodegradable substance. Biodegradation thus relates to the breaking down and

distributing of a substance through the patient's body, versus the penetration of the cells of the patient's body tissue. Biodegradable substances can cause inflammatory response due to either the parent substance or those formed during breakdown, and they may or may not be absorbed by tissues.

5

The phrase "controlled release" generally refers to the release of a biologically active agent in a predictable manner over the time period of weeks or months, as desired and predetermined upon formation of the biologically active agent on the medical device from which it is being released. Controlled release includes the provision of an initial  
10 burst of release upon implantation, followed by the predictable release over the aforementioned time period.

With regard to the aforementioned oils, it is generally known that the greater the degree of unsaturation in the fatty acids the lower the melting point of a fat, and the  
15 longer the hydrocarbon chain the higher the melting point of the fat. A polyunsaturated fat, thus, has a lower melting point, and a saturated fat has a higher melting point. Those fats having a lower melting point are more often oils at room temperature. Those fats having a higher melting point are more often waxes or solids at room temperature. Therefore, a fat having the physical state of a liquid at room temperature is an oil. In  
20 general, polyunsaturated fats are liquid oils at room temperature, and saturated fats are waxes or solids at room temperature.

Polyunsaturated fats are one of four basic types of fat derived by the body from food. The other fats include saturated fat, as well as monounsaturated fat and  
25 cholesterol. Polyunsaturated fats can be further composed of omega-3 fatty acids and omega-6 fatty acids. Under the convention of naming the unsaturated fatty acid according to the position of its first double bond of carbons, those fatty acids having their first double bond at the third carbon atom from the methyl end of the molecule are referred to as omega-3 fatty acids. Likewise, a first double bond at the sixth carbon  
30 atom is called an omega-6 fatty acid. There can be both monounsaturated and polyunsaturated omega fatty acids.

Omega-3 and omega-6 fatty acids are also known as essential fatty acids because they are important for maintaining good health, despite the fact that the human body cannot make them on its own. As such, omega-3 and omega-6 fatty acids must be obtained from external sources, such as food. Omega-3 fatty acids can be further  
5 characterized as containing eicosapentaenoic acid (EPA), docosahexanoic acid (DHA), and alpha-linolenic acid (ALA). Both EPA and DHA are known to have anti-inflammatory effects and wound healing effects within the human body.

Oil that is hydrogenated becomes a waxy solid. Attempts have been made to  
10 convert the polyunsaturated oils into a wax or solid to allow the oil to adhere to a device for a longer period of time. One such approach is known as hydrogenation, which is a chemical reaction that adds hydrogen atoms to an unsaturated fat (oil) thus saturating it and making it solid at room temperature. This reaction requires a catalyst, such as a heavy metal, and high pressure. The resultant material forms a non-crosslinked semi-  
15 solid. Hydrogenation can reduce or eliminate omega-3 fatty acids, and any therapeutic effects (both anti-inflammatory and wound healing) they offer.

In addition, some curing methods have been indicated to have detrimental effects on the therapeutic agent combined with the omega-3 fatty acid, making them partially or  
20 completely ineffective. As such, oils, and more specifically oils containing omega-3 fatty acids, have been utilized as a delivery agent for the short term uncontrolled release of a therapeutic agent, so that minimal or no curing is required. However, there are no known uses of oils containing omega-3 fatty acids for combination with a therapeutic agent in a controlled release application that makes use of the therapeutic benefits of the  
25 omega-3 fatty acids. Further, some heating of the omega-3 fatty acids to cure the oil can lessen the total therapeutic effectiveness of the omega-3 fatty acids, but not eliminate the therapeutic effectiveness. One characteristic that can remain after certain curing by heating methods is the non-inflammatory response of the tissue when exposed to the cured material. As such, an oil containing omega-3 fatty acids can be heated for curing  
30 purposes, and still maintain some or even a substantial portion of the therapeutic effectiveness of the omega-3 fatty acids. In addition, although the therapeutic agent combined with the omega-3 fatty acid and cured with the omega-3 fatty acid can be rendered partially ineffective, the portion remaining of the therapeutic agent can, in

accordance with the present invention, maintain pharmacological activity and in some cases be more effective than an equivalent quantity of agent delivered with other coating delivery agents. Thus, if for example, 80% of a therapeutic agent is rendered ineffective during curing, the remaining 20% of therapeutic agent, combined with and delivered by  
5 the coating can be efficacious in treating a medical disorder, and in some cases have a relatively greater therapeutic effect than the same quantity of agent delivered with a polymeric or other type of coating.

For long term controlled release applications, polymers, as previously  
10 mentioned, have been utilized in combination with a therapeutic agent. Such a combination provides a platform for the controlled long term release of the therapeutic agent from a medical device. However, polymers have been determined to themselves cause inflammation in body tissue. Therefore, the polymers often must include at least one therapeutic agent that has an anti-inflammatory effect to counter the inflammation  
15 caused by the polymer delivery agent. In addition, patients that received a polymer-based implant must also follow a course of long term systemic anti-platelet therapy, on a permanent basis, to offset the thrombogenic properties of the non-absorbable polymer. A significant percentage of patients that receive such implants are required to undergo additional medical procedures, such as surgeries (whether related follow-up surgery or  
20 non-related surgery) and are required to stop their anti-platelet therapy. This can lead to a thrombotic event, such as stroke, which can lead to death. Use of the inventive coating described herein can negate the necessity of anti-platelet therapy, and the corresponding related risks described, because there is no thrombogenic polymer reaction to the coating.

25

**FIGS. 1 through 8**, wherein like parts are designated by like reference numerals throughout, illustrate an example embodiment of a pre-drying apparatus and method of using the apparatus along with resulting coatings and coated medical devices according to the present invention. Although the present invention will be described with  
30 reference to the example embodiments illustrated in the figures, it should be understood that many alternative forms can embody the present invention. One of ordinary skill in the art will additionally appreciate different ways to alter the parameters of the

embodiments disclosed, such as the size, shape, or type of elements or materials, in a manner still in keeping with the spirit and scope of the present invention.

5 **FIG. 1** illustrates a stent 10 in accordance with one embodiment of the present invention. The stent 10 is representative of a medical device that is suitable for having a coating applied thereon to effect a therapeutic result. The stent 10 is formed of a series of interconnected struts 12 having gaps 14 formed therebetween. The stent 10 is generally cylindrically shaped. Accordingly, the stent 10 maintains an interior surface 16 and an exterior surface 18.

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One of ordinary skill in the art will appreciate that the illustrative stent 10 is merely exemplary of a number of different types of stents available in the industry. For example, the strut 12 structure can vary substantially. The material of the stent can also vary from a metal, such as stainless steel, Nitinol, nickel, and titanium alloys, to cobalt chromium alloy, ceramic, plastic, and polymer type materials. One of ordinary skill in the art will further appreciate that the present invention is not limited to use on stents. Instead, the present invention has application on a wide variety of medical devices. For purposes of clarity, the following description will refer to a stent as the exemplar medical device. The terms medical device and stent are interchangeable with regard to the applicability of the present invention. Accordingly, reference to one or another of the stent, or the medical device, is not intended to unduly limit the invention to the specific embodiment described.

20

**FIG. 2** illustrates one example embodiment of the stent 10 having a coating 20 applied thereon in accordance with the present invention. **FIG. 3** is likewise an alternative embodiment of the stent 10 having the coating 20 also applied thereon. The coating 20 is applied to the medical device, such as the stent 10, to provide the stent 10 with different surface properties, and also to provide a vehicle for therapeutic applications.

