

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
27 October 2005 (27.10.2005)

PCT

(10) International Publication Number
WO 2005/099786 A1

(51) International Patent Classification⁷: **A61L 29/08**,
29/16, 31/10, 31/16

New Brighton, MN 55112 (US). **MALINOFF, Harrison, R.** [US/US]; 2250 Wisconsin Avenue North, Golden Valley, MN 55427 (US).

(21) International Application Number:
PCT/US2005/011406

(74) Agents: **DOLAN, John, F.** et al.; Fredrikson & Byron, P.A., Suite 4000, 200 South Sixth Street, Minneapolis, MN 5402-1425 (US).

(22) International Filing Date: 6 April 2005 (06.04.2005)

(25) Filing Language: English

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(26) Publication Language: English

(30) Priority Data:
60/559,821 6 April 2004 (06.04.2004) US

(71) Applicant (*for all designated States except US*): **SURMODICS, INC.** [US/US]; 9924 West 74th Street, Eden Prairie, MN 55344-3523 (US).

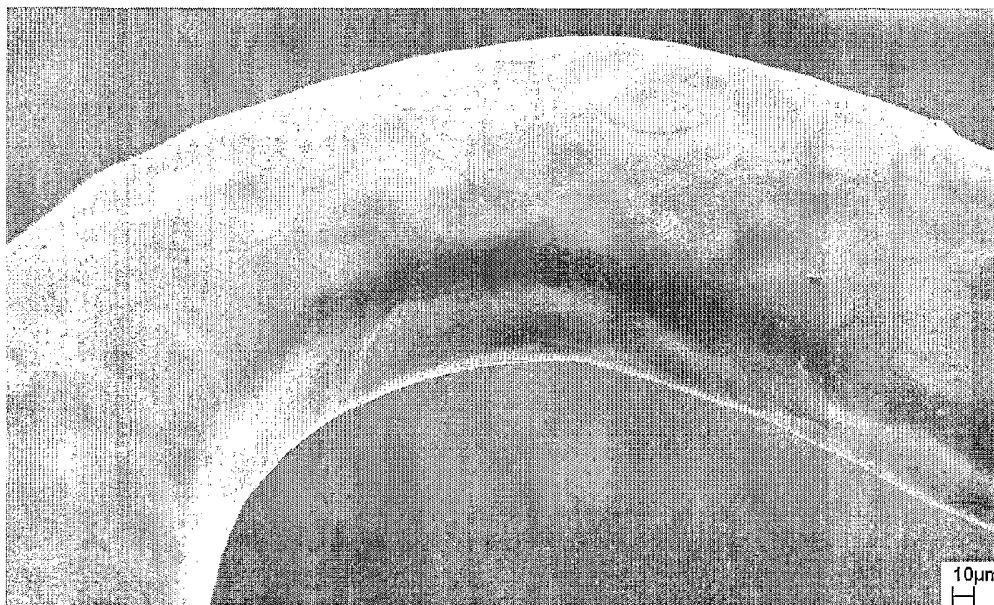
(72) Inventors; and

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,

(75) Inventors/Applicants (*for US only*): **DEWITT, David, M.** [US/US]; 410 North 2nd Street #219, Minneapolis, MN 55401 (US). **FINLEY, Michael, J.** [US/US]; 4205 Princeton Avenue South, St. Louis Park, MN 55416 (US). **LAWIN, Laurie, R.** [US/US]; 3170 Bent Tree Hills Drive,

[Continued on next page]

(54) Title: COATING COMPOSITIONS FOR BIOACTIVE AGENTS



(57) Abstract: Composite materials comprising a water-soluble compound adsorbed onto a basic inorganic material and a biodegradable polymer which yields acidic degradation products, methods of producing same, and methods of use thereof are described, wherein the composite materials are designed so as to provide controlled release of the water soluble molecule.

WO 2005/099786 A1



SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

COATING COMPOSITIONS FOR BIOACTIVE AGENTS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 60/559,821, titled Coating Compositions for Bioactive Agents, filed April 6, 2004, the contents of which are hereby incorporated by reference. This application is related to International PCT Application No. _____, filed April 6, 2005, titled Coating Compositions for Bioactive Agents and identified by Attorney Docket No. 9896.166.8, the contents of which is hereby incorporated by reference.

TECHNICAL FIELD

In one aspect, the present invention relates to a method of treating implantable medical devices with coating compositions to provide for the controlled release of bioactive (e.g., pharmaceutical) agents from the surface of the devices under physiological conditions. In another aspect, the invention relates to the coating compositions, *per se*. In yet another aspect, the invention relates to devices or surfaces coated with such compositions. In yet another aspect, the present invention relates to the local administration of bioactive agents for the prevention and treatment of diseases, such as vascular and ocular diseases.

BACKGROUND OF THE INVENTION

Many surgical interventions require the placement of a medical device into the body. One prevalent surgical intervention often requiring such a device is percutaneous transluminal coronary angioplasty ("PTCA"). Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels, which often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Percutaneous transluminal coronary angioplasty is a medical procedure performed to increase blood flow through a damaged artery and is now the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with PTCA is the abrupt closure of the vessel which can occur soon after angioplasty. Insertion of small spring-like medical devices called stents into such damaged vessels has proved to be a better approach to keep the vessels open as compared to systemic pharmacologic therapy.

While often necessary and beneficial for treating a variety of medical conditions, metal or polymeric devices (e.g., stents, catheters...), after placement in the body, can give rise to numerous physiological complications. Some of these complications include:

increased risk of infection; initiation of a foreign body response resulting in inflammation and fibrous encapsulation; and initiation of a detrimental wound healing response resulting in hyperplasia and restenosis. These problems have been particularly acute with the placement of stents in damaged arteries after angioplasty.

5 One promising approach is to provide the device with the ability to deliver bioactive agents in the vicinity of the implant. By doing so, some of the harmful effects associated with the implantation of medical devices can be diminished. Thus, for example, antibiotics can be released from the surface of the device to minimize the possibility of infection, and antiproliferative drugs can be released to inhibit hyperplasia.
10 Another benefit to the local release of bioactive agents is the avoidance of toxic concentrations of drugs encountered when given systemically at sufficiently high doses to achieve therapeutic concentrations at the site where they are needed.

 Although the potential benefit from using such bioactive agent-releasing medical devices is great, development of such medical devices has been slow. Progress has been
15 hampered by many challenges, including: 1) the requirement, in some instances, for long term (i.e., at least several weeks) release of bioactive agents; 2) the need for a biocompatible, non-inflammatory device surface; 3) the demand for significant durability (and particularly, resistance to delamination and cracking), particularly with devices that undergo flexion and/or expansion when being implanted or used in the body; 4) concerns
20 regarding the ability of the device to be manufactured in an economically viable and reproducible manner; and 5) the requirement that the finished device can be sterilized using conventional methods.

 Implantable medical devices capable of delivering medicinal agents from hydrophobic polymer coatings have been described. See, for instance, U.S. Patent No.
25 6,214,901; U.S. Patent No. 6,344,035; U.S. Publication No. 2002-0032434; U.S. Publication No. 2002-0188037; U.S. Publication No. 2003-0031780; U.S. Publication No. 2003-0232087; U.S. Publication No. 2003-0232122; PCT Publication No. WO 99/55396; PCT Publication No. WO 03/105920; PCT Publication No. WO 03/105918; PCT
Publication No. WO 03/105919 which collectively disclose, *inter alia*, coating
30 compositions having a bioactive agent in combination with a polymer component such as polyalkyl(meth)acrylate or aromatic poly(meth)acrylate polymer and another polymer

component such as poly(ethylene-co-vinyl acetate) for use in coating device surfaces to control and/or improve their ability to release bioactive agents in aqueous systems.

SUMMARY OF THE INVENTION

5 The present invention provides a coating composition, and related methods for preparing and using the coating composition to coat a surface with a bioactive agent, for instance to coat the surface of an implantable medical device in a manner that permits the surface to release the bioactive agent over time when implanted *in vivo*.

10 The coating composition of this invention comprises one or more bioactive agents in combination with a plurality of polymers, including: (a) a first polymer component comprising one or more diolefin derived non-aromatic polymers and copolymers; and (b) a second polymer component comprising one or more polymers selected from the group consisting of poly(alkyl(meth)acrylates) and poly(aromatic (meth)acrylates), where "(meth)" will be understood by those skilled in the art to include such molecules in either
15 the acrylic and/or methacrylic form (corresponding to the acrylates and/or methacrylates, respectively).

20 Applicants have discovered a group of first polymers that when used in combination with one or more second polymers can each meet or exceed the variety of criteria required of some embodiments of the composition of this invention, including in terms of its formulation, delivery, and/or coated characteristics.

25 With regard to its formulation, a coating composition of this invention is may be provided in the form of a true solution by the use of one or more solvents. Such solvents, in turn, are not only capable of dissolving the polymers and bioactive agent in solution, as compared to dispersion or emulsion, but they are also sufficiently volatile to permit the composition to be effectively applied to a surface (e.g., as by spraying) and quickly
30 removed (e.g., as by drying) to provide a stable and desirable coated composition. In turn, the coated composition is itself homogeneous, with the first and second polymers effectively serving as cosolvents for each other, and bioactive agent substantially equally sequestered within them both.

 The ability to form a true solution using the claimed polymer combinations is desired when considering the inclusion of potentially significant amounts of bioactive agent with the polymer blend. In various embodiments of the present invention, the

coating composition is not only in the form of a true solution, but one in which bioactive agent is present at saturated or supersaturated levels. Without intending to be bound by theory, it appears that it is by virtue of the ability to achieve such solutions, that release of the bioactive agent from the coated composition is best accomplished and facilitated. In
5 turn, it appears that the release of bioactive agent from such a system is due, at least in part, to its inherent instability within the coated composition itself, coupled with its physical/chemical preference for surrounding tissues and fluids. In turn, those skilled in the art will appreciate the manner in which the various ingredients and amounts in a composition of this invention can be adjusted to provide desired release kinetics and for
10 any particular bioactive agent, solvent and polymer combination.

With regard to its delivery, a some embodiments of the composition of this invention meets or exceeds further criteria in its ability to be sterilized, stored, and delivered to a surface in a manner that preserves its desired characteristics, yet using conventional delivery means, such as spraying. Such delivery may involve spraying the
15 composition onto a device surface in a manner that avoids or minimizes phase separation of the polymer components.

Finally, and with regard to its coated characteristics, a composition of this invention permits polymer ratios to be varied in a manner that provides not only an optimal combination of such attributes as biocompatibility, durability, and bioactive agent release kinetics, but also that provides a coated composition that is homogeneous, and
20 hence substantially optically clear upon microscopic examination. Even more surprisingly, some embodiments of compositions of this invention will provide these and other features, with or without optional pretreatment of a metallic surface. The ability to achieve or exceed any of these criteria, let alone most if not all of them, was not expected.

25 In turn, compositions of the present invention provide properties that are comparable or better than those obtained with previous polymer blend compositions. This, in turn, provides a variety of new and further opportunities, including with respect to both the type and concentration of bioactive agents that can be coated, as well as the variety of medical devices, and surfaces, themselves. In turn, the present invention also
30 provides a combination that includes a medical device coated with a composition of this invention, as well as a method of preparing and using such a combination.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts a graph illustrating the cumulative bioactive agent release profiles for coating compositions according to the present invention applied to stents, as described in Example 1.

- 5 Figure 1A depicts a bar chart illustrating the durability profiles for coating compositions according to the present invention applied to stents, as described in Example 1.

Figure 2 depicts a graph illustrating the cumulative bioactive agent release profiles for coating compositions according to the present invention applied to stents, as described in Example 2.

- 10 Figure 3 depicts a graph illustrating the cumulative bioactive agent release profiles for coating compositions according to the present invention applied to stents, as described in Example 3.

Figure 4 depicts a graph illustrating the stress/strain measurements of first polymer components used in coating compositions according to the present invention, as described in Example 5.

- 15 Figure 5 depicts a scanning electron microscope image a coated stent including a coating composition according to the present invention after conventional crimping and balloon expansion procedures.

- Figure 6 depicts a graph illustrating the cumulative bioactive agent release profiles for coating compositions according to the present invention applied to stents, as described in Example 7.

Figure 7 depicts a graph illustrating the cumulative bioactive agent release profiles for coating compositions according to the present invention applied to stents, as described in Example 7.

25 DETAILED DESCRIPTION

Without intending to be bound by theory, it appears that suitable first polymers for use in a composition of this invention provide an optimal combination of such properties as glass transition temperature (T_g) and diffusion constant for the particular bioactive agent of choice. Along with melting temperature (T_m), T_g is an important parameter of a given polymer (including copolymer), and particularly amorphous polymers, that can be used to characterize its properties over a wide temperature range. A polymer is typically brittle at temperatures below its T_g , and flexible at temperatures above. Both T_m and T_g

30

can be affected by such things as polymer structure and backbone flexibility, molecular weight, attractive forces, and pressure. For random copolymers and compatible polymer blends, only a single T_g is observed, usually lying intermediate between the T_g of the corresponding pure homopolymers. Different T_g 's are exhibited for incompatible polymer blends, and between the microdomains of block copolymers with mutually incompatible blocks. T_g can be measured by any suitable technique, e.g., dilatometry, refractive index, differential scanning calorimetry, dynamic mechanical measurement, and dielectric measurement.

Second polymers (e.g., poly (n-butyl methacrylate)) of the present composition generally provide a T_g in the range of room to body temperature (e.g., from about 20 °C to about 40 °C), and hence tend to be somewhat stiffer polymers, in turn, providing a slower diffusion constant for many bioactive agents. Applicants have discovered the manner in which certain new polymers can be used as a first polymer component, to essentially balance, or temper the desired properties of the second polymer. Such first polymers will generally provide a lower glass transition temperature (e.g., below room temperature, and in some embodiments in the range of about 0 °C or less), together with a relatively high diffusion constant for the bioactive agent. By appropriately combining the two polymers with bioactive agent, those skilled in the art, given the present description, will be able to vary both the selection and ratios of first and second polymers, in order to determine an optimal combination of physical and mechanical properties, including bioactive agent diffusion and release kinetics, as well as durability and tenacity of the coating itself upon a particular surface, that best fits their particular needs.

Hence the first polymer of this invention may provide an optimal combination of glass transition temperature (e.g., at or lower than that of the second polymer), compatibility with the bioactive agent of choice, acceptable solubility in the solvents of choice, as well as commercial availability and cost.

The term "coating composition", as used herein, will refer to one or more vehicles (e.g., solutions, mixtures, emulsions, dispersions, blends, etc.) used to effectively coat a surface with bioactive agent, first polymer component and/or second polymer component, either individually or in any suitable combination.

The term "coated composition" will refer to the effective combination, upon the surface of a device, of bioactive agent, first polymer component and second polymer

component, whether formed as the result of one or more coating vehicles or in one or more layers and/or steps.

Unless defined otherwise, the term "coating" will refer to the effective combination of bioactive agent, first polymer component and second polymer component, independent of the device surface, and whether formed as the result of one or more coating vehicles or in one or more layers.

Unless otherwise indicated, the term "molecular weight" and all polymeric molecular weights described herein are "weight average" molecular weights ("M_w"). As used herein "weight average molecular weight" or M_w, is an absolute method of measuring molecular weight and is particularly useful for measuring the molecular weight of a polymer preparation. The weight average molecular weight (M_w) can be defined by the following formula:

$$M_w = \frac{\sum_i N_i M_i^2}{\sum_i N_i M_i}$$

wherein N represents the number of moles of a polymer in the sample with a mass of M, and \sum_i is the sum of all N_iM_i (species) in a preparation. The M_w can be measured using common techniques, such as light scattering or ultracentrifugation. Discussion of M_w and other terms used to define the molecular weight of polymer preparations can be found in, for example, Allcock, H. R. and Lampe, F. W., Contemporary Polymer Chemistry; pg 271 (1990).

