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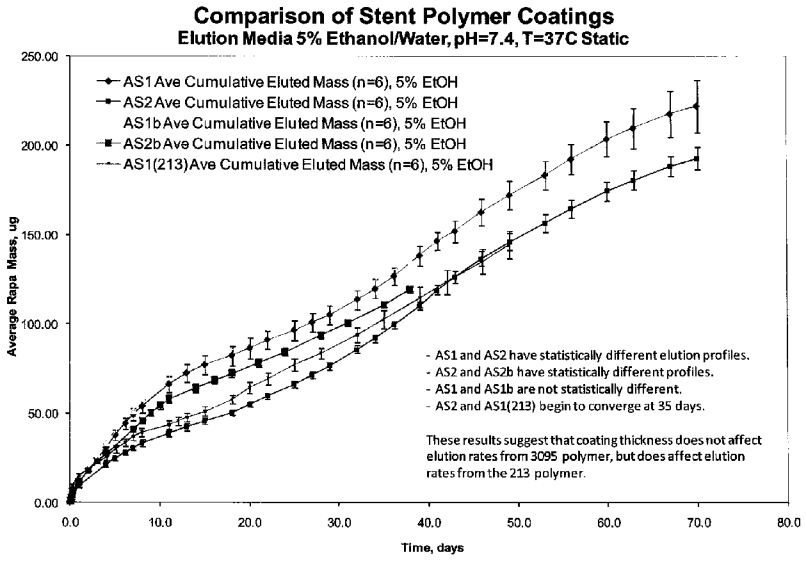

(57) Abstract: Provided herein is a coated coronary stent, comprising:. a. stent framework; b. a plurality of layers deposited on said stent framework to form said coronary stent; wherein at least one of said layers comprises a bioabsorbable polymer and at least one of said layers comprises one or more active agents; wherein at least part of the active agent is in crystalline form.

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STENTS HAVING BIODEGRADABLE LAYERS

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 60/912,408, filed April 17, 2007, U.S. Provisional Application No. 60/912,394, filed April 17, 2007, and U.S. Provisional Application No. 60/981,445, filed October 19, 2007. The contents of the applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] The present invention relates to methods for forming stents comprising a bioabsorbable polymer and a pharmaceutical or biological agent in powder form onto a substrate.

[0003] It is desirable to have a drug-eluting stent with minimal physical, chemical and therapeutic legacy in the vessel after a proscribed period of time. This period of time is based on the effective healing of the vessel after opening the blockage by PCI/stenting (currently believed by leading clinicians to be 6-18 months).

[0004] It is also desirable to have drug-eluting stents of minimal cross-sectional thickness for (a) flexibility of deployment (b) access to small vessels (c) minimized intrusion into the vessel wall and blood.

SUMMARY OF THE INVENTION

[0005] One embodiment provides a coated coronary stent, comprising: a stent framework and a rapamycin-polymer coating wherein at least part of rapamycin is in crystalline form and the rapamycin-polymer coating comprises one or more resorbable polymers.

[0006] In another embodiment the rapamycin-polymer coating has substantially uniform thickness and rapamycin in the coating is substantially uniformly dispersed within the rapamycin-polymer coating.

[0007] In another embodiment, the one or more resorbable polymers are selected from PLGA (poly(lactide-co-glycolide); DLPLA — poly(dl-lactide); LPLA — poly(l-lactide); PGA — polyglycolide; PDO — poly(dioxanone); PGA-TMC — poly(glycolide-co-trimethylene carbonate); PGA-LPLA — poly(l-lactide-co-glycolide); PGA-DLPLA — poly(dl-lactide-co-

glycolide); LPLA-DLPLA — poly(l-lactide-co-dl-lactide); PDO-PGA-TMC — poly(glycolide-co-trimethylene carbonate-co-dioxanone) and combinations thereof.

[0008] In yet another embodiment the polymer is 50/50 PLGA.

[0009] In still another embodiment the at least part of said rapamycin forms a phase separate from one or more phases formed by said polymer.

[0010] In another embodiment the rapamycin is at least 50% crystalline.

[0011] In another embodiment the rapamycin is at least 75% crystalline.

[0012] In another embodiment the rapamycin is at least 90% crystalline.

[0013] In another embodiment the rapamycin is at least 95% crystalline.

[0014] In another embodiment the rapamycin is at least 99% crystalline.

[0015] In another embodiment the polymer is a mixture of two or more polymers.

[0016] In another embodiment the mixture of polymers forms a continuous film around particles of rapamycin.

[0017] In another embodiment the two or more polymers are intimately mixed.

[0018] In another embodiment the mixture comprises no single polymer domain larger than about 20 nm.

[0019] In another embodiment the each polymer in said mixture comprises a discrete phase.

[0020] In another embodiment the discrete phases formed by said polymers in said mixture are larger than about 10nm.