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In **FIG. 2**, the coating 20 is applied on both the interior surface 16 and the exterior surface 18 of the strut 12 forming the stent 10. In other words, the coating 20 in **FIG. 2** substantially encapsulates the struts 12 of the stent 10. In **FIG. 3**, the coating 20

is applied only on the exterior surface 18 of the stent 10, and not on the interior surface 16 of the stent 10. The coating 20 in both configurations is the same coating; the difference is merely the portion of the stent 10 that is covered by the coating 20. One of ordinary skill in the art will appreciate that the coating 20 as described throughout the Description can be applied in both manners shown in **FIG. 2** and **FIG. 3**, in addition to other configurations such as, partially covering select portions of the stent 10 structure. All such configurations are described by the coating 20 reference.

In accordance with embodiments of the present invention, the stent 10 includes the coating 20, which is bio-absorbable. The coating 20 has a bio-absorbable carrier component, and can also include a therapeutic agent component that can also be bio-absorbable. When applied to a medical device such as a stent 10, it is often desirable for the coating to inhibit or prevent restenosis. Restenosis is a condition whereby the blood vessel experiences undesirable cellular remodeling after injury. When a stent is implanted in a blood vessel, and expanded, the stent itself may cause some injury to the blood vessel. The treated vessel typically has a lesion present which can contribute to the inflammation and extent of cellular remodeling. The end result is that the tissue has an inflammatory response to the conditions. Thus, when a stent is implanted, there is often a need for the stent to include a coating that inhibits inflammation, or is non-inflammatory, and prevents restenosis. These coatings have been provided using a number of different approaches as previously described in the Background. However, none of the prior coatings have utilized a bio-absorbable carrier component to create a bio-absorbable coating with suitable non-inflammatory properties for controlled release of a therapeutic agent.

25

In accordance with one embodiment of the present invention, the bio-absorbable carrier component is in the form of a naturally occurring oil. An example of a naturally occurring oil is fish oil or cod liver oil. A characteristic of the naturally occurring oil is that the oil includes lipids, which contributes to the lipophilic action described later herein, that is helpful in the delivery of therapeutic agents to the cells of the body tissue. In addition, the naturally occurring oil includes omega-3 fatty acids in accordance with several embodiments of the present invention. As previously described, omega-3 fatty acids and omega-6 fatty acids are known as essential fatty acids. Omega-3 fatty acids

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can be further characterized as eicosapentaenoic acid (EPA), docosahexanoic acid (DHA), and alpha-linolenic acid (ALA). Both EPA and DHA are known to have anti-inflammatory effects and wound healing effects within the human body.

5           In further detail, the term "bio-absorbable" generally refers to having the property or characteristic of being able to penetrate the tissues of a patient's body. In example embodiments of the present invention, the bio-absorbable coating contains lipids, many of which originate as triglycerides. It has previously been demonstrated that triglyceride products such as partially hydrolyzed triglycerides and fatty acid  
10 molecules can integrate into cellular membranes and enhance the solubility of drugs into the cell. Whole triglycerides are known not to enhance cellular uptake as well as partially hydrolyzed triglyceride, because it is difficult for whole triglycerides to cross cell membranes due to their relatively larger molecular size. Vitamin E compound can also integrate into cellular membranes resulting in decreased membrane fluidity and  
15 cellular uptake. There are no break down products of the coating that induce an inflammatory response.

          It is also known that damaged vessels undergo oxidative stress. A coating containing an antioxidant such as alpha-tocopherol may aid in preventing further  
20 damage by this mechanism.

          Compounds that move too rapidly through a tissue may not be effective in providing a sufficiently concentrated dose in a region of interest. Conversely, compounds that do not migrate in a tissue may never reach the region of interest.  
25 Cellular uptake enhancers such as fatty acids and cellular uptake inhibitors such as alpha-tocopherol can be used alone or in combination to provide an effective transport of a given compound to a given region or location. Both fatty acids and alpha-tocopherol are accommodated by the coating of the present invention described herein. Accordingly, fatty acids and alpha-tocopherol can be combined in differing amounts and  
30 ratios to contribute to a coating in a manner that provides control over the cellular uptake characteristics of the coating and any therapeutic agents mixed therein.

It should further be emphasized that the bio-absorbable nature of the carrier component and the resulting coating (in the instances where a bio-absorbable therapeutic agent component is utilized) results in the coating 20 being completely absorbed over time by the cells of the body tissue. There are no break down products of the coating that induce an inflammatory response. In short, the coating 20 is generally composed of fatty acids, including in some instances omega-3 fatty acids, bound to triglycerides, potentially also including a mixture of free fatty acids and vitamin E. The triglycerides are broken down by lipases (enzymes) which result in free fatty acids that can then be transported across cell membranes. Subsequently, fatty acid metabolism by the cell occurs to metabolize any substances originating with the coating. The bio-absorbable nature of the coating of the present invention thus results in the coating being absorbed, leaving only an underlying delivery or other medical device structure. There is no foreign body response to the bio-absorbable carrier component, including no inflammatory response. The modification of the oils from a more liquid physical state to a more solid, but still flexible, physical state is implemented through the curing process. As the oils are cured, especially in the case of fatty acid-based oils such as fish oil, cross-links form creating a gel. As the curing process is performed over increasing time durations and/or increasing temperature conditions, more cross-links form transitioning the gel from a relatively liquid gel to a relatively solid-like, but still flexible, gel structure.

As previously mentioned, the coating can also include a therapeutic agent component. The therapeutic agent component mixes with the bio-absorbable carrier component as described later herein. The therapeutic agent component can take a number of different forms including but not limited to anti-oxidants, anti-inflammatory agents, anti-coagulant agents, drugs to alter lipid metabolism, anti-proliferatives, anti-neoplastics, tissue growth stimulants, functional protein/factor delivery agents, anti-infective agents, anti-imaging agents, anesthetic agents, therapeutic agents, tissue absorption enhancers, anti-adhesion agents, germicides, antiseptics, proteoglycans, GAG's, gene delivery (polynucleotides), polysaccharides (e.g., heparin), anti-migratory agents, pro-healing agents, and ECM/protein production inhibitors, analgesics, prodrugs, and any additional desired therapeutic agents such as those listed in Table 1 below.