As described and exemplified herein, a resultant composition can be coated using a plurality of individual steps or layers, including for instance, an initial layer having only bioactive agent (or bioactive agent with one or both of the polymer components), over which are coated one or more additional layers containing suitable combinations of bioactive agent, first polymer component and/or second polymer component, the combined result of which is to provide a coated composition of the invention. In turn, in some embodiments, the invention further provides a method of reproducibly controlling the release (e.g., elution) of a bioactive agent from the surface of a medical device implanted *in vivo*. Those skilled in the art will appreciate the manner in which the combined effect of these various layers can be used and optimized to achieve various effects *in vivo*. In addition, the surface to which the composition is applied can itself be

pretreated in a manner sufficient to improve attachment of the composition to the underlying (e.g., metallic) surface. Examples of such pretreatments include the use of compositions such as Parylene™ coatings, as described herein. Additional examples of such pretreatments include silane coupling agents, photografted polymers, epoxy primers, polycarboxylate resins, and physical roughening of the surface. It is further noted that the pretreatment compositions may be used in combination with each other or may be applied in separate layers to form a pretreatment coating on the surface of the medical device.

While not intending to be bound by theory, the release kinetics of the bioactive agent *in vivo* are thought to generally include both a short term (“burst”) release component, within the order of minutes to hours after implantation, and a longer term release component, which can range from on the order of hours to days or even months or years of useful release.

Additionally, the ability to coat a device in the manner of the present invention provides greater latitude in the composition of various coating layers, e.g., permitting more or less of the second polymer component (i.e., poly(alkyl (meth)acrylate) and/or poly(aromatic (meth)acrylate)) to be used in coating compositions used to form different layers (e.g., as a topcoat layer). This, in turn, provides the opportunity to further control release and elution of the bioactive agent from the overall coating.

The coating composition and method can be used to control the amount and rate of bioactive agent (e.g., drug) release from one or more surfaces of implantable medical devices. In some embodiments, the method employs a mixture of hydrophobic polymers in combination with one or more bioactive agents, such as a pharmaceutical agent, such that the amount and rate of release of agent(s) from the medical device can be controlled, e.g., by adjusting the relative types and/or concentrations of hydrophobic polymers in the mixture. For a given combination of polymers, for instance, this approach permits the release rate to be adjusted and controlled by simply adjusting the relative concentrations of the polymers in the coating mixture. This provides an additional means to control rate of bioactive agent release besides the conventional approach of varying the concentration of bioactive agent in a coated composition.

Some embodiments of the invention include a method of coating a device comprising the step of applying the composition to the device surface under conditions of controlled relative humidity (at a given temperature), for instance, under conditions of

increased or decreased relative humidity as compared to ambient humidity. Humidity can be "controlled" in any suitable manner, including at the time of preparing and/or using (as by applying) the composition, for instance, by coating the surface in a confined chamber or area adapted to provide a relative humidity different than ambient conditions, and/or by
5 adjusting the water content of the coating or coated composition itself. Without intending to be bound by theory, it appears that the elution rate of a bioactive agent from a coating composition generally increases as relative humidity increases.

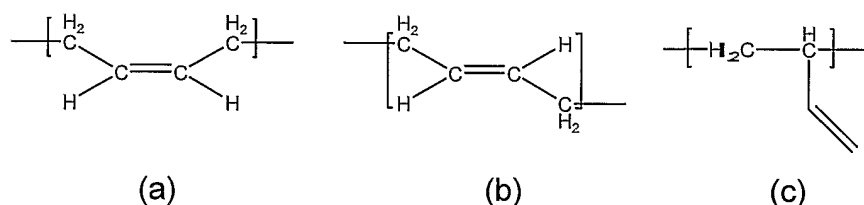
Some embodiments of a coating composition of this invention include a mixture of two or more polymers having complementary physical characteristics, and a bioactive
10 agent or agents applicable to the surface of an implantable medical device. The device can be of any suitable type or configuration, and in some embodiments undergoes flexion and/or expansion upon implantation or use, as in the manner of a stent or catheter. The applied coating composition is cured (e.g., by solvent evaporation) to provide a tenacious and flexible bioactive-releasing composition on the surface of the medical device. Such
15 coating compositions are particularly well suited for devices that are themselves sufficiently small, or have portions that are sufficiently small (as in the struts of an expandable stent or the twists of an ocular coil), to permit the coated composition to form a contiguous, e.g., circumferential, coating, thereby further improving the ability of the coating to remain intact (e.g., avoid delamination).

20 The complementary polymers are selected such that a broad range of relative polymer concentrations can be used without detrimentally affecting the desirable physical characteristics of the polymers. By use of the polymer combinations (including mixtures and blends) of the invention the bioactive release rate from a coated medical device can be manipulated by adjusting the relative concentrations of the polymers.

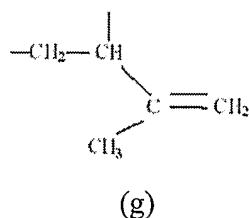
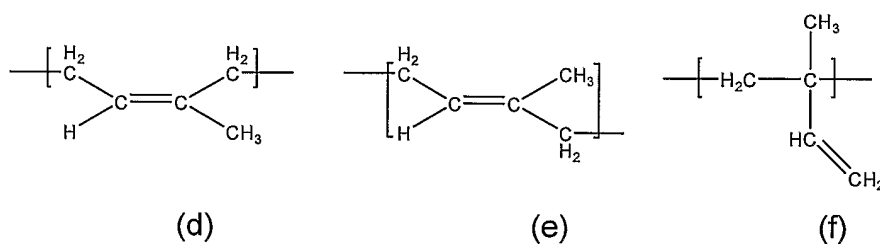
25 In some embodiments, the present invention relates to a coating composition and related method for coating an implantable medical device which undergoes flexion and/or expansion upon implantation. However it is noted that the coating composition may also be utilized with medical devices that have minimal or do not undergo flexion and/or expansion. The structure and composition of the underlying device can be of any suitable,
30 and medically acceptable, design and can be made of any suitable material that is compatible with the coating itself. The natural or pretreated surface of the medical device is provided with a coating containing one or more bioactive agents.

A first polymer component of this invention provides an optimal combination of similar properties, and particularly when used in admixture with the second polymer component. First polymers include diolefin derived non-aromatic polymers and copolymers. Examples of suitable polymers are commercially available from sources such as Sigma-Aldrich.

First polymers may include diolefin-derived, non-aromatic polymers and copolymers, including those in which the diolefin monomer used to prepare the polymer or copolymer is selected from butadiene ($\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$) and/or isoprene ($\text{CH}_2=\text{CH}-\text{C}(\text{CH}_3)=\text{CH}_2$). A butadiene polymer can include one or more butadiene monomer units which can be selected from the monomeric unit structures (a), (b), or (c):



An isoprene polymer can include one or more isoprene monomer units which can be selected from the monomeric unit structures (d), (e), (f) or (g):



In some embodiments, the polymer is a homopolymer derived from diolefin monomers or is a copolymer of diolefin monomer with non-aromatic mono-olefin monomer, and optionally, the homopolymer or copolymer can be partially hydrogenated. Such polymers can be selected from the group consisting of polybutadienes containing

polymerized *cis*-, *trans*- and/or 1,2- monomer units, and in some embodiments a mixture of all three co-polymerized monomer units, and polyisoprenes containing polymerized *cis*-1,4- and/or *trans*-1,4- monomer units, polymerized 1,2-vinyl monomer units, polymerized 3,4-vinyl monomer units and/or others as described in the Encyclopedia of Chemical
5 Technology, Vol. 8, page 915 (1993), the entire contents of which is hereby incorporated by reference.

Alternatively, the first polymer is a copolymer, including graft copolymers, and random copolymers based on a non-aromatic mono-olefin co-monomer such as acrylonitrile, an alkyl (meth)acrylate and/or isobutylene. In some embodiments, when the
10 mono-olefin monomer is acrylonitrile, the interpolymerized acrylonitrile is present at up to about 50% by weight; and when the mono-olefin monomer is isobutylene, the diolefin monomer is isoprene (e.g., to form what is commercially known as a "butyl rubber"). In some embodiments, the polymers and copolymers have a Mw between about 50 kilodaltons and about 1,000 kilodaltons. In other embodiments, the polymers and
15 copolymers have a Mw between about 100 kilodaltons and about 450 kilodaltons. In yet other embodiments the polymers and copolymers have a Mw between about 150 kilodaltons and about 1,000 kilodaltons, and optionally between about 200 kilodaltons and about 600 kilodaltons.

Other examples of suitable first polymers of this type are commercially available
20 from sources such as Sigma-Aldrich, such as the 2003-2004 Aldrich Handbook of Fine Chemicals and Laboratory Equipment, the contents of which are hereby incorporated by reference. For example, suitable first polymers include, but are not limited to, polybutadiene, poly(butadiene-co-acrylonitrile), polybutadiene-block-polyisoprene, polybutadiene-graft-poly(methyl acrylate-co-acrylonitrile), polyisoprene, and partially
25 hydrogenated polyisoprene.

A second polymer component of this invention provides an optimal combination of various structural/functional properties, including hydrophobicity, durability, bioactive agent release characteristics, biocompatibility, molecular weight, and availability. In one such an embodiment, the composition may comprise at least one second polymer
30 component selected from the group consisting of poly(alkyl (meth)acrylates) and poly(aromatic (meth)acrylates).

In some embodiments, the second polymer component is a poly(alkyl)methacrylate, that is, an ester of a methacrylic acid. Examples of suitable poly(alkyl (meth)acrylates) include those with alkyl chain lengths from 2 to 8 carbons, inclusive, and with molecular weights from 50 kilodaltons to 900 kilodaltons. In some
 5 embodiments the polymer mixture includes a poly(alkyl (meth)acrylate) with a molecular weight of from about 100 kilodaltons to about 1000 kilodaltons, in some embodiments from about 150 kilodaltons to about 500 kilodaltons, in some embodiments from about 200 kilodaltons to about 400 kilodaltons. An example of a second polymer is poly (n-butyl methacrylate). Examples of other polymers are poly(n-butyl methacrylate-co-methyl
 10 methacrylate, with a monomer ratio of 3:1, poly(n-butyl methacrylate-co-isobutyl methacrylate, with a monomer ratio of 1:1 and poly(t-butyl methacrylate). Such polymers are available commercially (e.g., from Sigma-Aldrich, Milwaukee, WI) with molecular weights ranging from about 150 kilodaltons to about 350 kilodaltons, and with varying inherent viscosities, solubilities and forms (e.g., as slabs, granules, beads, crystals or
 15 powder).

Examples of suitable poly(aromatic (meth)acrylates) include poly(aryl (meth)acrylates), poly(aralkyl (meth)acrylates), poly(alkaryl (meth)acrylates), poly(aryloxyalkyl (meth)acrylates), and poly (alkoxyaryl (meth)acrylates). Such terms are used to describe polymeric structures wherein at least one carbon chain and at least one
 20 aromatic ring are combined with (meth)acrylic groups, typically esters, to provide a composition of this invention. For instance, and more specifically, a poly(aralkyl (meth)acrylate) can be made from aromatic esters derived from alcohols also containing aromatic moieties, such as benzyl alcohol. Similarly, a poly(alkaryl (meth)acrylate) can be made from aromatic esters derived from aromatic alcohols such as p-anisole. Suitable
 25 poly(aromatic (meth)acrylates) include aryl groups having from 6 to 16 carbon atoms and with molecular weights from about 50 to about 900 kilodaltons. Examples of suitable poly(aryl (meth)acrylates) include poly(9-anthracenyl methacrylate), poly(chlorophenyl acrylate), poly(methacryloxy-2-hydroxybenzophenone), poly(methacryloxybenzotriazole), poly(naphthyl acrylate), poly(naphthylmethacrylate), poly-4-nitrophenylacrylate,
 30 poly(pentachloro(bromo, fluoro) acrylate) and methacrylate, poly(phenyl acrylate) and poly(phenyl methacrylate). Examples of suitable poly(aralkyl (meth)acrylates) include poly(benzyl acrylate), poly(benzyl methacrylate), poly(2-phenethyl acrylate), poly(2-

phenethyl methacrylate) and poly(1-pyrenylmethyl methacrylate). Examples of suitable poly(alkaryl(meth)acrylates include poly(4-sec-butylphenyl methacrylate), poly(3-ethylphenyl acrylate), and poly(2-methyl-1-naphthyl methacrylate). Examples of suitable poly(aryloxyalkyl (meth)acrylates) include poly(phenoxyethyl acrylate),
5 poly(phenoxyethyl methacrylate), and poly(polyethylene glycol phenyl ether acrylate) and poly(polyethylene glycol phenyl ether methacrylate) with varying polyethylene glycol molecular weights. Examples of suitable poly(alkoxyaryl(meth)acrylates) include poly(4-methoxyphenyl methacrylate), poly(2-ethoxyphenyl acrylate) and poly(2-methoxynaphthyl acrylate).

10 Acrylate or methacrylate monomers or polymers and/or their parent alcohols are commercially available from Sigma-Aldrich (Milwaukee, WI) or from Polysciences, Inc, (Warrington, PA).

Optionally, the coating composition may include one or more additional polymers in combination with the first and second polymer components, the additional polymers
15 being, for example, selected from the group consisting of (i) poly(alkylene-co-alkyl(meth)acrylates), (ii) ethylene copolymers with other alkylenes, (iii) polybutenes, (iv) aromatic group-containing copolymers, (v) epichlorohydrin-containing polymers and (vi) poly(ethylene-co-vinyl acetate). In some embodiments, the additional polymers may act as substitutes for a portion of the first polymer. For example, the additional polymers may
20 substitute up to about 25% of the first polymer. In other embodiments, the additional polymers may substitute up to about 50% of the first polymer

Suitable poly(alkylene-co-alkyl(meth)acrylates) include those copolymers in which
the alkyl groups are either linear or branched, and substituted or unsubstituted with non-interfering groups or atoms. Such alkyl groups may comprise from 1 to 8 carbon atoms,
25 inclusive, and in some embodiments, from 1 to 4 carbon atoms, inclusive. In some embodiments, the alkyl group is methyl.

In turn, copolymers that include such alkyl groups may comprise from about 15 % to about 80% (wt) of alkyl acrylate. When the alkyl group is methyl, the polymer may contain from about 20% to about 40% methyl acrylate, and in some embodiments, from
30 about 25 to about 30% methyl acrylate. When the alkyl group is ethyl, the polymer may contain from about 15% to about 40% ethyl acrylate, and when the alkyl group is butyl, the polymer may contain from about 20% to about 40% butyl acrylate.

The alkylene groups are selected from ethylene and/or propylene, and in some embodiments, the alkylene group is ethylene. In some embodiments, the (meth)acrylate comprises an acrylate (i.e., no methyl substitution on the acrylate group). Some embodiments of copolymers provide a molecular weight (Mw) of about 50 kilodaltons to about 500 kilodaltons, and in various embodiments, Mw is 50 kilodaltons to about 200 kilodaltons.

The glass transition temperature for these copolymers varies with ethylene content, alkyl length on the (meth)acrylate, and whether the co-polymer is an acrylate or methacrylate. At higher ethylene content, the glass transition temperature tends to be lower, and closer to that of pure polyethylene (-120°C). A longer alkyl chain also lowers the glass transition temperature. A methyl acrylate homopolymer has a glass transition temperature of about 10°C while a butyl acrylate homopolymer has one of -54°C .

Copolymers such as poly(ethylene-co-methyl acrylate), poly(ethylene-co-butyl acrylate) and poly(ethylene-co-2-ethylhexyl acrylate) copolymers are available commercially from sources such as Atofina Chemicals, Inc., Philadelphia, PA, and can be prepared using methods available to those skilled in the respective art.

Other examples of suitable additional polymers of this type are commercially available from sources such as Sigma-Aldrich, such as the 2003-2004 Aldrich Handbook of Fine Chemicals and Laboratory Equipment. For example, suitable additional polymers include, but are not limited to, poly(ethylene-co-methyl acrylate), poly(ethylene-co-ethyl acrylate), and poly(ethylene-co-butyl acrylate).