[0021] In another embodiment the discrete phases formed by said polymers in said mixture are larger than about 50nm.

[0022] In another embodiment the rapamycin in said stent has a shelf stability of at least 3 months.

[0023] In another embodiment the rapamycin in said stent has a shelf stability of at least 6 months.

[0024] In another embodiment the rapamycin in said stent has a shelf stability of at least 12 months.

[0025] In another embodiment the coating is substantially conformal.

[0026] In another embodiment the stent provides an elution profile wherein about 10% to about 50% of rapamycin is eluted at week 1 after the composite is implanted in a subject under physiological conditions, about 25% to about 75% of rapamycin is eluted at week 2 and about 50% to about 100% of rapamycin is eluted at week 6.

[0027] In another embodiment the stent provides an elution profile wherein about 10% to about 50% of rapamycin is eluted at week 1 after the composite is implanted in a subject under

physiological conditions, about 25% to about 75% of rapamycin is eluted at week 2 and about 50% to about 100% of rapamycin is eluted at week 10.

[0028] In another embodiment the stent framework is a stainless steel framework.

[0029] Still another embodiment provides a coated coronary stent, comprising: a stent and a macrolide immunosuppressive (limus) drug-polymer coating wherein at least part of the drug is in crystalline form and the macrolide immunosuppressive -polymer coating comprises one or more resorbable polymers.

[0030] In another embodiment the macrolide immunosuppressive drug comprises one or more of rapamycin, 40-O-(2-Hydroxyethyl)rapamycin (everolimus), 40-O-Benzyl-rapamycin, 40-O-(4'-Hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin, 40-O-Allyl-rapamycin, 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2':E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin 40-O-(2-Hydroxy)ethoxycar-bonylmethyl-rapamycin, 40-O-(3-Hydroxy)propyl-rapamycin 4O-O-(6-Hydroxy)hexyl-rapamycin 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin 4O-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin, 4O-O-(2-Acetoxy)ethyl-rapamycin 4O-O-(2-Nicotinoyloxy)ethyl-rapamycin, 4O-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin 4O-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 28-O-Methyl-rapamycin, 4O-O-(2-Aminoethyl)-rapamycin, 4O-O-(2-Acetaminoethyl)-rapamycin 4O-O-(2-Nicotinamidoethyl)-rapamycin, 4O-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 4O-O-(2-Ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-Tolylsulfonamidoethyl)-rapamycin, 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin, 42-Epi-(tetrazolyl)rapamycin (tacrolimus), and 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus).

[0031] In another embodiment the macrolide immunosuppressive drug is at least 50% crystalline.

[0032] Another embodiment provides a method for preparing a coated coronary stent comprising forming a macrolide immunosuppressive (limus) drug-polymer coating on the stent framework wherein at least part of the drug is in crystalline form and the macrolide immunosuppressive -polymer coating comprises one or more resorbable polymers.

[0033] The present invention provides several advantages which overcome or attenuate the limitations of current technology for bioabsorbable stents.

[0034] One embodiment provides a coated coronary stent, comprising: a stent framework and a rapamycin-polymer coating wherein at least part of rapamycin is in crystalline form and the rapamycin-polymer coating comprises one or more resorbable polymers.

[0035] In another embodiment the rapamycin-polymer coating has substantially uniform thickness and rapamycin in the coating is substantially uniformly dispersed within the rapamycin-polymer coating.

[0036] In another embodiment, the one or more resorbable polymers are selected from PLGA (poly(lactide-co-glycolide); DLPLA — poly(dl-lactide); LPLA — poly(l-lactide); PGA — polyglycolide; PDO — poly(dioxanone); PGA-TMC — poly(glycolide-co-trimethylene carbonate); PGA-LPLA — poly(l-lactide-co-glycolide); PGA-DLPLA — poly(dl-lactide-co-glycolide); LPLA-DLPLA — poly(l-lactide-co-dl-lactide); PDO-PGA-TMC — poly(glycolide-co-trimethylene carbonate-co-dioxanone) and combinations thereof.

[0037] Another embodiment provides a method for preparing a coated coronary stent comprising the following steps: providing a stainless or cobalt –chromium stent framework; forming a macrolide immunosuppressive (limus) drug-polymer coating on the stent framework wherein at least part of the drug is in crystalline form and the polymer is bioabsorbable.

[0038] In another embodiment the macrolide is deposited in dry powder form.

[0039] In another embodiment the bioabsorbable polymer is deposited in dry powder form.

[0040] In another embodiment the polymer is deposited by an e-SEDS process.

[0041] In another embodiment the polymer is deposited by an e-RESS process.

[0042] Another embodiment provides a method further comprising sintering said coating under conditions that do not substantially modify the morphology of said macrolide.