**Table #1**

<b>CLASS</b>	<b>EXAMPLES</b>
Antioxidants	Alpha-tocopherol, lascaroid, probucol, phenolic antioxidant, resveretrol, AGI-1067, vitamin E
Antihypertensive Agents	Diltiazem, nifedipine, verapamil
Antiinflammatory Agents	Glucocorticoids (e.g. dexamethazone, methylprednisolone), leflunomide, NSAIDS, ibuprofen, acetaminophen, hydrocortizone acetate, hydrocortizone sodium phosphate, macrophage-targeted bisphosphonates
Growth Factor Antagonists	Angiopeptin, trapidil, suramin
Antiplatelet Agents	Aspirin, dipyridamole, ticlopidine, clopidogrel, GP IIb/IIIa inhibitors, abciximab
Anticoagulant Agents	Bivalirudin, heparin (low molecular weight and unfractionated), warfarin, hirudin, enoxaparin, citrate
Thrombolytic Agents	Alteplase, reteplase, streptase, urokinase, TPA, citrate
Drugs to Alter Lipid Metabolism (e.g. statins)	Fluvastatin, colestipol, lovastatin, atorvastatin, amlopidine
ACE Inhibitors	Elanapril, fosinopril, cilazapril
Antihypertensive Agents	Prazosin, doxazosin
Antiproliferatives and Antineoplastics	Cyclosporine, cochicine, mitomycin C, sirolimus, micophenonolic acid, rapamycin, everolimus, tacrolimus, paclitaxel, QP-2, actinomycin, estradiols, dexamethasone, methatrexate, cilostazol, prednisone, cyclosporine, doxorubicin, ranpirnas, troglitzon, valsarten, pemirolast, C-MYC antisense, angiopeptin, vincristine, PCNA ribozyme, 2-chloro-deoxyadenosine
Tissue growth stimulants	Bone morphogeneic protein, fibroblast growth factor
Promotion of hollow organ occlusion or thrombosis	Alcohol, surgical sealant polymers, polyvinyl particles, 2-octyl cyanoacrylate, hydrogels, collagen, liposomes
Functional Protein/Factor delivery	Insulin, human growth hormone, estradiols, nitric oxide, endothelial progenitor cell antibodies
Second messenger targeting	Protein kinase inhibitors
Angiogenic	Angiopoetin, VEGF
Anti-Angiogenic	Endostatin
Inhibition of Protein Synthesis/ECM formation	Halofuginone, prolyl hydroxylase inhibitors, C-proteinase inhibitors

Antiinfective Agents	Penicillin, gentamycin, adriamycin, cefazolin, amikacin, ceftazidime, tobramycin, levofloxacin, silver, copper, hydroxyapatite, vancomycin, ciprofloxacin, rifampin, mupirocin, RIP, kanamycin, brominated furonone, algae byproducts, bacitracin, oxacillin, nafcillin, floxacillin, clindamycin, cephradine, neomycin, methicillin, oxytetracycline hydrochloride, Selenium.
Gene Delivery	Genes for nitric oxide synthase, human growth hormone, antisense oligonucleotides
Local Tissue perfusion	Alcohol, H <sub>2</sub> O, saline, fish oils, vegetable oils, liposomes
Nitric oxide Donor Derivatives	NCX 4016 – nitric oxide donor derivative of aspirin, SNAP
Gases	Nitric oxide, compound solutions
Imaging Agents	Halogenated xanthenes, diatrizoate meglumine, diatrizoate sodium
Anesthetic Agents	Lidocaine, benzocaine
Descaling Agents	Nitric acid, acetic acid, hypochlorite
Anti-Fibrotic Agents	Interferon gamma -1 b, Interleukin - 10
Immunosuppressive/Immunomodulatory Agents	Cyclosporine, rapamycin, mycophenolate mofetil, leflunomide, tacrolimus, tranilast, interferon gamma-1b, mizoribine
Chemotherapeutic Agents	Doxorubicin, paclitaxel, tacrolimus, sirolimus, fludarabine, ranpirinase
Tissue Absorption Enhancers	Fish oil, squid oil, omega 3 fatty acids, vegetable oils, lipophilic and hydrophilic solutions suitable for enhancing medication tissue absorption, distribution and permeation
Anti-Adhesion Agents	Hyaluronic acid, human plasma derived surgical sealants, and agents comprised of hyaluronate and carboxymethylcellulose that are combined with dimethylaminopropyl, ethylcarbodiimide, hydrochloride, PLA, PLGA
Ribonucleases	Ranpirinase
Germicides	Betadine, iodine, silver nitrate, furan derivatives, nitrofurazone, benzalkonium chloride, benzoic acid, salicylic acid, hypochlorites, peroxides, thiosulfates, salicylanilide
Antiseptics	Selenium
Analgesics	Bupivacaine, naproxen, ibuprofen, acetylsalicylic acid

Some specific examples of therapeutic agents useful in the anti-restenosis realm include cerivastatin, cilostazol, fluvastatin, lovastatin, paclitaxel, pravastatin, rapamycin,

a rapamycin carbohydrate derivative (for example as described in US Patent Application Publication 2004/0235762), a rapamycin derivative (for example as described in US Patent No. 6,200,985), everolimus, seco-rapamycin,, seco-everolimus and simvastatin. Depending on the type of therapeutic agent component added to the coating, the

5 resulting coating can be bio-absorbable if the therapeutic agent component is also bio-absorbable. As described in the Summary of the Invention, the present invention relates to coating a medical device such as the stent 10 with a coating such as coating 20. The coating 20 is formed of at least two primary components, namely a bio-absorbable carrier component and a therapeutic agent component. The therapeutic agent component

10 has some form of therapeutic or biological effect. The bio-absorbable carrier component can also have a therapeutic or biological effect. It should again be noted that the bio-absorbable carrier component is different from the conventional bio-degradable substances utilized for similar purposes. The bio-absorbable characteristic of the carrier component enables the cells of body tissue of a patient to absorb the bio-absorbable

15 carrier component itself, rather than breaking down the carrier component into inflammatory by-products and disbursing said by-products of the component for ultimate elimination by the patient's body. Accordingly, anti-inflammatory drug dosages to the patient do not need to be increased to additionally compensate for inflammation caused by the carrier component, as is otherwise required when using

20 polymer-based carriers that themselves cause inflammation.

It should also be noted that the present description makes use of the stent 10 as an example of a medical device that can be coated with the coating 20 of the present invention. However, the present invention is not limited to use with the stent 10.

25 Instead, any number of other implantable medical devices can be coated in accordance with the teachings of the present invention with the described coating 20. Such medical devices include catheters, grafts, balloons, prostheses, stents, other medical device implants, and the like. Implantation refers to both temporarily implantable medical devices, as well as permanently implantable medical devices. In the instance of the

30 example stent 10, a common requirement of stents is that they include some substance or agent that inhibits restenosis. Accordingly, the example coating 20 as described is directed toward the reduction or the elimination of restenosis. However, one of ordinary skill in the art will appreciate that the coating 20 can have other therapeutic or biological

benefits. The composition of the coating 20 is simply modified or mixed in a different manner to result in a different biological effect.

**FIG. 4** illustrates one method of making a coated medical device, such as stent 10, in accordance with one embodiment of the present invention. The process involves providing a medical device, such as the stent 10 (step 100). A coating, such as coating 20, is then applied to the medical device (step 102). One of ordinary skill in the art will appreciate that this basic method of application of a coating to a medical device such as the stent 10 can have a number of different variations falling within the process described. Depending on the particular application, the stent 10 with the coating 20 applied thereon can be implanted after the coating 20 is applied, or additional steps such as curing and sterilization can be applied to further prepare the stent 10 and coating 20. Furthermore, if the coating 20 includes a therapeutic agent that requires some form of activation (such as UV light), such actions can be implemented accordingly.

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Furthermore, the step of applying a coating substance to form a coating on the medical device (such as the stent 10) can include a number of different application methods. For example, the coating substance can be sprayed onto the stent 10, which results in application of the coating substance on the exterior surface 18 of the stent 10 as shown in **FIG. 3**. Another alternative application method is painting the coating substance on to the stent 10, which also results in the coating substance forming the coating 20 on the exterior surface 18 as shown in **FIG. 3**. One of ordinary skill in the art will appreciate that other methods, such as electrostatic adhesion and other application methods, can be utilized to apply the coating substance to the medical device such as the stent 10. Some application methods may be particular to the coating substance and/or to the structure of the medical device receiving the coating. Accordingly, the present invention is not limited to the specific embodiment described herein, but is intended to apply generally to the application of the coating substance to the medical device, taking whatever precautions are necessary to make the resulting coating maintain desired characteristics.