Suitable additional polymers also include ethylene copolymers with other alkylenes, which in turn, can include straight chain and branched alkylenes, as well as substituted or unsubstituted alkylenes. Examples include copolymers prepared from alkylenes that comprise from 3 to 8 branched or linear carbon atoms, inclusive, alkylene groups that comprise from 3 to 4 branched or linear carbon atoms, inclusive, and alkylene groups containing 3 carbon atoms (e.g., propylene). In some embodiments, the other alkylene is a straight chain alkylene (e.g., 1-alkylene).

Copolymers of this type can comprise from about 20% to about 90% (based on moles) of ethylene, and in some embodiments, from about 35% to about 80% (mole) of ethylene. Such copolymers will have a molecular weight of between about 30 kilodaltons to about 500 kilodaltons. Examples of copolymers are selected from the group consisting

of poly(ethylene-co-propylene), poly(ethylene-co-1-butene), poly(ethylene-co-1-butene-co-1-hexene) and/or poly(ethylene-co-1-octene).

Examples of copolymers include poly(ethylene-co-propylene) random copolymers in which the copolymer contains from about 35% to about 65% (mole) of ethylene; and in
5 some embodiments, from about 55% to about 65% (mole) ethylene, and the molecular weight of the copolymer is from about 50 kilodaltons to about 250 kilodaltons, and in some embodiments from about 100 kilodaltons to about 200 kilodaltons.

Copolymers of this type can optionally be provided in the form of random terpolymers prepared by the polymerization of both ethylene and propylene with
10 optionally one or more additional diene monomers, such as those selected from the group consisting of ethylidene norbornane, dicyclopentadiene and/or hexadiene. In some embodiments terpolymers of this type can include up to about 5% (mole) of the third diene monomer.

Other examples of suitable additional polymers of this type are commercially
15 available from sources such as Sigma-Aldrich, such as the 2003-2004 Aldrich Handbook of Fine Chemicals and Laboratory Equipment. For example, suitable additional polymers include, but are not limited to, poly(ethylene-co-propylene), poly(ethylene-co-1-butene), poly(ethylene-co-1-butene-co-1-hexene), poly(ethylene-co-1-octene), and poly(ethylene-co-propylene-co-5-methylene-2-norbornene).

20 "Polybutenes" suitable for use in the present invention as additional polymers include polymers derived by homopolymerizing or randomly interpolymerizing isobutylene, 1-butene and/or 2-butene. The polybutene can be a homopolymer of any of the isomers or it can be a copolymer or a terpolymer of any of the monomers in any ratio. In some embodiments, the polybutene contains at least about 90% (wt) of isobutylene or
25 1-butene, and in some embodiments, the polybutene contains at least about 90% (wt) of isobutylene. The polybutene may contain non-interfering amounts of other ingredients or additives, for instance it can contain up to 1000 ppm of an antioxidant (e.g., 2,6-di-tert-butyl-methylphenol).

In some embodiments, the polybutene has a molecular weight between about 100
30 kilodaltons and about 1,000 kilodaltons, in some embodiments, between about 150 kilodaltons and about 600 kilodaltons, and in some embodiments, between about 150 kilodaltons and about 250 kilodaltons. In other embodiments, the polybutene has a

molecular weight between about 150 kilodaltons and about 1,000 kilodaltons, optionally, between about 200 kilodaltons and about 600 kilodaltons, and further optionally, between about 350 kilodaltons and about 500 kilodaltons. Polybutenes having a molecular weight greater than about 600 kilodaltons, including greater than 1,000 kilodaltons are available
5 but are expected to be more difficult to work with and, will in turn, be less desired. Other examples of suitable copolymers of this type are commercially available from sources such as Sigma-Aldrich.

Other examples of suitable additional polymers of this type are commercially available from sources such as Sigma-Aldrich, such as the 2003-2004 Aldrich Handbook
10 of Fine Chemicals and Laboratory Equipment.

Other additional polymers include aromatic group-containing copolymers, including random copolymers, block copolymers and graft copolymers. In some embodiments, the aromatic group is incorporated into the copolymer via the polymerization of styrene, and in some embodiments, the random copolymer is a
15 copolymer derived from copolymerization of styrene monomer and one or more monomers selected from butadiene, isoprene, acrylonitrile, a C₁-C₄ alkyl (meth)acrylate (e.g., methyl methacrylate) and/or butene (e.g., isobutylene). Useful block copolymers include copolymer containing (a) blocks of polystyrene, (b) blocks of a polyolefin selected from polybutadiene, polyisoprene and/or polybutene (e.g., isobutylene), and (c) optionally
20 a third monomer (e.g., ethylene) copolymerized in the polyolefin block.

The aromatic group-containing copolymers may contain about 10% to about 50% (wt) of polymerized aromatic monomer and the molecular weight of the copolymer may be from about 50 kilodaltons to about 500 kilodaltons. In some embodiments, the molecular weight of the copolymer may be from about 300 kilodaltons to about 500
25 kilodaltons. In other embodiments, the molecular weight of the copolymer may be from about 100 kilodaltons to about 300 kilodaltons.

Other examples of suitable additional polymers of this type are commercially available from sources such as Sigma-Aldrich, such as the 2003-2004 Aldrich Handbook of Fine Chemicals and Laboratory Equipment. For example, suitable additional polymers
30 include, but are not limited to, poly(styrene-co-butadiene) (random), polystyrene-block-polybutadiene, polystyrene-block-polybutadiene-block-polystyrene, polystyrene-block-poly(ethylene-ran-butylene)-block-polystyrene, polystyrene-block-polyisoprene-block-

polystyrene, polystyrene-block-polyisobutylene-block-polystyrene, poly(styrene-co-acrylonitrile), poly(styrene-co-butadiene-co-acrylonitrile), and poly(styrene-co-butadiene-co-methyl methacrylate).

Other suitable additional polymers include epichlorohydrin homopolymers and
5 poly(epichlorohydrin-co-alkylene oxide) copolymers. In some embodiments in the case of the copolymer, the copolymerized alkylene oxide is ethylene oxide. In some embodiments, epichlorohydrin content of the epichlorohydrin-containing polymer is from about 30% to 100% (wt), and in some embodiments from about 50% to 100% (wt). In some embodiments, the epichlorohydrin-containing polymers have an Mw from about 100
10 kilodaltons to about 300 kilodaltons.

Other examples of suitable additional copolymers of this type are commercially available from sources such as Sigma-Aldrich, such as the 2003-2004 Aldrich Handbook of Fine Chemicals and Laboratory Equipment. For example, suitable additional polymers include, but are not limited to, polyepichlorohydrin, and poly(epichlorohydrin-co-ethylene
15 oxide).

One additional polymer that may be utilized in the coating composition of the present invention includes poly(ethylene-co-vinyl acetate) (pEVA). Examples of suitable polymers of this type are available commercially and include poly(ethylene-co-vinyl acetate) having vinyl acetate concentrations of from about 8% and about 90%, in some
20 embodiments from about 20 to about 40 weight percent and in some embodiments from about 30 to about 34 weight percent. Such polymers are generally found in the form of beads, pellets, granules, etc. It has generally been found that pEVA co-polymers with lower percent vinyl acetate become increasingly insoluble in typical solvents.

Coating compositions for use in this invention may include mixtures of first and
25 second polymer components as described herein. Optionally, both first and second polymer components are purified for such use to a desired extent and/or provided in a form suitable for *in vivo* use. Moreover, biocompatible additives such as antioxidants (e.g., butylated hydroxytoluene (BHT), vitamin E (tocopherol), BN^XTM, and/or dilauryl thiodipropionate (DLTDP)) and permeation enhancers (e.g., vitamin C) may be added.
30 Other suitable additives include dyes and pigments (e.g., titanium dioxide, Solvent Red 24, iron oxide, and Ultramarine Blue); slip agents (e.g., amides such as oleyl palmitamide, N,N'-ethylene bisoleamide, erucamide, stearamide, and oleamide); antioxidants (e.g.

Irganox™ series, phenolic and hindered phenolic antioxidants, organophosphites (e.g., trisnonylphenyl phosphite, Irgafos™ 168), lactones (e.g., substituted benzofuranone), hydroxylamine, and MEHQ (monomethyl ether of hydroquinone)); surfactants (e.g., anionic fatty acid surfactants (e.g., sodium lauryl sulfate, sodium
5 dodecylbenzenesulfonate, sodium stearate, and sodium palmitate), cationic fatty acid surfactants (e.g., quaternary ammonium salts and amine salts), and nonionic ethoxylated surfactants (e.g., ethoxylated p-octylphenol)); and leachable materials (i.e., permeation enhancers) (e.g., hydrophilic polymers (e.g., poly(ethylene glycol), polyvinylpyrrolidone, and poly(vinyl alcohol)) and hydrophilic small molecules (e.g., sodium chloride,
10 glucose)). In addition, any impurities may be removed by conventional methods available to those skilled in the art.

In some embodiments the polymer mixture includes a first polymer component comprising one or more polymers selected from the group consisting of diolefin derived non-aromatic polymers and copolymers, and a second polymer component selected from
15 the group consisting of poly (alkyl(meth)acrylates) and poly (aromatic(meth)acrylates) and having a molecular weight of in some embodiments from about 150 kilodaltons to about 500 kilodaltons, and in some embodiments from about 200 kilodaltons to about 400 kilodaltons.

These mixtures of polymers have proven useful with absolute polymer
20 concentrations (i.e., the total combined concentrations of both polymers in the coating composition), of between about 0.1 and about 50 percent (by weight), and in some embodiments between about 0.1 and about 35 percent (by weight). In various embodiments, the polymer mixtures contain at least about 10 percent by weight of either the first polymer or the second polymer.

25 In some embodiments, the polymer composition may comprise about 5% to about 95% of the first and/or second polymers based on the total weights of the first and second polymers. In some embodiments, the composition may comprise about 15% to about 85% of the first and/or second polymers. In various embodiments, the composition may include about 25% to about 75% of the first and/or second polymers.

30 In some embodiments, the bioactive agent may comprise about 1% to about 75% of the first polymer, second polymer, and bioactive agent mixture (i.e., excluding solvents and other additives). In some embodiments, the bioactive agent may comprise about 5%

to about 60% of such a mixture. In various embodiments, the bioactive agent may comprise about 25% to about 45% of such a mixture. The concentration of the bioactive agent or agents dissolved or suspended in the coating mixture can range from about 0.01 to about 90 percent, by weight, based on the weight of the final coating composition, and optionally from about 0.1 to about 50 percent by weight.

The term "bioactive agent", as used herein, will refer to a wide range of biologically active materials or drugs that can be incorporated into a coating composition of the present invention. In some embodiments, the bioactive agent(s) to be incorporated do not chemically interact with the coating composition during fabrication or during the bioactive agent release process.

Bioactive agent will, in turn, refer to a peptide, protein, carbohydrate, nucleic acid, lipid, polysaccharide or combinations thereof, or synthetic or natural inorganic or organic molecule, that causes a biological effect when administered in vivo to an animal, including but not limited to birds and mammals, including humans. Nonlimiting examples are antigens, enzymes, hormones, receptors, peptides, and gene therapy agents. Examples of suitable gene therapy agents include a) therapeutic nucleic acids, including antisense DNA and antisense RNA, and b) nucleic acids encoding therapeutic gene products, including plasmid DNA and viral fragments, along with associated promoters and excipients. Examples of other molecules that can be incorporated include nucleosides, nucleotides, antisense, vitamins, minerals, and steroids.

Controlled release of bioactive agent is vitally important in many medical areas, including cardiology, oncology, central nervous system disorders, neurology, immunology, diabetes control, musculoskeletal and joint diseases, ophthalmology, vaccination, respiratory, endocrinology, dermatology, and diagnostics/imaging.

Furthermore, it is recognized that thrombus formation on or around medical devices such as stents may create variations in biological agent uptake in target tissue sites and can act to either increase or decrease wall deposition according to the clot and device geometry. The embodiments of this invention further enable reliable and predictable delivery and update of bioactive agents through enhancement of the conformable, durable and stable coatings which result, regardless of flexion or other motion of the medical device substrate.

Coating compositions prepared according to this process can be used to deliver drugs such as nonsteroidal anti-inflammatory compounds, anesthetics, chemotherapeutic agents, immunotoxins, immunosuppressive agents, steroids, antibiotics, antivirals, antifungals, steroidal antiinflammatories, anticoagulants, antiproliferative agents, angiogenic agents, and anti-angiogenic agents. In some embodiments, the bioactive agent to be delivered is a hydrophobic drug having a relatively low molecular weight (i.e., a molecular weight no greater than about two kilodaltons, and optionally no greater than about 1.5 kilodaltons). For example, hydrophobic drugs such as rapamycin, paclitaxel, dexamethasone, lidocaine, triamcinolone acetone, retinoic acid, estradiol, pimecrolimus, tacrolimus or tetracaine can be included in the coating and are released over several hours or longer.

Classes of medicaments which can be incorporated into coatings of this invention include, but are not limited to, anti-AIDS substances, anti-neoplastic substances, antibacterials, antifungals and antiviral agents, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, immunomodulators (e.g., cyclosporine), tranquilizers, anti-convulsants, muscle relaxants and anti-Parkinsonism substances, anti-spasmodics and muscle contractants, miotics and anti-cholinergics, immunosuppressants (e.g. cyclosporine), anti-glaucoma solutes, anti-parasite and/or anti-protozoal solutes, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents (such as NSAIDs), local anesthetics, ophthalmics, prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, and cell response modifiers. A more complete listing of classes of medicaments may be found in the *Pharmazeutische Wirkstoffe*, ed. A. Von Kleemann and J. Engel, Georg Thieme Verlag, Stuttgart/New York, 1987, incorporated herein by reference.

Antibiotics are recognized as substances which inhibit the growth of or kill microorganisms. Antibiotics can be produced synthetically or by microorganisms. Examples of antibiotics include penicillin, tetracycline, chloramphenicol, minocycline, doxycycline, vancomycin, bacitracin, kanamycin, neomycin, gentamycin, erythromycin, cephalosporins, geldanamycin and analogs thereof. Examples of cephalosporins include cephalothin, cephapirin, cefazolin, cephalixin, cephadrine, cefadroxil, cefamandole, cefoxitin, cefaclor, cefuroxime, cefonicid, ceforanide, cefotaxime, moxalactam, ceftizoxime, ceftriaxone, and cefoperazone.

Antiseptics are recognized as substances that prevent or arrest the growth or action of microorganisms, generally in a nonspecific fashion, e.g., either by inhibiting their activity or destroying them. Examples of antiseptics include silver sulfadiazine, chlorhexidine, glutaraldehyde, peracetic acid, sodium hypochlorite, phenols, phenolic compounds, iodophor compounds, quaternary ammonium compounds, and chlorine compounds.

Anti-viral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include methyl-P-adamantane methylamine, hydroxy-ethoxymethylguanine, adamantanamine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, and adenine arabinoside.

Enzyme inhibitors are substances which inhibit an enzymatic reaction. Examples of enzyme inhibitors include edrophonium chloride, N-methylphysostigmine, neostigmine bromide, physostigmine sulfate, tacrine HCl, tacrine, 1-hydroxymaleate, iodotubercidin, p-bromotetramisole, 10-(α -diethylaminopropionyl)-phenothiazine hydrochloride, calmidazolium chloride, hemicholinium-3,3,5-dinitrocatechol, diacylglycerol kinase inhibitor I, diacylglycerol kinase inhibitor II, 3-phenylpropargylamine, N-monomethyl-L-arginine acetate, carbidopa, 3-hydroxybenzylhydrazine HCl, hydralazine HCl, clorgyline HCl, deprenyl HCl, L(-), deprenyl.HCl, D(+), hydroxylamine HCl, iproniazid phosphate, 6-MeO-tetrahydro-9H-pyrido-indole, nialamide, pargyline HCl, quinacrine HCl, semicarbazide HCl, tranlycypromine HCl, N,N-diethylaminoethyl-2,2-diphenylvalerate hydrochloride, 3-isobutyl-1-methylxanthine, papaverine HCl, indomethacin, 2-cyclooctyl-2-hydroxyethylamine hydrochloride, 2, 3-dichloro-a-methylbenzylamine (DCMB), 8,9-dichloro-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride, p-aminogluthethimide, p-aminogluthethimide tartrate, R(+), p-aminogluthethimide tartrate, S(-), 3-iodotyrosine, alpha-methyltyrosine, L(-), alpha-methyltyrosine, D L(-), cetazolamide, dichlorphenamide, 6-hydroxy-2-benzothiazolesulfonamide, and allopurinol.

Anti-pyretics are substances capable of relieving or reducing fever. Anti-inflammatory agents are substances capable of counteracting or suppressing inflammation. Examples of such agents include aspirin (acetylsalicylic acid), indomethacin, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac, diflunisal, diclofenac, indoprofen and sodium salicylamide.

Local anesthetics are substances which inhibit pain signals in a localized region. Examples of such anesthetics include procaine, lidocaine, tetracaine and dibucaine.

Imaging agents are agents capable of imaging a desired site, e.g., tumor, in vivo. Examples of imaging agents include substances having a label which is detectable in vivo, e.g., antibodies attached to fluorescent labels. The term antibody includes whole antibodies or fragments thereof.

Cell response modifiers are chemotactic factors such as platelet-derived growth factor (pDGF). Other chemotactic factors include neutrophil-activating protein, monocyte chemoattractant protein, macrophage-inflammatory protein, SIS (small inducible secreted), platelet factor, platelet basic protein, melanoma growth stimulating activity, epidermal growth factor, transforming growth factor (alpha), fibroblast growth factor, platelet-derived endothelial cell growth factor, estradiols, insulin-like growth factor, nerve growth factor, bone growth/cartilage-inducing factor (alpha and beta), and matrix metallo proteinase inhibitors. Other cell response modifiers are the interleukins, interleukin inhibitors or interleukin receptors, including interleukin 1 through interleukin 10; interferons, including alpha, beta and gamma; hematopoietic factors, including erythropoietin, granulocyte colony stimulating factor, macrophage colony stimulating factor and granulocyte-macrophage colony stimulating factor; tumor necrosis factors, including alpha and beta; transforming growth factors (beta), including beta-1, beta-2, beta-3, inhibin, activin, DNA that encodes for the production of any of these proteins, antisense molecules, androgenic receptor blockers and statin agents.

Examples of bioactive agents include sirolimus, including analogues and derivatives thereof (including rapamycin, ABT-578, everolimus). Sirolimus has been described as a macrocyclic lactone or triene macrolide antibiotic and is produced by *Streptomyces hygroscopicus*, having a molecular formula of $C_{51}H_{79}O_{13}$ and a molecular weight of 914.2. Sirolimus has been shown to have antifungal, antitumor and immunosuppressive properties. Another suitable bioactive agent includes paclitaxel (Taxol) which is a lipophilic (i.e., hydrophobic) natural product obtained via a semi-synthetic process from *Taxus baccata* and having antitumor activity.

Other suitable bioactive agents include, but are not limited to, the following compounds, including analogues and derivatives thereof: dexamethasone, betamethasone, retinoic acid, vinblastine, vincristine, vinorelbine, etoposide, teniposide, dactinomycin

(actinomycin D), daunorubicin, doxorubicin, idarubicin, anthracyclines, mitoxantrone, bleomycin, plicamycin (mithramycin), mitomycin, mechlorethamine, cyclophosphamide and its analogs, melphalan, chlorambucil, ethylenimines and methylmelamines, alkyl sulfonates-busulfan, nitrosoureas, carmustine (BCNU) and analogs, streptozocin, trazes-
5 dacarbazine, methotrexate, fluorouracil, floxuridine, cytarabine, mercaptopurine, thioguanine, pentostatin, 2-chlorodeoxyadenosine, cisplatin, carboplatin, procarbazine, hydroxyurea, mitotane, aminoglutethimide, estrogen, heparin, synthetic heparin salts, tissue plasminogen activator, streptokinase, urokinase, dipyridamole, ticlopidine, clopidogrel, abciximab, breveldin, cortisol, cortisone, fludrocortisone, prednisone,
10 prednisolone, 6U-methylprednisolone, triamcinolone, triamcinolone acetone, acetaminophen, etodolac, tolmetin, ketorolac, ibuprofen and derivatives, mefenamic acid, meclofenamic acid, piroxicam, tenoxicam, phenylbutazone, oxyphenthatrazone, nabumetone, auranofin, aurothioglucose, gold sodium thiomalate, tacrolimus (FK-506), azathioprine, mycophenolate mofetil, vascular endothelial growth factor (VEGF),
15 angiotensin receptor blocker, nitric oxide donors, anti-sense oligonucleotides and combinations thereof, cell cycle inhibitors, mTOR inhibitors, and growth factor signal transduction kinase inhibitors. Another suitable bioactive agent includes morpholino phosphorodiamidate oligmer.

A comprehensive listing of bioactive agents can be found in The Merck Index,
20 Thirteenth Edition, Merck & Co. (2001), the entire contents of which is incorporated by reference herein. Bioactive agents are commercially available from Sigma Aldrich (e.g., vincristine sulfate). The concentration of the bioactive agent or agents dissolved or suspended in the coating mixture can range from about 0.01 to about 90 percent, by weight, based on the weight of the final coated composition. Additives such as inorganic
25 salts, BSA (bovine serum albumin), and inert organic compounds can be used to alter the profile of bioactive agent release, as known to those skilled in the art.

In order to provide a some embodiments of a coating, a coating composition is prepared to include one or more solvents, a combination of complementary polymers dissolved in the solvent, and the bioactive agent or agents dispersed in the polymer/solvent
30 mixture. The solvent may be one in which the polymers form a true solution. The pharmaceutical agent itself may either be soluble in the solvent or form a dispersion throughout the solvent. Suitable solvents include, but are not limited to, alcohols (e.g.,

methanol, butanol, propanol and isopropanol), alkanes (e.g., halogenated or unhalogenated alkanes such as hexane, cyclohexane, methylene chloride and chloroform), amides (e.g., dimethylformamide), ethers (e.g., tetrahydrofuran (THF), dioxolane, and dioxene), ketones (e.g., methyl ethyl ketone), aromatic compounds (e.g., toluene and xylene), nitriles (e.g., acetonitrile) and esters (e.g., ethyl acetate). THF and chloroform have been found to be desirable solvents due to their excellent solvency for a variety of polymers and bioactive agents of the present invention.

A coating composition of this invention can be used to coat the surface of a variety of devices, and is particularly useful for those devices that will come in contact with aqueous systems. Such devices are coated with a coating composition adapted to release bioactive agent in a prolonged and controlled manner, generally beginning with the initial contact between the device surface and its aqueous environment.

The coated composition provides a means to deliver bioactive agents from a variety of biomaterial surfaces. Biomaterials include those formed of synthetic polymers, including oligomers, homopolymers, and copolymers resulting from either addition or condensation polymerizations. Examples of suitable addition polymers include, but are not limited to, acrylics such as those polymerized from methyl acrylate, methyl methacrylate, hydroxyethyl methacrylate, hydroxyethyl acrylate, acrylic acid, methacrylic acid, glyceryl acrylate, glyceryl methacrylate, methacrylamide, and acrylamide; vinyls, such as those polymerized from ethylene, propylene, styrene, vinyl chloride, vinyl acetate, vinyl pyrrolidone, and vinylidene difluoride. Examples of condensation polymers include, but are not limited to, nylons such as polycaprolactam, poly(lauryl lactam), poly(hexamethylene adipamide), and poly(hexamethylene dodecanediamide), and also polyurethanes, polycarbonates, polyamides, polysulfones, poly(ethylene terephthalate), poly(lactic acid), poly(glycolic acid), poly(lactic acid-co-glycolic acid), polydimethylsiloxanes, polyetheretherketone, poly(butylene terephthalate), poly(butylene terephthalate-co-polyethylene glycol terephthalate), esters with phosphorus containing linkages, non-peptide polyamino acid polymers, polyiminocarbonates, amino acid-derived polycarbonates and polyarylates, and copolymers of polyethylene oxides with amino acids or peptide sequences.

Certain natural materials are also suitable biomaterials, including human tissue such as bone, cartilage, skin and teeth; and other organic materials such as wood,

cellulose, compressed carbon, and rubber. Other suitable biomaterials include metals and ceramics. The metals include, but are not limited to, titanium, stainless steel, and cobalt chromium. A second class of metals include the noble metals such as gold, silver, copper, and platinum. Alloys of metals may be suitable for biomaterials as well, such as nitinol (e.g., MP35). The ceramics include, but are not limited to, silicon nitride, silicon carbide, zirconia, and alumina, as well as glass, silica, and sapphire. Yet other suitable biomaterials include combinations of ceramics and metals, as well as biomaterials that are fibrous or porous in nature.

Optionally, the surface of some biomaterials can be pretreated (e.g., with a silane and/or Parylene™ coating composition in one or more layers) in order to alter the surface properties of the biomaterial. For example, in various embodiments of the present invention a layer of silane may be applied to the surface of the biomaterial followed by a layer of Parylene™. Parylene™ C is the polymeric form of the low-molecular-weight dimer of para-chloro-xylylene. Silane and/or Parylene™ C (a material supplied by Specialty Coating Systems (Indianapolis)) can be deposited as a continuous coating on a variety of medical device parts to provide an evenly distributed, transparent layer. In one embodiment, the deposition of Parylene™ is accomplished by a process termed vapor deposition polymerization, in which dimeric Parylene™ C is vaporized under vacuum at 150°C, pyrolyzed at 680°C to form a reactive monomer, then pumped into a chamber containing the component to be coated at 25°C. At the low chamber temperature, the monomeric xylylene is deposited on the part, where it immediately polymerizes via a free-radical process. The polymer coating reaches molecular weights of approximately 500 kilodaltons.

Deposition of the xylylene monomer takes place in only a moderate vacuum (0.1 torr) and is not line-of-sight. That is, the monomer has the opportunity to surround all sides of the part to be coated, penetrating into crevices or tubes and coating sharp points and edges, creating what is called a "conformal" coating. With proper process control, it is possible to deposit a pinhole-free, insulating coating that will provide very low moisture permeability and high part protection to corrosive biological fluids.

Adherence is a function of the chemical nature of the surface to be coated. It has been reported, for instance, that tantalum and silicon surfaces can be overcoated with

silicon dioxide, then with plasma-polymerized methane, and finally with Parylene™ C to achieve satisfactory adherence.

Most applications of Parylene™ C coating in the medical device industry are for protecting sensitive components from corrosive body fluids or for providing lubricity to surfaces. Typical anticorrosion applications include blood pressure sensors, cardiac-assist devices, prosthetic components, bone pins, electronic circuits, ultrasonic transducers, bone-growth stimulators, and brain probes. Applications to promote lubricity include mandrels, injection needles, cannulae, and catheters.

Also, as previously described above, the surface to which the composition is applied can itself be pretreated in other manners sufficient to improve attachment of the composition to the underlying (e.g., metallic) surface. Additional examples of such pretreatments include photografted polymers, epoxy primers, polycarboxylate resins, and physical roughening of the surface. It is further noted that the pretreatment compositions and/or techniques may be used in combination with each other or may be applied in separate layers to form a pretreatment coating on the surface of the medical device.

In some embodiments, a tie-in layer may be utilized to facilitate one or more physical and/or covalent bonds between layers. For example, the pretreatment layer may include a multi-interface system to facilitate adhesion and cohesion interaction relative to the different materials positioned at the interface of each layer. For example, the application of Parylene pretreatments to metal surfaces may be aided by a first application of a reactive organosilane reagent. A reactive organosilane reagent containing an unsaturated pendant group is capable of participating with the Parylene radicals as they deposit on the surface from the vapor phase. After cleaning of the metal surface, an organosilane reagent with an unsaturated pendant group may be applied to the metal oxide surface on a metal substrate. Without intending to be bound by theory, it appears that the silicon in the organosilane reagent couples covalently to the metal oxide, linking the organosilane group to the surface. The substrate may then be placed in a Parylene reactor and exposed to the vapor-phase Parylene process. During this process, the unsaturated pendant groups on the organosilane-treated surface can react with the Parylene diradicals depositing from the vapor phase. This forms a covalent link between the Parylene and the organosilane layer. The Parylene also forms covalent bonds to itself as it deposits. Thus, this process yields a layered surface in which the layers are covalently bonded to each

other. This forms a very strong bond between the Parylene and the metal surface, resulting in high durability to mechanical challenges. Further, in some embodiments, the Parylene may physically bond with the bioactive agent delivery coating or may include a reactive acrylate group that can be reacted with the bioactive agent delivery coating to improve durability to mechanical challenges.

The coating composition of the present invention can be used in combination with a variety of devices, including those used on a temporary, transient, or permanent basis upon and/or within the body.

Compositions of this invention can be used to coat the surface of a variety of implantable devices, for example: drug-delivering vascular stents (e.g., self-expanding stents typically made from nitinol, balloon-expanded stents typically prepared from stainless steel); other vascular devices (e.g., grafts, catheters, valves, artificial hearts, heart assist devices); implantable defibrillators; blood oxygenator devices (e.g., tubing, membranes); surgical devices (e.g., sutures, staples, anastomosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, vascular implants, tissue adhesives and sealants, tissue scaffolds); membranes; cell culture devices; chromatographic support materials; biosensors; shunts for hydrocephalus; wound management devices; endoscopic devices; infection control devices; orthopedic devices (e.g., for joint implants, fracture repairs); dental devices (e.g., dental implants, fracture repair devices), urological devices (e.g., penile, sphincter, urethral, bladder and renal devices, and catheters); colostomy bag attachment devices; ophthalmic devices (e.g. ocular coils); glaucoma drain shunts; synthetic prostheses (e.g., breast); intraocular lenses; respiratory, peripheral cardiovascular, spinal, neurological, dental, ear/nose/throat (e.g., ear drainage tubes); renal devices; and dialysis (e.g., tubing, membranes, grafts).

Examples of useful devices include urinary catheters (e.g., surface-coated with antimicrobial agents such as vancomycin or norfloxacin), intravenous catheters (e.g., treated with antithrombotic agents (e.g., heparin, hirudin, coumadin), small diameter grafts, vascular grafts, artificial lung catheters, atrial septal defect closures, electro-stimulation leads for cardiac rhythm management (e.g., pacemaker leads), glucose sensors (long-term and short-term), degradable coronary stents (e.g., degradable, non-degradable, peripheral), blood pressure and stent graft catheters, birth control devices, benign prostate and prostate cancer implants, bone repair/augmentation devices, breast implants, cartilage

repair devices, dental implants, implanted drug infusion tubes, intravitreal drug delivery devices, nerve regeneration conduits, oncological implants, electrostimulation leads, pain management implants, spinal/orthopedic repair devices, wound dressings, embolic protection filters, abdominal aortic aneurysm grafts, heart valves (e.g., mechanical, polymeric, tissue, percutaneous, carbon, sewing cuff), valve annuloplasty devices, mitral valve repair devices, vascular intervention devices, left ventricle assist devices, neuro aneurysm treatment coils, neurological catheters, left atrial appendage filters, hemodialysis devices, catheter cuff, anastomotic closures, vascular access catheters, cardiac sensors, uterine bleeding patches, urological catheters/stents/implants, in vitro diagnostics, aneurysm exclusion devices, and neuropatches.