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**FIG. 5** is a flowchart illustrating one example implementation of the method of **FIG. 4**. In accordance with the steps illustrated in **FIG. 5**, a bio-absorbable carrier

component is provided along with a therapeutic agent component (step 110). The provision of the bio-absorbable carrier component and the provision of the therapeutic agent component can occur individually, or in combination, and can occur in any order or simultaneously. The formation of the bio-absorbable carrier component and the

5 therapeutic agent component can be done in accordance with different methods. **FIG. 6A** is a flow chart illustrating one example method for forming each of the components. Vitamin E is mixed with a bio-absorbable carrier to form a bio-absorbable carrier component (step 120). A solvent is mixed with a therapeutic agent to form a therapeutic agent component (step 122). The solvent can be chosen from a number of different

10 alternatives, including but not limited to ethanol or N-Methyl-2-Pyrrolidone (NMP). The solvent can be a solvent or mixture of solvents and include solvents that are generally acceptable for pharmaceutical use. Suitable solvents include, for example: alcohols and polyols, such as C<sub>2</sub>-C<sub>6</sub> alkanols, 2-ethoxyethanol, ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers

15 thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, and polypropylene glycol; amides, such as 2-pyrrolidone, 2-piperidone, 2-caprolactam, N-alkylpyrrolidone, N-methyl-2-pyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide; esters, such as ethyl acetate, methyl acetate, butyl acetate, ethylene glycol diethyl ether,

20 ethylene glycol dimethyl ether, propylene glycol dimethyl ether, ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl cutyrate, tracetin, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solvents, such as water, dimethylsulfoxide, benzyl benzoate, ethyl lactate, acetone,

25 methylethyl ketone, dimethylsulfone, tetrahydrofuran, decylmethylsulfone, N,N-diethyl-m-toulamide or 1-dodecylazacycloheptan-2-one, hexane, chloroform, dichloromethane. The solvent can be removed with vacuum or heat. The bio-absorbable carrier component is mixed with the therapeutic agent component or vice versa to form a coating substance (step 112 in **FIG. 5**). In **FIG. 6A**, the bio-absorbable

30 carrier component is mixed with the therapeutic agent component to form the coating substance (step 124).

Referring back to **FIG. 5**, the solvent is removed or pre-dried from the coating substance before the coating substance is applied to the medical device (step 113). The term “drying” is used to refer to removing solvent from the coating material in the description of the embodiment. The solvent can be removed with vacuum or heat. The removal of the solvent will be described below in more detail with reference to **FIG. 6B**. The coating substance is applied to the medical device, such as the stent 10, to form the coating (step 114). The coated medical device is then sterilized using any number of different sterilization processes (step 116). For example, sterilization can be implemented utilizing ethylene oxide, gamma radiation, E beam, steam, gas plasma, or vaporized hydrogen peroxide. One of ordinary skill in the art will appreciate that other sterilization processes can also be applied, and that those listed herein are merely examples of sterilization processes that result in a sterilization of the coated stent, preferably without having a detrimental effect on the coating 20.

**FIG. 6B** shows an exemplary apparatus for removing the solvent from the coating substance in accordance with one embodiment of the present invention. The apparatus includes a rotating fixture set up in a bell jar or in a vacuum oven 125. The vacuum controller 144 controls the vacuum condition within the bell jar or vacuum oven 125. One of ordinary skill in the art will appreciate that the bell jar and the vacuum oven are illustrative, and other types of devices can be used to provide a vacuum. The rotating fixture can include a syringe 126 disposed within the bell jar or in the vacuum oven 125 for containing the coating substance 127. The syringe 126 can be coupled to and rotated by an electrical mechanism, such as a motor 128 powered by a power supply 129. Those of skill in the art will appreciate that the syringe 126 can be rotated by a different mechanism in other embodiments, such as a mechanical mechanism. One of ordinary skill in the art will also appreciate that the rotating device is illustrative and the apparatus may include a different mechanism for agitating, mixing, stirring or otherwise replenishing the surface of coating substance to increase the rate of solvent evaporation. The mechanism accelerates the transfer of solvent to the surrounding environment.

By rotating the syringe 126 containing the coating substance under vacuum, the illustrative embodiment continuously disturbs and refreshes the surface of the coating substance in the syringe 126, and hence increases the drying rate of the coating

substance in the syringe 126. The apparatus can also include a temperature controller 140 for making the apparatus versatile. The temperature controller 140 can change the temperature within the bell jar or the vacuum oven 125 so that the solvent can be dried or removed at various temperatures, such as room temperature or elevated temperatures.

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**FIG. 6C** shows another exemplary apparatus for removing the solvent from the coating substance in accordance with one embodiment of the present invention. The apparatus includes a rotating fixture. The rotating fixture can include the syringe 126 for containing the coating substance 127. The syringe 126 can be coupled to and rotated by an electrical mechanism, such as the motor 128 powered by the power supply 129. The apparatus can also include a heater 142 powered by the power supply for applying heat to the coating substance 127 in the syringe 126. The heat from the heater 142 dries the coating substance 127 in the syringe 126. By rotating the syringe 126 containing the coating substance, the illustrative embodiment increases the drying rate of the coating substance in the syringe 126. One of ordinary skill in the art will appreciate that the apparatus may or may not be set up in the vacuum oven 125 including the vacuum controller 144, as described in **FIG 6B**.

Those of ordinary skill in the art will appreciate that the use of vacuum or heat is illustrative and the coating material can be dried using other method in different embodiments. For example, the coating material can be dried while blowing air or an inert gas over the surface of the coating material either in an oven or on the bench.

The pre-drying of the coating substance in the present invention is a unique technique because this technique is not applicable to the conventional polymer based stent coating. The conventional polymer coating requires the solvent to dissolve the polymer so that it can be coated onto the stent. Therefore, the solvent cannot be removed before the coating substance is applied to the medical device. In the illustrative embodiment of the present invention, however, the solvent is required to load the drug and the coating substance can be applied to the stent without the use of solvent. This characteristic of the present invention enables the solvent to be removed before the coating substance is applied to the medical device.

Additionally, the pre-drying of the present invention reduces the solvent drying time and hence drastically increases the number of medical devices that can be coated within a limited time period. The pre-drying of the present invention allows the application of a precise amount of coating substance or drug to the stent by using a dispenser. The pre-drying of the present invention reduces the amount of capital equipment needed for the production of the coated medical devices. The pre-drying of the present invention increases the drug loading compared to dip coating. The pre-drying of the present invention reduces the handling and associated risk of damage and/or contamination of the coating and the medical device.

10

In accordance with another aspect of the present invention, the coating substance can be pre-dried to the state of viscosity where all of the solvent is not removed from the coating substance. The rest of the solvent in the coating material can be removed after the coating material is applied to the medical device, such as the stent 10.