Examples of other suitable devices include, but are not limited to, vena cava filters, urinary dialators, endoscopic surgical tissue extractors, atherectomy catheters, clot extraction catheters, percutaneous transluminal angioplasty catheters, PTCA catheters, stylets (vascular and non-vascular), coronary guidewires, drug infusion catheters, esophageal stents, circulatory support systems, angiographic catheters, transition sheaths and dilators, coronary and peripheral guidewires, hemodialysis catheters, neurovascular balloon catheters, tympanostomy vent tubes, cerebro-spinal fluid shunts, defibrillator leads, percutaneous closure devices, drainage tubes, thoracic cavity suction drainage catheters, electrophysiology catheters, stroke therapy catheters, abscess drainage catheters, biliary drainage products, dialysis catheters, central venous access catheters, and parental feeding catheters.

Examples of medical devices suitable for the present invention include, but are not limited to catheters, implantable vascular access ports, blood storage bags, vascular stents, blood tubing, arterial catheters, vascular grafts, intraaortic balloon pumps, cardiovascular sutures, total artificial hearts and ventricular assist pumps, extracorporeal devices such as blood oxygenators, blood filters, hemodialysis units, hemoperfusion units, plasmapheresis units, hybrid artificial organs such as pancreas or liver and artificial lungs, as well as filters adapted for deployment in a blood vessel in order to trap emboli (also known as “distal protection devices”).

The compositions are particularly useful for those devices that will come in contact with aqueous systems, such as bodily fluids. Such devices are coated with a coating composition adapted to release bioactive agent in a prolonged and controlled manner,

generally beginning with the initial contact between the device surface and its aqueous environment. It is important to note that the local delivery of combinations of bioactive agents may be utilized to treat a wide variety of conditions utilizing any number of medical devices, or to enhance the function and/or life of the device. Essentially, any type of medical device may be coated in some fashion with one or more bioactive agents that enhances treatment over use of the individual use of the device or bioactive agent.

In some embodiments, the coating composition can also be used to coat stents, e.g., either self-expanding stents, which are typically prepared from nitinol, or balloon-expandable stents, which are typically prepared from stainless steel. Other stent materials, such as cobalt chromium alloys, can be coated by the coating composition as well.

Devices which are particularly suitable include vascular stents such as self-expanding stents and balloon expandable stents. Examples of self-expanding stents useful in the present invention are illustrated in U.S. Pat. Nos. 4,655,771 and 4,954,126 issued to Wallsten and 5,061,275 issued to Wallsten et al. Examples of suitable balloon-expandable stents are shown in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco and U.S. Pat. No. 4,886,062 issued to Wiktor.

In various embodiments, the coating composition can also be used to coat ophthalmic devices, e.g. ocular coils. A therapeutic agent delivery device that is particularly suitable for delivery of a therapeutic agent to limited access regions, such as the vitreous chamber of the eye and inner ear is described in U.S. patent number 6,719,750 and U.S. Patent Application Publication No. 2005/0019371 A1.

The resultant coating composition can be applied to the device in any suitable fashion (e.g., the coating composition can be applied directly to the surface of the medical device, or alternatively, to the surface of a surface-modified medical device, by dipping, spraying, ultrasonic deposition, or using any other conventional technique). The suitability of the coating composition for use on a particular material, and in turn, the suitability of the coated composition can be evaluated by those skilled in the art, given the present description. In one such embodiment, for instance, the coating comprises at least two layers which are themselves different. For instance, a base layer may be applied having bioactive agent(s) alone, or together with or without one or more of the polymer components, after which one or more topcoat layers are coated, each with either first and/or second polymers as described herein, and with or without bioactive agent. These

different layers, in turn, can cooperate in the resultant composite coating to provide an overall release profile having certain desired characteristics, and, in some embodiments, for use with bioactive agents of high molecular weight. In various embodiments, the composition is coated onto the device surface in one or more applications of a single composition that includes first and second polymers, together with bioactive agent. However, as previously suggested a pretreatment layer or layers may be first applied to the surface of the device, wherein subsequent coating with the composition may be performed onto the pretreatment layer(s). The method of applying the coating composition to the device is typically governed by the geometry of the device and other process considerations. The coating is subsequently cured by evaporation of the solvent. The curing process can be performed at room or elevated temperature, and optionally with the assistance of vacuum and/or controlled humidity.

It is also noted that one or more additional layers may be applied to the coating layer(s) that include bioactive agent. Such layer(s) or topcoats can be utilized to provide a number of benefits, such as biocompatibility enhancement, delamination protection, durability enhancement, bioactive agent release control, to just mention a few. In one embodiment the topcoat may include one or more of the first, second, and/or additional polymers described herein with or without the inclusion of a bioactive agent, as appropriate to the application. In some embodiments, the topcoat includes a second polymer that is a poly(alkyl(meth)acrylate). An example of a poly(alkyl(meth)acrylate) includes poly (n-butyl methacrylate). In another embodiment, the first or second polymers could further include functional groups (e.g. hydroxy, thiol, methylol, amino, and amine-reactive functional groups such as isocyanates, thioisocyanates, carboxylic acids, acyl halides, epoxides, aldehydes, alkyl halides, and sulfonate esters such as mesylate, tosylate, and tresylate) that could be utilized to bind the topcoat to the adjacent coating composition. In another embodiment of the present invention one or more of the pretreatment materials (e.g. Parylene™) may be applied as a topcoat. Additionally, biocompatible topcoats (e.g. heparin, collagen, extracellular matrices, cell receptors...) may be applied to the coating composition of the present invention. Such biocompatible topcoats may be adjoined to the coating composition of the present invention by utilizing photochemical or thermochemical techniques known in the art. Additionally, release layers may be applied to the coating composition of the present invention as a friction

barrier layer or a layer to protect against delamination. Examples of biocompatible topcoats that may be used include those disclosed in U.S. Patent No. U.S. Patent No. 4,979,959 and 5,744,515.

In some embodiments, the polymer composition for use in this invention is
5 biocompatible, e.g., such that it results in no significant induction of inflammation or irritation when implanted. In addition, the polymer combination may be useful throughout a broad spectrum of both absolute concentrations and relative concentrations of the polymers. This means that the physical characteristics of the coating, such as tenacity, durability, flexibility and expandability, will typically be adequate over a broad range of
10 polymer concentrations. In turn, in some embodiments, the ability of the coating to control the release rates of a variety of bioactive agents can be manipulated by varying the absolute and relative concentrations of the polymers.

Additionally, the coatings of the present invention are generally hydrophobic and limit the intake of aqueous fluids. For example, many embodiments of the present
15 invention are coating compositions including two or more hydrophobic polymers wherein the resulting coating shows <10% (wt) weight change when exposed to water, and optionally <5% (wt) weight change when exposed to water.

A coating composition can be provided in any suitable form, e.g., in the form of a true solution, or fluid or paste-like emulsion, mixture, dispersion or blend. In some
20 embodiments, polymer combinations of this invention are capable of being provided in the form of a true solution, and in turn, can be used to provide a coating that is both optically clear (upon microscopic examination), while also containing a significant amount of bioactive agent. In turn, the coated composition will generally result from the removal of solvents or other volatile components and/or other physical-chemical actions (e.g., heating
25 or illuminating) affecting the coated composition *in situ* upon the surface.

A further example of a coating composition embodiment may include a configuration of one or more bioactive agents within an inner matrix structure, for example, bioactive agents within or delivered from a degradable encapsulating matrix or a microparticle structure formed of semipermeable cells and/or degradable polymers. One or
30 more inner matrices may be placed in one or more locations within the coating composition and at one or more locations in relation to the substrate. Examples of inner matrices, for example degradable encapsulating matrices formed of semipermeable cells

and/or degradable polymers, are disclosed and/or suggested in U.S. Publication No. 20030129130, U.S. Patent Application Serial No. 60/570,334 filed May 12, 2004, U.S. Patent Application Serial No. 60/603,707, filed August 23, 2004, U.S. Publication No. 20040203075, filed April 10, 2003, U.S. Publication No. 20040202774 filed on April 10, 2003, and U.S. Patent Application Serial No. 10/723,505, filed November 26, 2003, the entire contents of which are incorporated by reference herein.

The overall weight of the coating upon the surface may vary depending on the application. However, the weight of the coating attributable to the bioactive agent is optionally in the range of about one microgram to about 10 milligram (mg) of bioactive agent per cm^2 of the effective surface area of the device. By "effective" surface area it is meant the surface amenable to being coated with the composition itself. For a flat, nonporous, surface, for instance, this will generally be the macroscopic surface area itself, while for considerably more porous or convoluted (e.g., corrugated, pleated, or fibrous) surfaces the effective surface area can be significantly greater than the corresponding macroscopic surface area. In some embodiments, the weight of the coating attributable to the bioactive agent is between about 0.005 mg and about 10 mg, and optionally between about 0.01 mg and about 1 mg of bioactive agent per cm^2 of the gross surface area of the device. This quantity of bioactive agent is generally required to provide desired activity under physiological conditions.

In turn, the final coating thickness of some embodiments of the coated composition will typically be in the range of about 0.1 micrometers to about 100 micrometers, and optionally about 0.5 micrometers and about 25 micrometers. This level of coating thickness is generally required to provide an adequate concentration of drug to provide adequate activity under physiological conditions.

The invention will be further described with reference to the following non-limiting Examples. It will be apparent to those skilled in the art that many changes can be made in the embodiments described without departing from the scope of the present invention. Thus the scope of the present invention should not be limited to the embodiments described in this application, but only by the embodiments described by the language of the claims and the equivalents of those embodiments. Unless otherwise indicated, all percentages are by weight.

EXAMPLES

TEST PROCEDURES

The potential suitability of particular coated compositions for *in vivo* use can be determined by a variety of screening methods, examples of each of which are described herein.

Sample Preparation Procedure

Stainless steel stents used in the following examples were manufactured by Laserage Technology Corporation, Waukegan, IL. In some cases, the metal surface of the stents were coated without any pretreatment beyond washing. In other cases, a primer was applied to the stents by first cleaning the stents with aqueous base, then pre-treating with a silane followed by vapor deposition of Parylene™ polymer. The silane used was [3-(methacroyloxy)propyl] trimethoxysilane, available from Sigma-Aldrich Fine Chemicals as Product No. 44,015-9. The silane was applied as essentially a monolayer by mixing the silane at a low concentration in 50/50 (vol) isopropanol/water, soaking the stents in the aqueous silane solution for a suitable length of time to allow the water to hydrolyze the silane and produce some cross-linking, washing off residual silane, then baking the silane-treated stent at 100°C for conventional periods of time. Following the silane treatment, Parylene™ C coating (available from Union Carbide Corporation, Danbury, CT) was vapor-deposited at a thickness of about 1 mm. Prior to coating, the stents were weighed on a microbalance to determine a tare weight.

Bioactive agent/polymer solutions were prepared at a range of concentrations in an appropriate solvent (typically tetrahydrofuran or chloroform), in the manner described herein. In all cases the coating solutions were applied to respective stents by spraying, and the solvent was allowed to evaporate under ambient conditions. The coated stents were then re-weighed to determine the mass of coating and consequently the mass of polymer and bioactive agent.

Rapamycin Release Assay Procedure

The Rapamycin Release Assay Procedure, as described herein, was used to determine the extent and rate of release of an exemplary bioactive agent, rapamycin, under

in vitro elution conditions. Spray-coated stents prepared using the Sample Preparation Procedure were placed in sample baskets into 10 milliliters of SotaxTM dissolution system (elution media containing 2% (wt) surfactant/water solution, available from Sotax Corporation, Horsham, PA). Amount of bioactive agent elution was monitored by UV spectrometry over the course of several days. The elution media was held at 37°C. After the elution measurements, the stents were removed, rinsed, dried, and weighed to compare measured bioactive agent elution to weighed mass loss.

Dexamethasone Release Assay Procedure

The Dexamethasone Release Assay Procedure, as described herein, was used to determine the extent and rate of dexamethasone release under *in vitro* conditions. Spray-coated stents made using the Sample Preparation Procedure were placed in 10 milliliters of pH 7 phosphate buffer solution ("PBS") contained in an amber vial. A magnetic stirrer bar was added to the vial, and the vial with its contents were placed into a 37°C water bath. After a sample interval, the stent was removed and placed into a new buffer solution contained in a new vial. Dexamethasone concentration in the buffer was measured using ultraviolet spectroscopy and the concentration converted to mass of bioactive agent released from the coating. After the experiment, the stent was dried and weighed to correlate actual mass loss to the loss measured by the elution experiment.

Durability Test Procedure

The durability of the coated composition can be determined by the following manner. To simulate use of the coated devices, the coated stents are placed over sample angioplasty balloons. The stent is then crimped onto the balloon using a laboratory test crimper (available from Machine Solutions, Brooklyn, NY). The stent and balloon are then placed in a phosphate buffer bath having a pH of 7.4 and temperature of 37°C. After 5 minutes of soaking, the balloon is expanded using air at 5 atmospheres (3800 torr) of pressure. The balloon is then deflated, and the stent is removed.

The stent is then examined by optical and scanning electron microscopy to determine the amount of coating damage caused by cracking and/or delamination and a rating may be assigned. Coatings with extensive damage are considered unacceptable for a commercial medical device. The "Rating" is a qualitative scale used to describe the

amount of damage to the coating from the stent crimping and expansion procedure based on optical microscopy examination by an experienced coating engineer. A low rating indicates a large percentage of the coating cracked, smeared, and/or delaminated from the surface. For example, a coating with a rating of ten shows no damage while one with a rating of 1 will show a majority of the coating damaged to the point where clinical efficacy may be diminished. Commercially attractive coatings typically have a rating of nine or higher.

Stress-Strain Measurement Test Procedure

Polymer films were prepared by hot pressing polymer beads at 100°C in a constant film maker kit to a thickness of approximately 0.5 mm. The resulting films were cut into strips using a razor blade. A Q800 Dynamic Mechanical Analyzer (available from Texas Instruments, Dallas, TX) was fitted with a film tension clamp. Each sample was equilibrated at 35°C for five minutes prior to straining the sample. Then the sample was loaded into the clamp such that the sample length was between 5 and 7 mm in length. A static force of 0.01N was applied to each sample throughout the measurements. Simultaneously, a 0.5 N/min force was applied to the sample until the movable clamp reached its maximum position. Films were elongated at constant stress and the average tensile modulus (i.e., the initial slope of the stress-strain curve, in MPa) was determined.

Example 1

Release of Rapamycin from Poly(butadiene) and Poly(butyl methacrylate)

Three solutions were prepared for coating the stents. The solutions included mixtures of poly(1,2-butadiene) ("PBD", available from Scientific Polymers Products, Inc., Ontario, NY, as Catalog # 688; CAS #31567-90-5; 7% cis 1,4; 93% vinyl 1,2; Mw approx. 100 kilodaltons), poly(butyl methacrylate) ("PBMA", available from Sigma-Aldrich Fine Chemicals as Product No. 18,152-8, having a weight average molecular weight (Mw) of about 337 kilodaltons), and rapamycin ("RAPA", available from LC Laboratories, Woburn, MA) dissolved in THF to form a homogeneous solution. The stents were not given a primer pre-treatment.

The solutions were prepared to include the following ingredients at the stated weights per milliliter of THF:

- 1) 16 mg/ml PBD / 4 mg/ml PBMA / 10 mg/ml RAPA
- 2) 10 mg/ml PBD / 10 mg/ml PBMA / 10 mg/ml RAPA
- 3) 4 mg/ml PBD / 16 mg/ml PBMA / 10 mg/ml RAPA

Using the Sample Preparation Procedure, two stents were spray coated using each
5 solution. After solvent removal via ambient evaporation, the drug elution for each coated
stent was monitored using the Rapamycin Release Assay Procedure.

Results, provided in Figure 1, demonstrate the ability to control the elution rate of
rapamycin, a pharmaceutical agent, from a coated stent surface by varying the relative
concentrations of PBD and PBMA in the polymer mixture as described herein. The lines
10 in Figure 1 and similar figures are expressed in terms of percent by weight of the first and
second polymers, respectively, in the coated compositions. This can be compared to the
amounts provided above, which are stated in terms of "mg/ml" of the respective polymers
in the coating compositions themselves, which are applied to the stents. Hence "54/13"
corresponds to the coated compositions that results from the use of the first coating
15 composition above, which upon removal of the solvent provides a coated composition
having 54% PBD and 13% PBMA respectively, by weight. Alternatively, solutions such
as the second solution above, e.g., which includes equal amounts (by weight) of the
ingredients, will alternatively be referred to herein as "33/33/33", representing the weight
ratio of ingredients to each other.

20 Additionally, the durability for PBD/PBMA coatings was also analyzed. Stents
were coated with PBD and PBMA in a procedure as described above but without any
bioactive agent. The stents were then tested according to the method described in the
Durability Test Procedure section. The results are displayed in Figure 1A. The
PBD/PBMA coatings showed very little damage in the form of some small cracks that did
25 not appear to reach the stent surface. These coatings were applied to bare metal stents
before ethylene oxide sterilization ("sterilization"), Parylene™ coated stents before
sterilization, and Parylene™ coated stents after sterilization. These were labeled in
Figure 1A "Bare Metal Pre-Sterile," "Parylene Pre-Sterile," and "Parylene Post-Sterile,"
respectively. Parylene™ treatments and sterilization had little effect on the exceptional
30 durability of the PBD/PBMA coatings.

Example 2

Release of Rapamycin from Poly(butadiene-co-acrylonitrile) and Poly(butyl methacrylate)

Three solutions were prepared for coating the stents. The solutions included
5 mixtures of
poly(butadiene-co-acrylonitrile) ("PBDA," available from Scientific Polymer Products, Inc., Catalog #533, contains 41% (wt) acrylonitrile), "PBMA" and "RAPA" ("PBMA" and "RAPA" were obtained and used as described in Example 1) dissolved in THF to form a homogeneous solution. The stents were not given a primer pre-treatment.

10 The solutions were prepared to include the following ingredients at the stated weights per milliliter of THF:

- 1) 16 mg/ml PBDA / 4 mg/ml PBMA / 10 mg/ml RAPA
- 2) 10 mg/ml PBDA / 10 mg/ml PBMA / 10 mg/ml RAPA
- 3) 4 mg/ml PBDA / 16 mg/ml PBMA / 10 mg/ml RAPA

15 Using the Sample Preparation Procedure, two stents were spray coated using each solution. After solvent removal via ambient evaporation, the drug elution for each coated stent was monitored using the Rapamycin Release Assay Procedure.

Results, provided in Figure 2, demonstrate the ability to control the elution rate of rapamycin, a pharmaceutical agent, from a coated stent surface by varying the relative
20 concentrations of PBDA and PBMA in the polymer mixture as described herein.

Example 3

Release of Dexamethasone from Poly(butadiene) and Poly(butyl methacrylate)

Three solutions were prepared for coating the stents. All three solutions included
25 mixtures of poly(1,2-butadiene) "PBD", poly(butyl methyl acrylate) ("PBMA"), and dexamethasone ("DEXA") dissolved in THF to form a homogeneous solution. The stents were not given a primer pre-treatment.

The solutions were prepared to include the following ingredients at the stated weights per milliliter of THF:

- 30
- 1) 20 mg/ml PBD / 0 mg/ml PBMA / 10 mg/ml DEXA
 - 2) 10 mg/ml PBD / 10 mg/ml PBMA / 10 mg/ml DEXA
 - 3) 0 mg/ml PBD / 20 mg/ml PBMA / 10 mg/ml DEXA

Using the Sample Preparation Procedure, two stents were spray coated using each solution. After solvent removal via ambient evaporation, the drug elution for each coated stent was monitored using the Dexamethasone Release Assay Procedure.

Results, provided in Figure 3, demonstrate the ability to control the elution rate of dexamethasone, a pharmaceutical agent, from a stent surface by varying the relative concentrations of PBD and PBMA in the polymer mixture.

Example 4

Surface Characterization of Coated Stents after Crimping and Expansion

Using the Sample Preparation Procedure, stents were sprayed with a coating of second polymer/poly(butyl methacrylate) ("PBMA")/rapamycin ("RAPA"), mixed at a weight ratio of 33/33/33 at 10 mg/ml each of THF. The first polymer was polybutadiene ("PBD", available from Scientific Polymers Products, Inc., Ontario, NY, as Catalog # 688; CAS #31567-90-5; 7% cis 1,4; 93% vinyl 1,2; Mw approx. 100 kilodaltons), and a polymer from the additional polymer class was poly(ethylene-co-methyl acrylate) ("PEMA", available from Focus Chemical Corp. Portsmouth, NH, containing 28% (wt) methyl acrylate). The second polymer used was PBMA from Sigma-Aldrich Fine Chemicals as Product No. 18,152-8, having a weight average molecular weight (Mw) of about 337 kilodaltons. Stents were either used as received (i.e., uncoated metal), were pre-treated with a silane/Parylene™ primer using the primer procedure described in the Sample Preparation Procedure, were not pre-treated with primer but were given a subsequent PBMA topcoat using the spraying process described in the Sample Preparation Procedure, or were given both a silane/Parylene™ pre-treatment primer and subsequent PBMA topcoat.

After preparing the coated stents and allowing all solvents to dry at ambient conditions, the stents were examined with an optical microscope under both "bright field" and "dark field" conditions. All coatings were optically transparent (i.e., clear, showing no cloudiness). Raman microscopy taken of the coated stents of (PEMA as the additional polymer, applied to bare metal stent) and (PBD as the first polymer, applied to bare metal stent) indicated a high degree of homogeneity of mixing of drug and polymers.

The coated stents were crimped down on balloons and were expanded following the Durability Test Procedure, which showed that, overall, all the coatings remained intact

(i.e., the coating did not peel off or flake off, etc.), with only a few localized sites where coating delaminated from the metal stent. When primer coatings were used, essentially no delamination was evident and cracks were all smaller than about 10 microns in width.

Almost all stents had some degree of cracking of the coating around bends in the struts, as well as some mechanical damage caused by handling or balloon expansion. Adding a PBMA topcoat did not adversely affect the mechanical integrity of the coating on the stent after crimping and expansion, as might be expected with an overall thicker stent coating.

Based on both the drug-eluting test results and mechanical test results, coatings containing bioactive agents incorporated into blends of PBMA with either PEMA or PBD as the other polymer are viable candidates for commercial applications in drug-eluting stents and are expected to be particularly effective in minimizing the onset of restenosis after stent implantation.

Example 5 and Comparative Examples C1-C3

Stress-Strain Measurements for Polymers

Tensile properties of various first and additional polymers of this invention were tested and average tensile modulus calculated using the Stress-Strain Measurement Test Procedure. The first polymer evaluated was polybutadiene ("PBD", same as used in Example 1), and the additional polymers evaluated were poly(ethylene-co-methyl acrylate) ("PEMA", available from Focus Chemical Corp. Portsmouth, NH, containing 28% (wt) methyl acrylate), poly(ethylene-co-butyl acrylate) ("PEBA", containing 35% (wt) butyl acrylate, available from Focus Chemical Corp., Portsmouth, NH), and poly(ethylene-co-vinyl acetate) ("PEVA", available as Product No. 34,691-8 from Sigma-Aldrich Fine Chemicals). These polymers were run as comparative examples.

Stress-strain curves are shown in Figure 4. The calculated average tensile modulus for each of the four tested polymers is shown in Table 1.

Table 1

Example	Polymer	Average Tensile Modulus, MPa (SD)
C1	PEMA	5.54 (0.49)
C2	PEBA	3.66 (0.67)
18c	PBD	34.87 (4.83)
C3	PEVA	2.17 (0.46)

The data from Table 1 show that the average tensile modulus for the PBD was significantly higher than that for any of the other polymers.

Example 6
Scanning Electron Microscopy

Scanning Electron Microscopy can be used to observe coating quality and uniformity on stents at any suitable point in their manufacture or use. Crimped and expanded stents were examined for coating failures in fine microscopic detail using a scanning electron microscope (SEM) at magnifications varying from 150X to 5000X.

Various coating defects tend to affect the manufacture and use of most polymer coated stents in commercial use today, including the appearance of cracks or tears within the coating, smearing or displacement of the coating, as well as potentially even delamination of the coating in whole or in part. Such defects can occur upon formation of the coating itself, or more commonly, in the course of its further fabrication, including crimping the stent upon an inflatable balloon, or in surgical use, which would include manipulating the stent and expanding the balloon to position the stent *in vivo*.

Figure 5 shows a scanning electron microscope image from a LEO Supra-35 VP at 250X of a 33/33/33 PBD/PBMA/rapamycin coating on a stent after conventional crimping and balloon expansion procedures. The image shows that the coated composition maintains integrity after expansion, showing no evidence of delamination or cracks.

When observed by SEM, many other compositions tended to show cracks, however, typically of a type and number that are certainly on par with those in commercial use today, and would tend to be well within acceptable range, particularly considering that neither the coating compositions, or manner of applying particular compositions, have yet
5 been optimized for any particular combination of surface, polymers, bioactive agent. The cracks were typically a few microns in width, with thin strands of polymer stretching between the edges of the crack. Overall, however, the coatings looked smooth, uniform, and in good condition.

Almost all the stents had some degree of cracking of the coating around bends in the struts, as well as some mechanical damage caused by handling or balloon expansion. Most surprisingly, polybutadiene-containing coatings exhibited less cracking and in one case no cracks, and when cracks occurred, they were typically smaller in size in comparison with the cracks found in PEMA or PEVA-containing coatings. For comparison, cracks which opened up and delaminated from the metal stent surface were
15 found in coatings containing PEMA and PEVA in the absence of a Parylene™ primer coating. Polybutadiene-containing coatings without Parylene™ primer, as well as comparative PEMA (or comparative PEVA)-containing coatings with Parylene™ primer, showed cracks which tended to not result in delamination.

20 Example 7
Release of Rapamycin from Poly(butadiene) and Poly(butyl methacrylate) provided with a Topcoat

Several solutions were prepared for coating non-sterile, non-deployed, self-expanding nitinol coronary stents having a primer layer. The solutions included mixtures
25 of poly(1,2-butadiene) ("PBD", available from Scientific Polymers Products, Inc., Ontario, NY), poly(butyl methacrylate) ("PBMA", available from Sigma-Aldrich Fine Chemicals), and rapamycin ("RAPA", available from LC Laboratories, Woburn, MA) dissolved to form a homogeneous solution. In addition, a topcoat of PBMA was also prepared and applied to the coating composition on some of the stents, and the elution rate profiles into
30 a 2% SLS buffer on a Sotax USP IV Apparatus were determined.

Results, provided in Figure 6, illustrates several elution rates of rapamycin, a pharmaceutical agent, from a coated stent surface by varying the relative concentrations of rapamycin, PBD, and PBMA with and without utilizing a topcoat. Further, Figure 7

demonstrates the ability to control the elution rate of a bioactive agent by varying the amount of topcoat provided relative to the coating composition.

The lines in Figure 6 and Figure 7 are expressed in terms of percent by weight of the Rapamycin, PBD, and PBMA, respectively, in the coated compositions. Hence
5 "40/30/30" corresponds to the coated compositions that results from the use of 40% Rapamycin, 30% PBD, and 30% PBMA, respectively, by weight. In Figure 7, the weight of the topcoat relative to the weight of the coating composition is shown. For example, 6% topcoat corresponds to an amount of topcoat totaling 6% by weight of the coating composition weight.

10 Other embodiments of this invention will be apparent to those skilled in the art upon consideration of this specification or from practice of the invention disclosed herein. Various omissions, modifications, and changes to the principles and embodiments described herein may be made by one skilled in the art without departing from the true scope and spirit of the invention which is indicated by the following claims. All patents,
15 patent documents, and publications cited herein are hereby incorporated by reference as if individually incorporated.

What is Claimed is:

1. A composition for coating the surface of a medical device with at least one bioactive agent in a manner that permits the coated surface to release the bioactive agent over time when implanted in vivo, the composition comprising at least one bioactive agent
5 in combination with a plurality of polymers, including a first polymer component comprising at least one diolefin-derived non-aromatic polymer or copolymer and a second polymer component comprising a polymer selected from the group consisting of poly(alkyl(meth)acrylates) and poly(aromatic(meth)acrylates).

2. A composition according to claim 1 wherein the first polymer component is
10 selected from the group consisting of the polymers of butadiene and isoprene.

3. A composition according to claim 1 wherein the first polymer component includes a homopolymer derived from diolefin monomers.

4. A composition according to claim 3 wherein the homopolymer is partially hydrogenated.

15 5. A composition according to claim 1 wherein the first polymer component includes a copolymer of a diolefin monomer with a non-aromatic mono-olefin monomer.

6. A composition according to claim 5 wherein the copolymer is partially hydrogenated.

7. A composition according to claim 1 wherein the first polymer component is
20 selected from the group consisting of polybutadienes containing polymerized *cis*-, *trans*- and 1,2- monomer units and polyisoprenes containing polymerized *cis*-1,4- and *trans*-1,4- monomer units, polymerized 1,2-vinyl monomer units, and polymerized 3,4-vinyl monomer units.

8. A composition according to claim 1, the first polymer component having a
25 molecular weight from about 50 kilodaltons to about 1,000 kilodaltons.

9. A composition according to claim 1, the first polymer component having a molecular weight from about 150 kilodaltons to about 1,000 kilodaltons.

10. A composition according to claim 1, the first polymer component having a molecular weight from about 200 kilodaltons to about 600 kilodaltons.

30 11. A composition according to claim 1, the first polymer component having a molecular weight from about 100 kilodaltons to about 450 kilodaltons.

12. A composition according to claim 1 wherein the composition includes at least one additional polymer selected from the group consisting of poly(alkylene-co-alkyl(meth)acrylates), ethylene copolymers with other alkylenes, polybutenes, aromatic group-containing copolymers, epichlorohydrin-containing polymers and poly (ethylene-co-vinyl acetate).

13. A composition according to claim 12 wherein the poly(alkylene-co-alkyl(meth)acrylates) are selected from the group consisting of poly(ethylene-co-methyl acrylate), poly(ethylene-co-ethyl acrylate), poly(ethylene-co-2-ethylhexyl acrylate) and poly(ethylene-co-butyl acrylate), ethylene copolymers with other alkylenes are selected from the group consisting of poly(ethylene-co-propylene), poly(ethylene-co-1-butene), poly(ethylene-co-1-butene-co-1-hexene) and poly(ethylene-co-1-octene), the polybutenes are selected from the group consisting of polyisobutylene, poly-1-butene and poly-2-butene, the aromatic group-containing copolymers include a copolymer derived from copolymerization of styrene monomer and one or more monomers selected from the group consisting of butadiene, isoprene, acrylonitrile, a C₁-C₄ alkyl (meth)acrylate and butene, the epichlorohydrin-containing polymers are selected from the group consisting of epichlorohydrin homopolymers and poly(epichlorohydrin-co-alkylene oxide) copolymers and the poly (ethylene-co-vinyl acetate) polymers have a vinyl acetate concentration from about 8% to about 90%.

14. A composition according to claim 1 wherein the poly(alkyl(meth)acrylate) includes an alkyl chain length from two to eight carbons.

15. A composition according to claim 1, the poly(alkyl(meth)acrylate) having a molecular weight from about 50 kilodaltons to about 900 kilodaltons.

16. A composition according to claim 1 wherein the poly(alkyl(meth)acrylate) is selected from the group consisting of poly(n-butyl methacrylate), poly(n-butyl methacrylate-co-isobutyl methacrylate), and poly(t-butyl methacrylate).

17. A composition according to claim 1 wherein the poly(aromatic(meth)acrylate) includes aryl groups having from six to sixteen carbon atoms.

18. A composition according to claim 1, the poly(aromatic(meth)acrylate) having a molecular weight from about 50 kilodaltons to about 900 kilodaltons.