15

In accordance with another embodiment of the present invention a surface preparation or pre-treatment 22, as shown in **FIG. 8**, is provided on a stent 10. More specifically and in reference to the flowchart of **FIG. 7**, a pre-treatment substance is first provided (step 130). The pre-treatment substance is applied to a medical device, such as the stent 10, to prepare the medical device surface for application of the coating (step 132). If desired, the pre-treatment 22 is cured (step 134). Curing methods can include processes such as application of UV light or application of heat to cure the pre-treatment 22. A coating substance is then applied on top of the pre-treatment 22 (step 136). The coated medical device is then sterilized using any number of sterilization processes as previously mentioned (step 138).

25

**FIG. 8** illustrates the stent 10 having two coatings, specifically, the pre-treatment 22 and the coating 20. The pre-treatment 22 serves as a base or primer for the coating 20. The coating 20 conforms and adheres better to the pre-treatment 22 versus directly to the stent 10, especially if the coating 20 is not heat or UV cured. The pre-treatment can be formed of a number of different materials or substances. In accordance with one example embodiment of the present invention, the pre-treatment is formed of a bio-absorbable substance, such as a naturally occurring oil (e.g., fish oil). The bio-

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absorbable nature of the pre-treatment 22 results in the pre-treatment 22 ultimately being absorbed by the cells of the body tissue after the coating 20 has been absorbed.

5 It has been previously mentioned that curing of substances such as fish oil can reduce or eliminate some of the therapeutic benefits of the omega-3 fatty acids, including anti-inflammatory properties and healing properties. However, if the coating 20 contains the bio-absorbable carrier component formed of the oil having the therapeutic benefits, the pre-treatment 22 can be cured to better adhere the pre-treatment 22 to the stent 10, without losing all of the therapeutic benefits resident in the pre-treatment 22, or in the subsequently applied coating 20. Furthermore, the cured pre-treatment 22 provides better adhesion for the coating 20 relative to when the coating 20 is applied directly to the stent 10 surface. In addition, the pre-treatment 22, despite being cured, remains bio-absorbable, like the coating 20.

15 The pre-treatment 22 can be applied to both the interior surface 16 and the exterior surface 18 of the stent 10, if desired, or to one or the other of the interior surface 16 and the exterior surface 18. Furthermore, the pre-treatment 22 can be applied to only portions of the surfaces 16 and 18, or to the entire surface, if desired.

20 The application of the coating 20 to the stent 10, or other medical device, can take place in a manufacturing-type facility and subsequently shipped and/or stored for later use. Alternatively, the coating 20 can be applied to the stent 10 just prior to implantation in the patient. The process utilized to prepare the stent 10 will vary according to the particular embodiment desired. In the case of the coating 20 being applied in a manufacturing-type facility, the stent 10 is provided with the coating 20 and subsequently sterilized in accordance with any of the methods provided herein, and/or any equivalents. The stent 10 is then packaged in a sterile environment and shipped or stored for later use. When use of the stent 10 is desired, the stent is removed from the packaging and implanted in accordance with its specific design.

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In the instance of the coating being applied just prior to implantation, the stent can be prepared in advance. The stent 10, for example, can be sterilized and packaged in a sterile environment for later use. When use of the stent 10 is desired, the stent 10 is

removed from the packaging, and the coating substance is applied to result in the coating 20 resident on the stent 10. The coating 20 can result from application of the coating substance by, for example, the spraying, brushing, swabbing, wiping, printing, or painting methods.

5

The present invention provides the coating 20 for medical devices such as the stent 10. The coating is bio-absorbable. The coating 20 includes the bio-absorbable carrier component and can include the therapeutic agent component. The coating 20 of the present invention provides a unique vehicle for the delivery of beneficial substances to the body tissue of a patient.

The bio-absorbable carrier component itself, in the form of fish oil for example, can provide therapeutic benefits in the form of reduced inflammation, and improved healing, if the fish oil composition is not substantially modified during the process that takes the naturally occurring fish oil and forms it into the coating 20. Some prior attempts to use natural oils as coatings have involved mixing the oil with a solvent, or curing the oil in a manner that destroys the beneficial aspects of the oil. The solvent utilized in the coating 20 of the present invention (NMP) does not have such detrimental effects on the therapeutic properties of the fish oil. Thus the omega-3 fatty acids, and the EPA and DHA substances are substantially preserved in the coating of the present invention.

Therefore, the coating 20 of the present invention includes the bio-absorbable carrier component in the form of the naturally occurring oil (i.e., fish oil, or any equivalent). The bio-absorbable carrier component is thus able to be absorbed by the cells of the body tissue. More specifically, there is a phospholipid layer in each cell of the body tissue. The fish oil, and equivalent oils, contain lipids as well. There is a lipophilic action that results where the lipids are attracted by each other in an effort to escape the aqueous environment surrounding the lipids. Accordingly the lipids attract, the fish oil fatty acids bind to the cells of the tissue, and subsequently alter cell membrane fluidity and cellular uptake. If there is a therapeutic agent component mixed with the bio-absorbable carrier component, the therapeutic component associated with the fish oil lipids penetrates the cells in an altered manner.

As previously mentioned, prior attempts to create drug delivery platforms such as coatings on stents primarily make use of polymer based coatings to provide the ability to better control the release of the therapeutic agent. Essentially, the polymer in the coating releases the drug or agent at a predetermined rate once implanted at a location within the patient. Regardless of how much of the therapeutic agent would be most beneficial to the damaged tissue, the polymer releases the therapeutic agent based on properties of the polymer coating. Accordingly, the effect of the coating is substantially local at the surface of the tissue making contact with the coating and the stent. In some instances the effect of the coating is further localized to the specific locations of stent struts pressed against the tissue location being treated. These prior approaches can create the potential for a localized toxic effect.

Contrarily with the present invention, because of the lipophilic mechanism enabled by the bio-absorbable lipid based coating 20 formed using a cross-linked gel derived from at least one fatty acid compound in accordance with the present invention, the uptake of the therapeutic agent is facilitated by the delivery of the therapeutic agent to the cell membrane by the bio-absorbable carrier component. Further, the therapeutic agent is not freely released into the body fluids, but rather, is delivered directly to the cells and tissue. In prior configurations using polymer based coatings, the drugs were released at a rate regardless of the reaction or need for the drug on the part of the cells receiving the drug.

In addition, the bio-absorbable nature of the carrier component and the resulting coating (in the instances where a bio-absorbable therapeutic agent component is utilized) results in the coating 20 being completely absorbed over time by the cells of the body tissue. There is no break down of the coating into sub parts and substances which induce an inflammatory response that are eventually distributed throughout the body and in some instances disposed of by the body, as is the case with biodegradable coatings. The bio-absorbable nature of the coating 20 of the present invention results in the coating being absorbed, leaving only the stent structure, or other medical device structure. The bio-absorbable carrier component does not induce a foreign body inflammatory response.

Despite action by the cells, the coating 20 of the present invention is further configured to release the therapeutic agent component at a rate no faster than a selected controlled release rate over a period of weeks to months. The controlled release rate  
5 action is achieved by providing an increased level of vitamin E in the mixture with the fish oil, to create a more viscous, sticky, coating substance that better adheres and lasts for a longer duration on the implanted medical device. The controlled release rate can include an initial burst of release, followed by the sustained multi-week to multi-month period of release. Correspondingly, with a greater amount of fatty acids relative to the  
10 level of vitamin E, the controlled release rate can be increased. The fatty acids can be found in the oil, and/or fatty acids such as myristic acid can be added to the oil. Thus, the ratio of fatty acids to alpha-tocopherol can be varied in the preparation of the coating 20 to vary the subsequent release rate of the therapeutic agent in a controlled and predictable manner.