19. A composition according to claim 1 wherein the poly(aromatic(meth)acrylate) is selected from the group consisting of poly(aryl (meth)acrylates), poly(aralkyl

(meth)acrylates), poly(alkaryl (meth)acrylates), poly(aryloxyalkyl (meth)acrylates), and poly (alkoxyaryl (meth)acrylates).

20. A composition according to claim 19, wherein the poly(aryl (meth)acrylates) are selected from the group consisting of poly(9-anthracenyl methacrylate),
5 poly(chlorophenyl acrylate), poly(methacryloxy-2-hydroxybenzophenone),
poly(methacryloxybenzotriazole), poly(naphthyl acrylate), poly(naphthylmethacrylate),
poly-4-nitrophenylacrylate, poly(pentachloro(bromo, fluoro) acrylate) and methacrylate,
poly(phenyl acrylate) and poly(phenyl methacrylate); the poly(alkaryl (meth)acrylates) are
selected from the group consisting of poly(benzyl acrylate), poly(benzyl methacrylate),
10 poly(2-phenethyl acrylate), poly(2-phenethyl methacrylate) and poly(1-pyrenylmethyl
methacrylate); the poly(alkaryl(meth)acrylates) are selected from the group consisting of
poly(4-sec-butylphenyl methacrylate), poly(3-ethylphenyl acrylate), and poly(2-methyl-1-
naphthyl methacrylate); the poly(aryloxyalkyl (meth)acrylates) are selected from the group
consisting of poly(phenoxyethyl acrylate), poly(phenoxyethyl methacrylate), and
15 poly(polyethylene glycol phenyl ether acrylate) and poly(polyethylene glycol phenyl ether
methacrylate) with varying polyethylene glycol molecular weights; and the
poly(alkoxyaryl(meth)acrylates) are selected from the group consisting of poly(4-
methoxyphenyl methacrylate), poly(2-ethoxyphenyl acrylate) and poly(2-
methoxynaphthyl acrylate).

20 21. A composition according to claim 1 wherein the composition further comprises
a solvent in which the first and second polymer components form a true solution.

22. A composition according to claim 1 wherein the bioactive agent is dissolved or
suspended in the coating mixture at a concentration of 0.01% to 90% by weight.

23. A composition according to claim 1 wherein the device is one that undergoes
25 flexion and expansion in the course of implantation or use in vivo.

24. A composition according to claim 1 wherein the composition permits the
amount and rate of release of agent(s) from the medical device to be controlled by
adjusting the relative types and concentrations of the first and second polymer components
in the mixture.

30 25. A combination comprising a medical device and a composition for coating the
surface of a medical device with at least one bioactive agent in a manner that permits the
coated surface to release the bioactive agent over time when implanted in vivo, the

composition comprising at least one bioactive agent in combination with a plurality of polymers, including a first polymer component comprising at least one diolefin-derived non-aromatic polymer or copolymer and a second polymer component comprising a polymer selected from the group consisting of poly(alkyl(meth)acrylates) and poly(aromatic(meth)acrylates).

26. A combination according to claim 25 wherein a pretreatment coating, adapted to alter the surface properties of the medical device, is applied to the surface of the medical device.

27. A combination according to claim 25 wherein the first polymer component is selected from the group consisting of the polymers of butadiene and isoprene.

28. A combination according to claim 25 wherein the first polymer component includes a homopolymer derived from diolefin monomers.

29. A combination according to claim 25 wherein the first polymer component includes a copolymer of a diolefin monomer with a non-aromatic mono-olefin monomer.

30. A combination according to claim 25 wherein the first polymer component is selected from the group consisting of polybutadienes containing polymerized *cis*-, *trans*- and 1,2- monomer units and polyisoprenes containing polymerized *cis*-1,4- and *trans*-1,4- monomer units, polymerized 1,2-vinyl monomer units, and polymerized 3,4-vinyl monomer units.

31. A combination according to claim 25 wherein the composition includes at least one additional polymer selected from the group consisting of poly(alkylene-co-alkyl(meth)acrylates), ethylene copolymers with other alkylenes, polybutenes, aromatic group-containing copolymers, epichlorohydrin-containing polymers and poly (ethylene-co-vinyl acetate).

32. A combination according to claim 26 wherein the pretreatment composition is selected from the group consisting of Parylene™, silane, photografted polymers, epoxy primers, and polycarboxylate resins and combinations thereof.

33. A combination according to claim 25 wherein the composition permits the amount and rate of release of agent(s) from the medical device to be controlled by adjusting the relative types and concentrations of the first and second polymer components in the mixture.

34. A composition for coating the surface of a medical device with at least one bioactive agent in a manner that permits the coated surface to release the bioactive agent over time when implanted in vivo, the composition comprising at least one bioactive agent in combination with a plurality of polymers, including a first polymer component
5 comprising at least one diolefin-derived non-aromatic polymer or copolymer and a second polymer component comprising a polymer selected from the group consisting of poly(alkyl(meth)acrylates) and poly(aromatic(meth)acrylates), wherein the composition includes at least one additional polymer selected from the group consisting of ethylene copolymers with other alkylenes, polybutenes, aromatic group-containing copolymers,
10 epichlorohydrin-containing polymers, and poly (ethylene-co-vinyl acetate).

35. A composition according to claim 34 wherein the first polymer component is selected from the group consisting of the polymers of butadiene and isoprene.

36. A method of coating the surface of a medical device, the method comprising the steps of providing a composition including at least one bioactive agent in combination
15 with a plurality of polymers, including a first polymer component comprising at least one diolefin-derived non-aromatic polymer or copolymer and a second polymer component comprising a polymer selected from the group consisting of poly(alkyl(meth)acrylates) and poly(aromatic(meth)acrylates), and applying the composition to the surface of the device.

20 37. A combination comprising a stent and a composition for coating the surface of a stent with at least one bioactive agent in a manner that permits the coated surface to release the bioactive agent over time when implanted in vivo, the composition comprising at least one bioactive agent in combination with a plurality of polymers, including a first polymer component comprising polybutadiene, a second polymer component comprising
25 poly(n-butyl methacrylate), a solvent in which the first and second polymer components form a true solution, and at least one biocompatible additive, and further comprising a pretreatment layer including a multi-interface system to facilitate adhesion and cohesion interaction relative to the stent and coating composition.

30 38. A combination according to claim 37, wherein the bioactive agent is selected from the group consisting of rapamycin, paclitaxel, dexamethasone, and estradiol.

39. A combination according to claim 37, wherein the stent includes a material selected from the group consisting of polymers, tissue, metals, ceramics, and combinations thereof.

40. A combination according to claim 39, wherein the polymers include polycarbonates and the metals are selected from the group consisting of titanium, stainless steel, gold, silver, and nitinol.

41. A combination according to claim 37, wherein the solvent is selected from the group consisting of tetrahydrofuran, chloroform, methylene chloride, and cyclohexane.

42. A combination according to claim 37, wherein the biocompatible additive includes one or more antioxidants selected from the group consisting of butylated hydroxytoluene, vitamin E, BNX, and dilauryl thiodipropionate.

43. A combination according to claim 37, wherein the pretreatment layer includes organosilane and Parylene.

44. A composition according to claim 1, further comprising a pretreatment layer including a multi-interface system to facilitate adhesion and cohesion interaction relative to the medical device and composition.

45. A composition according to claim 44, wherein the pretreatment layer includes organosilane and Parylene.

46. A combination comprising a medical device and a composition for coating the surface of a medical device with at least one bioactive agent in a manner that permits the coated surface to release the bioactive agent over time when implanted in vivo, the composition comprising at least one bioactive agent in combination with a plurality of polymers, including a first polymer component comprising polybutadiene, a second polymer component comprising poly(n-butyl methacrylate), a solvent in which the first and second polymer components form a true solution selected from the group consisting of tetrahydrofuran, chloroform, methylene chloride, and cyclohexane, and at least one biocompatible additive including one or more antioxidants selected from the group consisting of butylated hydroxytoluene, vitamin E, BNX, and dilauryl thiodipropionate, and further comprising a pretreatment layer including a multi-interface system to facilitate adhesion and cohesion interaction relative to the medical device and coating composition.

47. A combination according to claim 46, wherein the bioactive agent is selected from the group consisting of rapamycin, paclitaxel, dexamethasone, and estradiol.

48. The combination of claim 46 further comprising a topcoat including poly(butyl methacrylate).

49. The combination of claim 46, wherein the medical device comprises a stent.

50. A method of manufacturing a medical device for delivering one or more
5 bioactive agents to a subject comprising: providing a medical device comprising a substrate surface; applying a pretreatment coating including a plurality of bonding layer-sites to enhance the cohesion and adhesion of the pretreatment coating and a bioactive agent coating to at least a portion of the medical device substrate surface; and bonding the bioactive agent coating comprising a bioactive agent in combination with a plurality of
10 polymers, including a first polymer component comprising at least one diolefin-derived non-aromatic polymer or copolymer and a second polymer component comprising a polymer selected from the group consisting of poly(alkyl(meth)acrylates) and poly(aromatic(meth)acrylates).

51. The method of claim 50 further comprising the step of applying a topcoat layer
15 to the bioactive agent coating for the purpose of biocompatibility enhancement.

52. The method of claim 50 further comprising the step of applying a topcoat layer to the bioactive agent coating for the purpose of delamination protection.

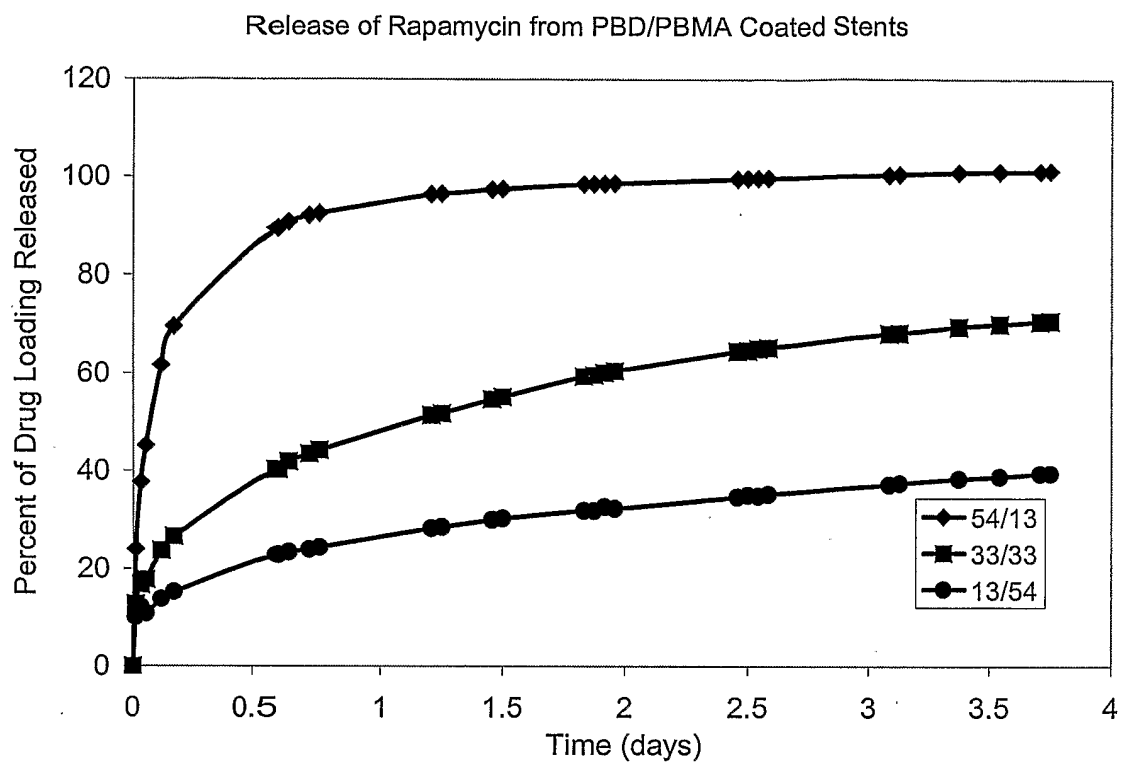
53. The method of claim 50 further comprising the step of applying a topcoat layer to the bioactive agent coating for the purpose of durability enhancement.

20 54. The method of claim 50 further comprising the step of applying a topcoat layer to the bioactive agent coating for the purpose of bioactive agent release control.

55. The method of claim 50 further comprising the step of applying a topcoat layer to the bioactive agent coating, the topcoat layer configured to function as a medical device deployment protective release layer.

25 56. The method of claim 50, wherein the medical device comprises a stent.