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In addition, the oil provides a lubricious surface against the vessel walls. As the stent 10 having the coating 20 applied thereon is implanted within a blood vessel, for example, there can be some friction between the stent walls and the vessel walls. This can be injurious to the vessel walls, and increase injury at the diseased vessel location.  
20 The use of the naturally occurring oil, such as fish oil, provides extra lubrication to the surface of the stent 10, which reduces the initial injury. With less injury caused by the stent, there is less of an inflammatory response, and less healing required.

Several example implementations have been carried out to demonstrate the  
25 effectiveness of the coating 20 of the present invention. Details concerning the example implementations follow.

#### Example 1

30 A fish oil: vitamin E coating was mixed at a ratio of 50:50. 1.5 grams of this mixture was blended with 1.5 grams of ethanol. When placed in a bell jar vacuum (50 to 60 mTorr) in a weigh pan (19.63 cm<sup>2</sup> area), it took 24 hours to completely remove the ethanol. When placed in a Petri dish (62.07 cm<sup>2</sup> area), it took 4 hours to completely

remove the ethanol under similar vacuum conditions. When the same formulation was placed in the rotating fixture (figure 6B) and the surface area was continually refreshed, it took 1 hour to remove the ethanol under similar vacuum conditions. The removal of ethanol was confirmed by FTIR.

5

### Example 2

A fish oil: vitamin E coating was mixed at a ratio of 50:50. 1.5 grams of this mixture was blended with 1.5 grams of nMP. When placed in a bell jar vacuum (50 to 10 60 mTorr) in a weigh pan (19.63 cm<sup>2</sup> area), the nMP could not be removed even after 120 hours of vacuum. When placed in a Petri dish (62.07 cm<sup>2</sup> area), it took 96 hours to completely remove the nMP under similar vacuum conditions. When the same formulation was placed in the rotating fixture (figure 6B) and the surface area was continually refreshed, it took 30 hours to remove the nMP under similar vacuum 15 conditions. The removal of NMP was confirmed by FTIR.

### Example 3

A 30:70 fish oil: vitamin E formulation was prepared. A rapamycin pro-drug was 20 dissolved in ethanol and 1.9169 grams of the drug solution was added to 1.0751 grams of the coating formulation. This mixture was placed in the rotating fixture (Figure 6B) and the surface area was continually refreshed. The final drug concentration was 24.26% and was confirmed by HPLC analysis. The ethanol solvent was completely removed after 24 hours of operation. The removal of the ethanol was confirmed by 25 FTIR analysis.

Numerous modifications and alternative embodiments of the present invention will be apparent to those skilled in the art in view of the foregoing description. Accordingly, this description is to be construed as illustrative only and is for the purpose 30 of teaching those skilled in the art the best mode for carrying out the present invention. Details of the structure may vary substantially without departing from the spirit of the invention, and exclusive use of all modifications that come within the scope of the

appended claims is reserved. It is intended that the present invention be limited only to the extent required by the appended claims and the applicable rules of law.

CLAIMS

What is claimed is:

- 5 1. A coated medical device, comprising:  
a coating having a bio-absorbable carrier component, the coating further  
including a therapeutic agent and solvent;  
wherein at least a portion of the solvent is removed from the coating before the  
coating is applied to the medical device.
- 10 2. The device of claim 1, wherein a remaining portion of the solvent is removed  
from the coating after the coating is applied to the medical device.
3. The device of claim 1, wherein the coated medical device is implantable in a  
15 patient to effect controlled delivery of the therapeutic agent to the patient.
4. The device of claim 1, wherein the solvent comprises C<sub>2</sub>-C<sub>6</sub> alkanols, 2-  
ethoxyethanol, ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene  
glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol,  
20 transcitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, 2-  
pyrrolidone, 2-piperidone, 2-caprolactam, N-alkylpyrrolidone, N-methyl-2-pyrrolidone,  
N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam,  
dimethylacetamide; ethyl acetate, methyl acetate, butyl acetate, ethylene glycol diethyl  
ether, ethylene glycol dimethyl ether, propylene glycol dimethyl ether, ethyl propionate,  
25 tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate,  
ethyl caprylate, ethyl cutyrate, tracetin, ε-caprolactone and isomers thereof, δ-  
valerolactone and isomers thereof, β-butyrolactone and isomers thereof; water,  
dimethylsulfoxide, benzyl benzoate, ethyl lactate, acetone, methylethyl ketone,  
dimethylsulfone, tetrahydrofuran, decylmethylsulfoxide, N,N-diethyl-m-toulamide or 1-  
30 dodecylazacycloheptan-2-one, hexane, chloroform, dichloromethane, or a combination  
thereof.

5. The device of claim 1, wherein the coating further comprises at least one component selected from a group of components comprising a compatibilizer and a preservative.
- 5 6. The device of claim 1, wherein the bio-absorbable carrier component comprises at least one component selected from a group of components comprised of a naturally occurring oil, and an oil composition.
7. The device of claim 1, wherein the medical device comprises a stent.
- 10 8. The device of claim 1, wherein the solvent is removed from the coating with vacuum or heat.
9. The device of claim 1, wherein the solvent is removed from the coating with  
15 blowing air or an inert gas over the coating.
10. The device of claim 1, wherein the solvent is removed during rotation of the coating.
- 20 11. The device of claim 1, wherein the solvent is removed with mixing the coating to accelerate a removal rate of the solvent.
12. The device of claim 1, wherein the solvent is removed with stirring the coating to accelerate a removal rate of the solvent.
- 25 13. The device of claim 1, wherein the solvent is removed with agitating the coating to accelerate a removal rate of the solvent.
14. An apparatus for drying a coating material prior to application to a medical  
30 device, the apparatus comprising:  
a first container providing a vacuum within the first container;

a second container disposed within the first container for containing a coating material having a bio-absorbable carrier component, the coating material further including a therapeutic agent and solvent; and

5 a rotator for rotating the second container to remove the solvent from the coating material.

15. The apparatus of claim 14, wherein the first container comprises a vacuum oven.

16. The apparatus of claim 14, wherein the first container comprises a bell jar.

10

17. The apparatus of claim 14, wherein the second container comprises a syringe.

18. The apparatus of claim 14, wherein the rotator comprises an electric rotator.

15 19. The apparatus of claim 14, wherein the rotator comprises a mechanical rotator.

20. The apparatus of claim 14, further comprising a temperature controller for controlling a temperature within the first container.

20 21. The apparatus of claim 14, further comprising a vacuum controller for controlling a vacuum within the first container.

22. The apparatus of claim 14, wherein the coating material is mixed to accelerate a removal rate of the solvent.

25

23. The apparatus of claim 14, wherein the coating material is stirred to accelerate a removal rate of the solvent.

24. The apparatus of claim 14, wherein the coating material is agitated to accelerate  
30 a removal rate of the solvent.

25. A method of making a coated medical device, the method comprising:

providing a coating material having a bio-absorbable carrier component, the coating material further including a therapeutic agent and solvent;  
removing the solvent from the coating material; and  
applying the dried coating material to the medical device to form a coating.

5

26. The method of claim 25, wherein the coated medical device is implantable in a patient to effect controlled delivery of the therapeutic agent to the patient.

27. The method of claim 25, wherein the step of removing comprises the step of:  
10 providing a vacuum in a first container within which the solvent is removed from the coating material.

28. The method of claim 27, wherein the step of removing comprises the step of:  
15 disposing a second container within the first container for containing the coating material; and  
rotating the second container to remove the solvent from the coating material under vacuum.

29. The method of claim 28, further comprising the step of:  
20 mixing the coating material to accelerate a removal rate of the solvent.

30. The method of claim 28, wherein the step of removing comprises the step of:  
stirring the coating material to accelerate a removal rate of the solvent.

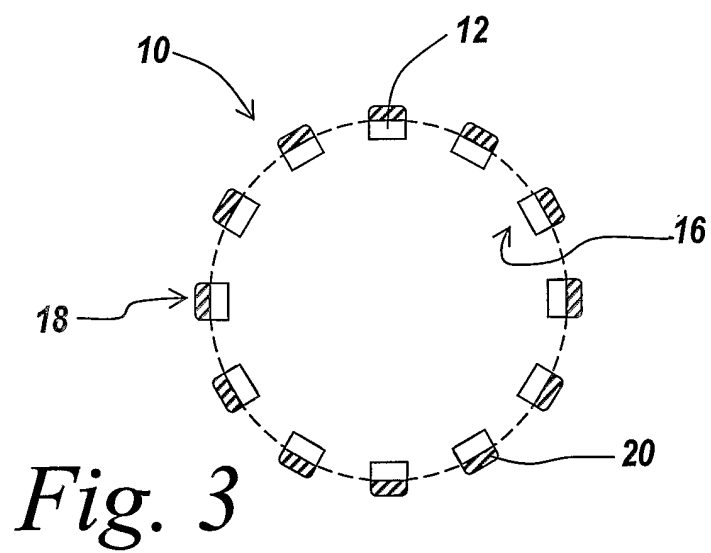
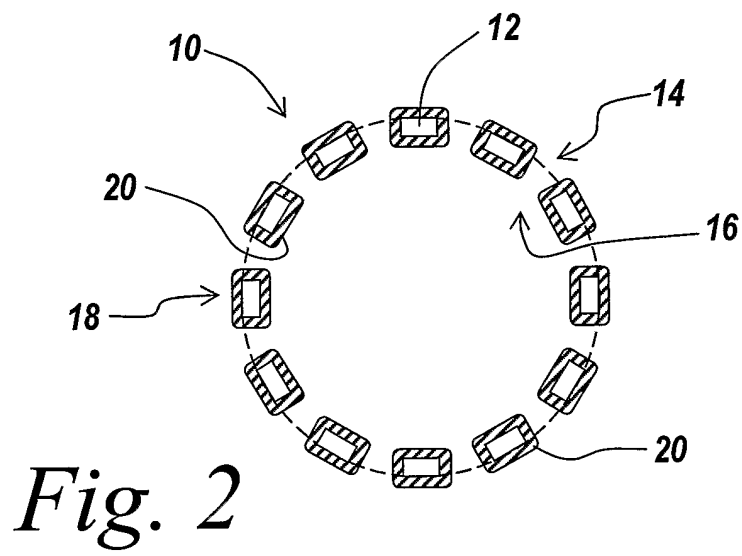
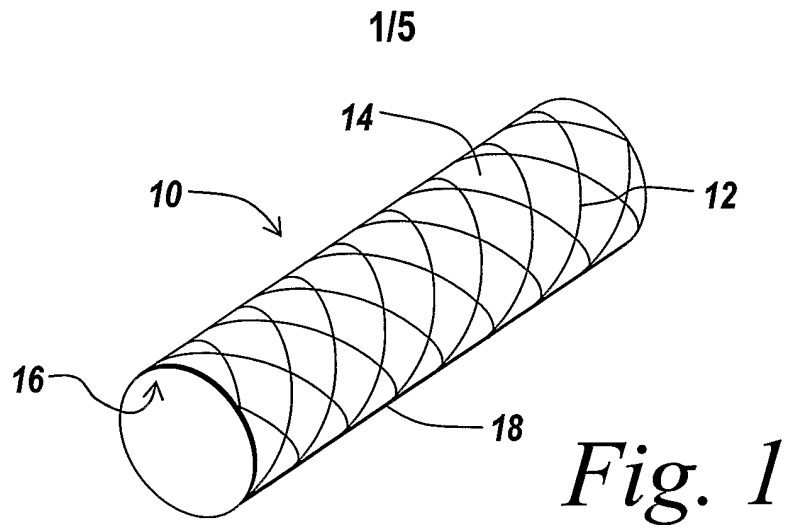
25 31. The method of claim 28, wherein the step of removing comprises the step of:  
agitating the coating material to accelerate a removal rate of the solvent.

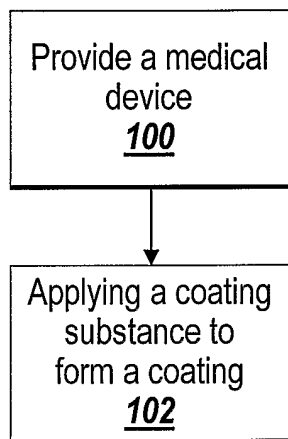
32. The method of claim 25, wherein the step of removing comprises the step of:  
removing the solvent with heat.

30

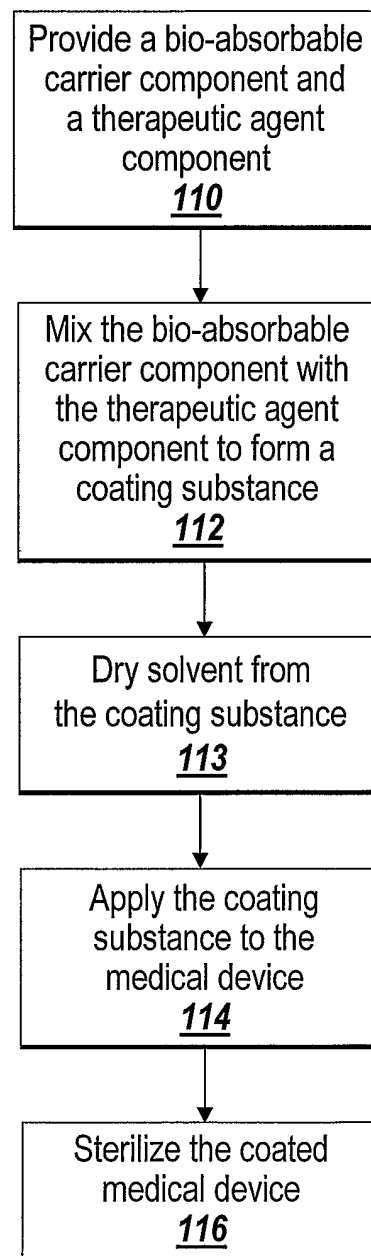
33. The method of claim 25, wherein the step of removing comprises the step of:  
removing the solvent with blowing air over the coating material.