1/8

*Figure 1*

2/8

Durability of poly(1,2-butadiene)/PBMA coatings on stents

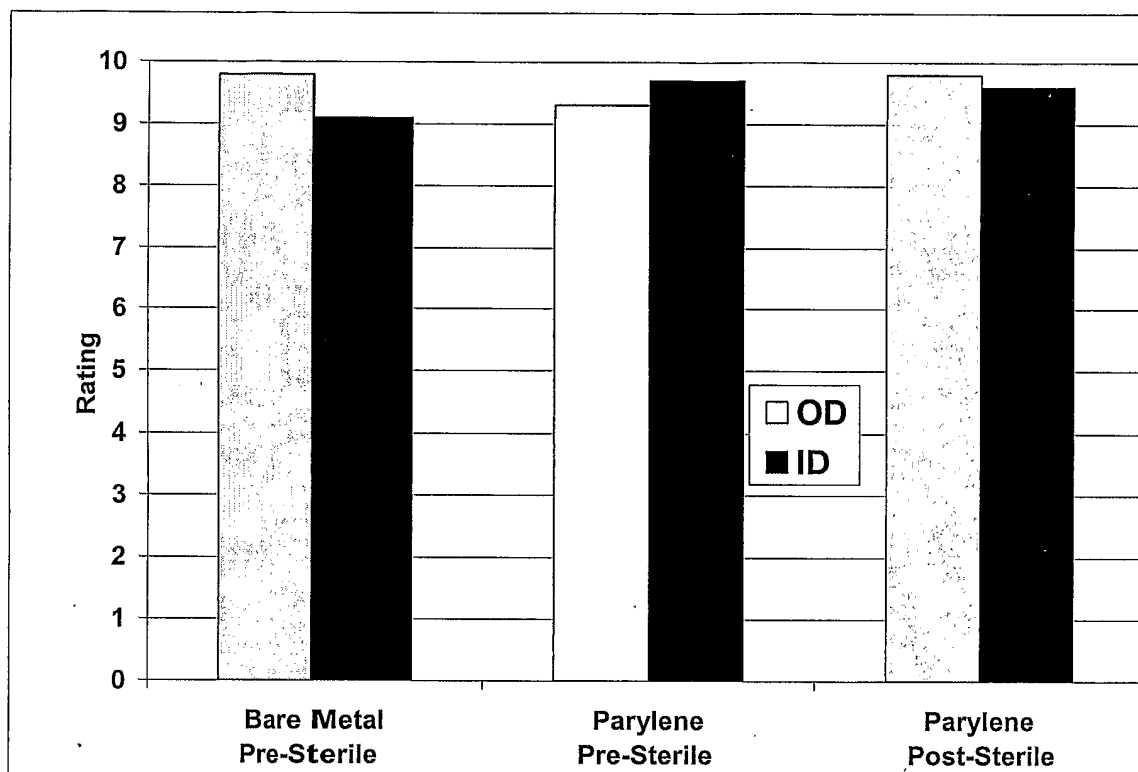


Figure 1A

3/8

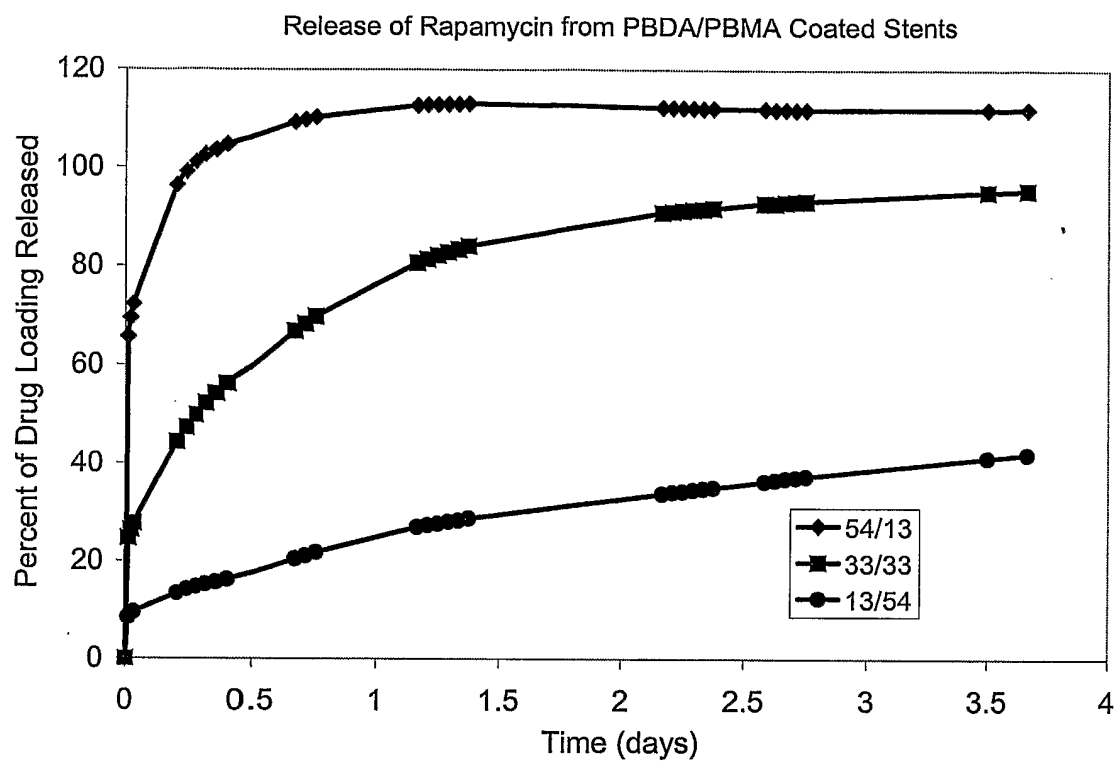


Figure 2

4/8

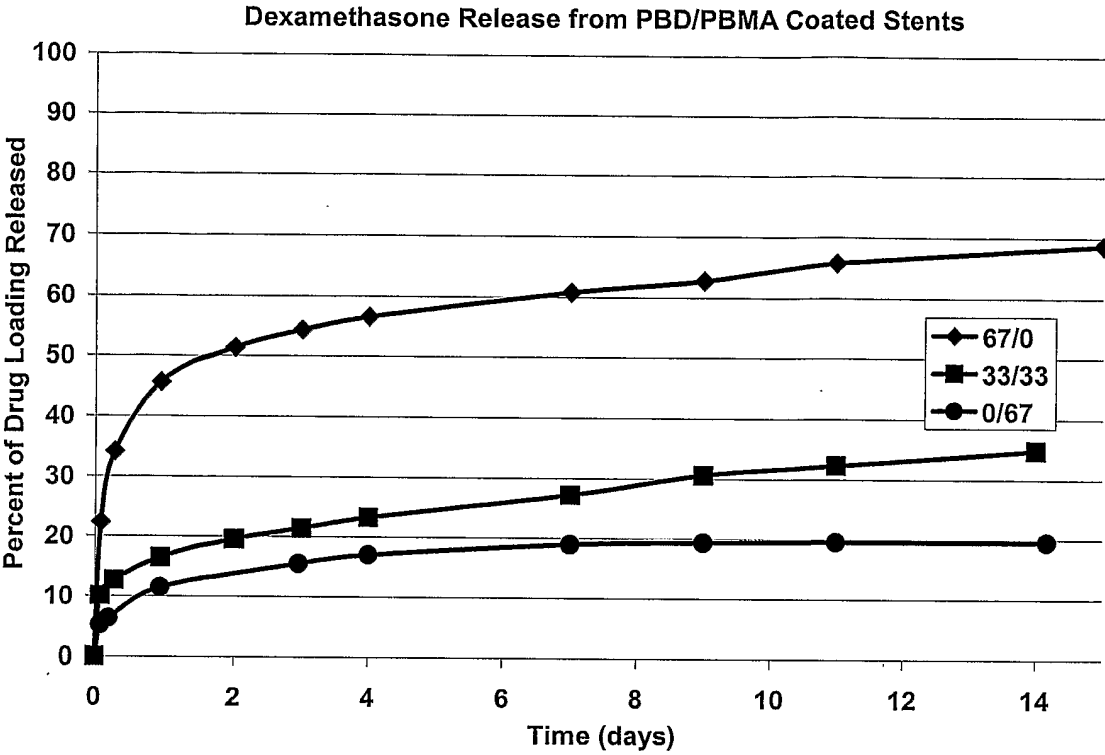
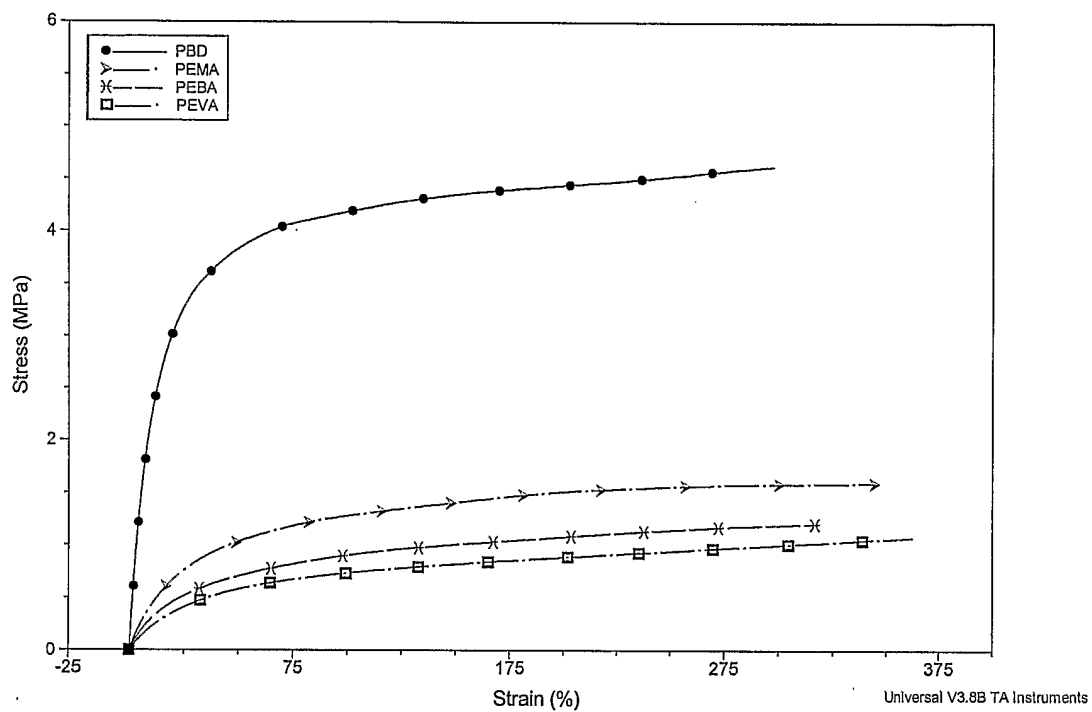


Figure 3

5/8

*Figure 4*

6/8

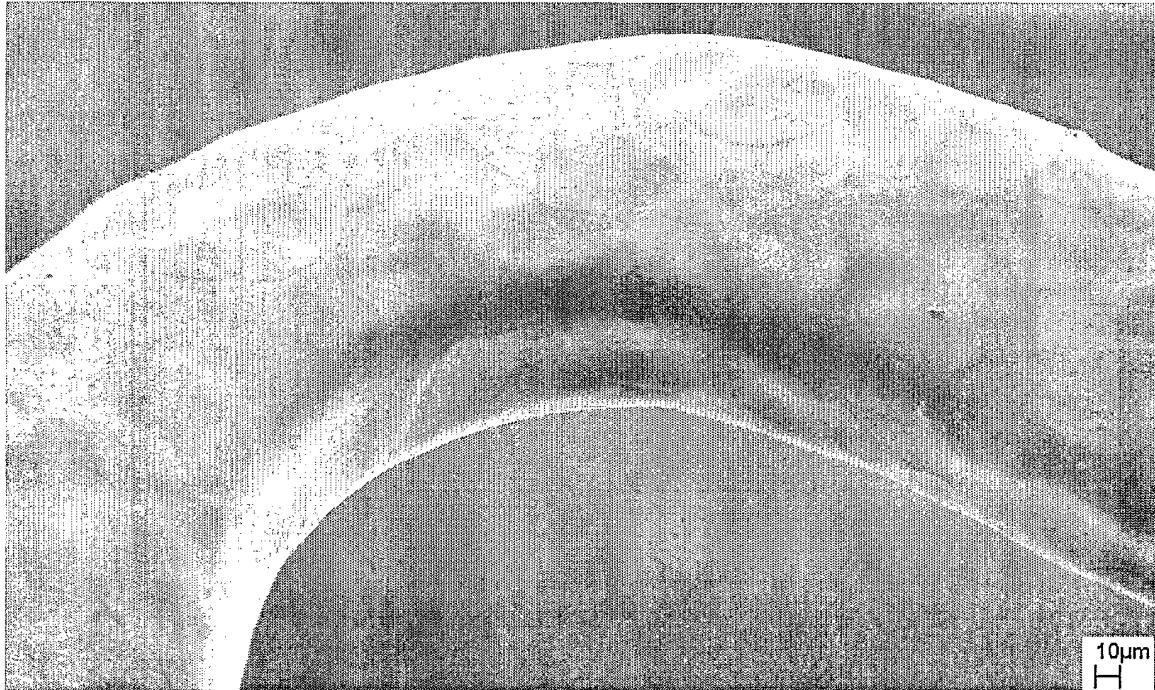


Figure 5

7/8

Release Rapamycin from PBD/PBMA and PBMA Topcoat Coated Stents

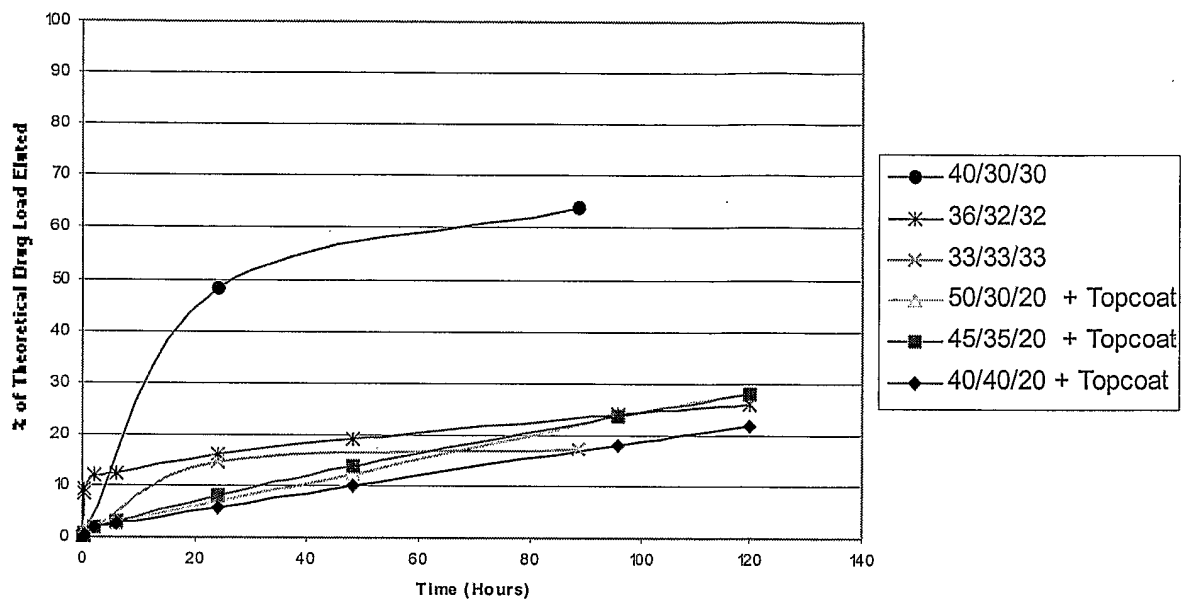


Figure 6

8/8

Release of Rapamycin from PBD/PBMA and PBMA Topcoat Coated Stents

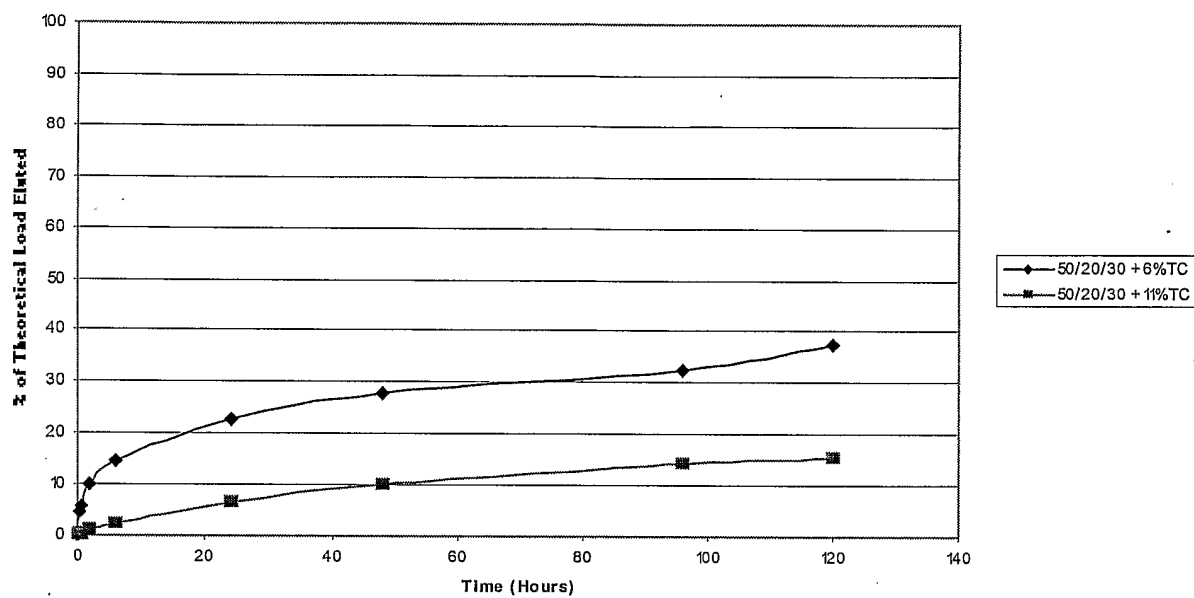


Figure 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/011406

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L29/08 A61L29/16 A61L31/10 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, COMPENDEX, INSPEC, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/87372 A (CORDIS CORPORATION) 22 November 2001 (2001-11-22) examples 1-7 claims	1-56
A	WO 03/105920 A (SURMODICS, INC; CHUDZIK, STEPHEN, J; KLOKE, TIMOTHY, M; LAWIN, LAURIE,) 24 December 2003 (2003-12-24) cited in the application examples claims	1-56

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

28 September 2005

Date of mailing of the international search report

06/10/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Thornton, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/011406

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0187372	A	22-11-2001	AT 298592 T	15-07-2005
			AU 6158101 A	26-11-2001
			AU 6295701 A	26-11-2001
			CA 2408606 A1	22-11-2001
			DE 60111743 D1	04-08-2005
			EP 1289576 A1	12-03-2003
			JP 2003533493 T	11-11-2003
<hr/>				
WO 03105920	A	24-12-2003	AU 2003251570 A1	31-12-2003
			CA 2490241 A1	24-12-2003
			EP 1534354 A1	01-06-2005
<hr/>				