34. The method of claim 25, wherein the step of removing comprises the step of:  
removing the solvent with blowing an inert gas over the coating material.
35. The method of claim 25, wherein the step of removing comprises the step of:  
5 mixing the coating material to accelerate a removal rate of the solvent.
36. The method of claim 25, wherein the step of removing comprises the step of:  
stirring the coating material to accelerate a removal rate of the solvent.
- 10 37. The method of claim 25, wherein the step of removing comprises the step of:  
agitating the coating material to accelerate a removal rate of the solvent.
38. A method of making a coated medical device, the method comprising:  
providing a coating material having a bio-absorbable carrier component, the bio-  
15 absorbable carrier component being at least partially formed of a cellular uptake  
inhibitor and a cellular uptake enhancer, and the coating material further including a  
therapeutic agent and solvent;  
removing the solvent from the coating material to modify the coating material to  
a state of viscosity; and  
20 applying the coating material to the medical device to form a coating.
39. A method of making a coated medical device, the method comprising:  
providing a coating material having a bio-absorbable carrier component, the  
coating material further including a therapeutic agent and solvent;  
25 removing a portion of the solvent from the coating material;  
applying the coating material to the medical device; and  
removing a remaining portion of the solvent from the coating material applied to  
the medical device.



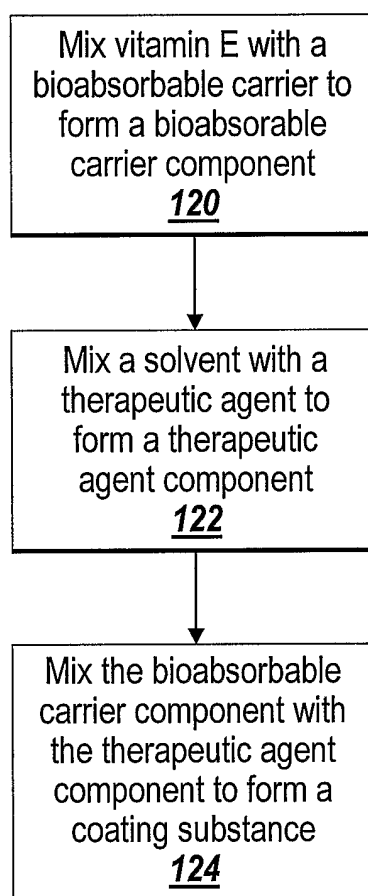


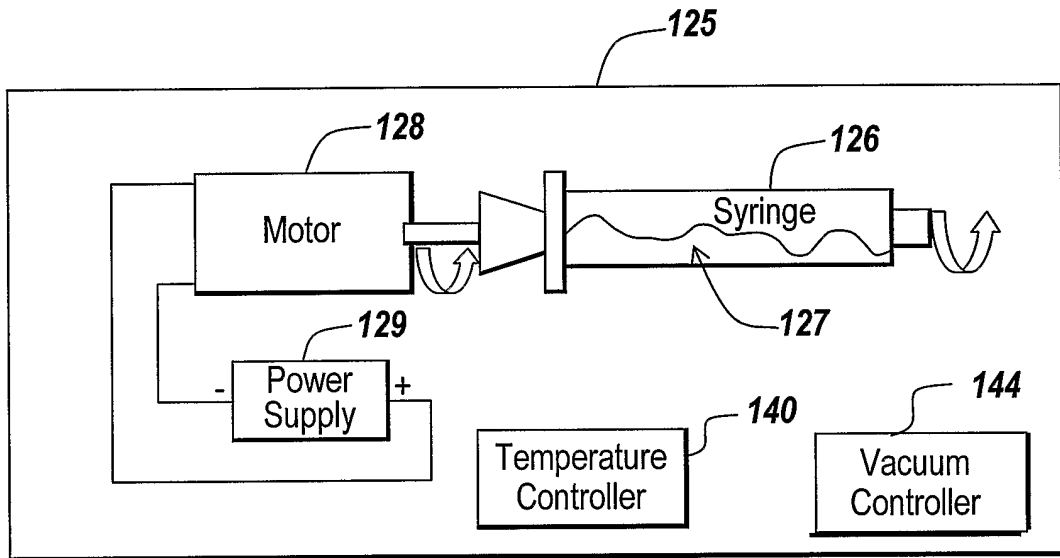
*Fig. 4*



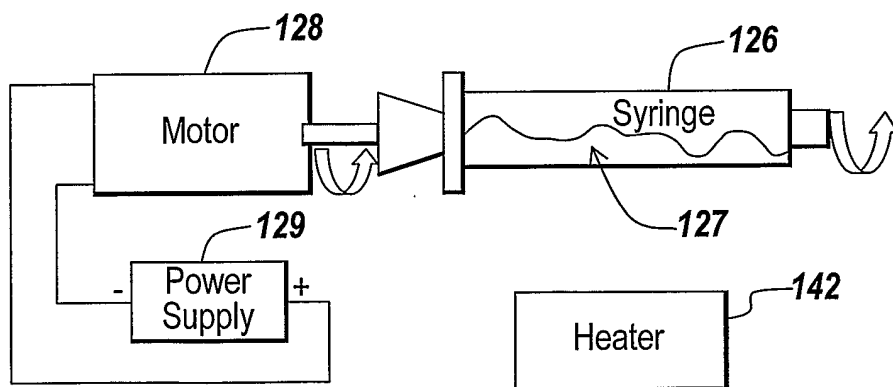
*Fig. 5*

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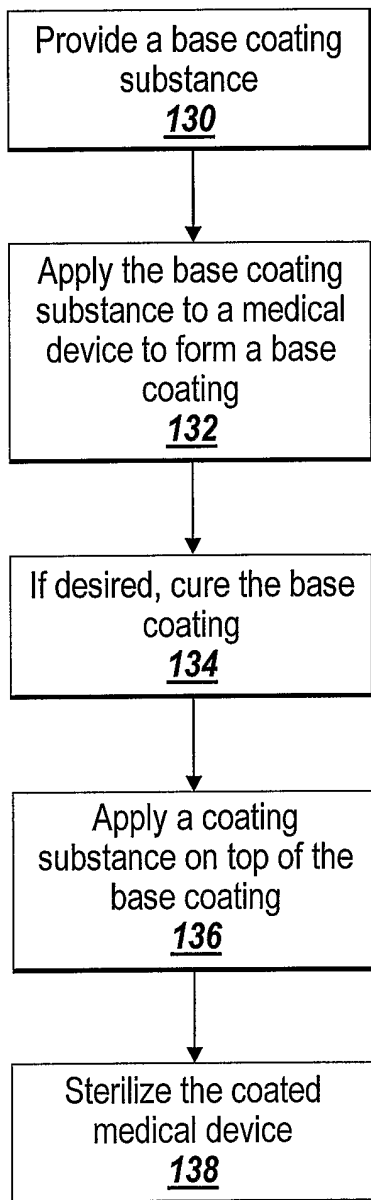
*Fig. 6A*



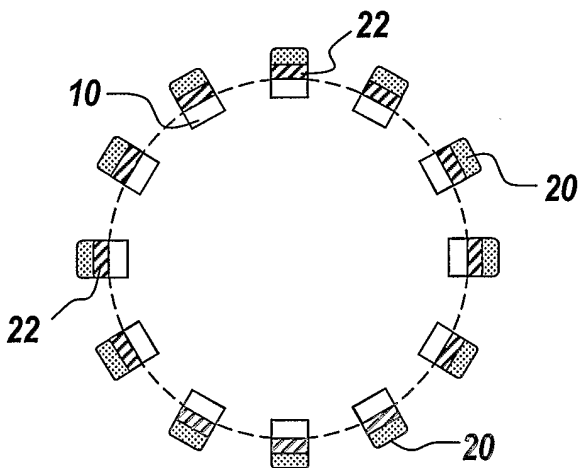
*Fig. 6B*



*Fig. 6C*



*Fig. 7*



*Fig. 8*