[0043] Yet another embodiment provides a coated coronary stent, comprising: a stent framework a first layer of bioabsorbable polymer; and a rapamycin-polymer coating comprising rapamycin and a second bioabsorbable polymer wherein at least part of rapamycin is in crystalline form and wherein the first polymer is a slow absorbing polymer and the second polymer is a fast absorbing polymer.

[0044] Yet another embodiment provides a coated coronary stent, comprising: a stent framework; a first layer of bioabsorbable polymer; and a rapamycin-polymer coating comprising rapamycin and a second bioabsorbable polymer wherein at least part of rapamycin is in crystalline form and wherein the first polymer is a slow absorbing polymer and the second polymer is a fast absorbing polymer.

INCORPORATION BY REFERENCE

[0045] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0046] Illustration of selected embodiments of the inventions is provided in appended Figures 1-12.

[0047] The present invention is explained in greater detail below. This description is not intended to be a detailed catalog of all the different ways in which the invention may be implemented, or all the features that may be added to the instant invention. For example, features illustrated with respect to one embodiment may be incorporated into other embodiments, and features illustrated with respect to a particular embodiment may be deleted from that embodiment. In addition, numerous variations and additions to the various embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention. Hence, the following specification is intended to illustrate some particular embodiments of the invention, and not to exhaustively specify all permutations, combinations and variations thereof.

Definitions

[0048] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0049] "Substrate" as used herein, refers to any surface upon which it is desirable to deposit a coating comprising a polymer and a pharmaceutical or biological agent, wherein the coating process does not substantially modify the morphology of the pharmaceutical agent or the activity of the biological agent. Biomedical implants are of particular interest for the present invention; however the present invention is not intended to be restricted to this class of substrates. Those of skill in the art will appreciate alternate substrates that could benefit from the coating process described herein, such as pharmaceutical tablet cores, as part of an assay apparatus or as components in a diagnostic kit (e.g. a test strip).

[0050] "Biomedical implant" as used herein refers to any implant for insertion into the body of a human or animal subject, including but not limited to stents (e.g., vascular stents), electrodes, catheters, leads, implantable pacemaker, cardioverter or defibrillator housings, joints, screws, rods, ophthalmic implants, femoral pins, bone plates, grafts, anastomotic devices, perivascular wraps, sutures, staples, shunts for hydrocephalus, dialysis grafts,

colostomy bag attachment devices, ear drainage tubes, leads for pace makers and implantable cardioverters and defibrillators, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, vascular implants, tissue adhesives and sealants, tissue scaffolds, various types of dressings (e.g., wound dressings), bone substitutes, intraluminal devices, vascular supports, etc.

[0051] The implants may be formed from any suitable material, including but not limited to organic polymers (including stable or inert polymers and biodegradable polymers), metals, inorganic materials such as silicon, and composites thereof, including layered structures with a core of one material and one or more coatings of a different material. Substrates made of a conducting material facilitate electrostatic capture. However, the invention contemplates the use of electrostatic capture in conjunction with substrate having low conductivity or which non-conductive. To enhance electrostatic capture when a non-conductive substrate is employed, the substrate is processed while maintaining a strong electrical field in the vicinity of the substrate.

[0052] Subjects into which biomedical implants of the invention may be applied or inserted include both human subjects (including male and female subjects and infant, juvenile, adolescent, adult and geriatric subjects) as well as animal subjects (including but not limited to dog, cat, horse, monkey, etc.) for veterinary purposes.

[0053] In a preferred embodiment the biomedical implant is an expandable intraluminal vascular graft or stent (e.g., comprising a wire mesh tube) that can be expanded within a blood vessel by an angioplasty balloon associated with a catheter to dilate and expand the lumen of a blood vessel, such as described in US Patent No. 4,733,665 to Palmaz Shaz.

[0054] "Pharmaceutical agent" as used herein refers to any of a variety of drugs or pharmaceutical compounds that can be used as active agents to prevent or treat a disease (meaning any treatment of a disease in a mammal, including preventing the disease, i.e. causing the clinical symptoms of the disease not to develop; inhibiting the disease, i.e. arresting the development of clinical symptoms; and/or relieving the disease, i.e. causing the regression of clinical symptoms). It is possible that the pharmaceutical agents of the invention may also comprise two or more drugs or pharmaceutical compounds. Pharmaceutical agents, include but are not limited to antirestenotic agents, antidiabetics, analgesics, antiinflammatory agents, antirheumatics, antihypotensive agents, antihypertensive agents, psychoactive drugs, tranquillizers, antiemetics, muscle relaxants, glucocorticoids, agents for treating ulcerative colitis or Crohn's disease, antiallergics, antibiotics, antiepileptics, anticoagulants, antimycotics, antitussives, arteriosclerosis remedies, diuretics, proteins, peptides, enzymes, enzyme

inhibitors, gout remedies, hormones and inhibitors thereof, cardiac glycosides, immunotherapeutic agents and cytokines, laxatives, lipid-lowering agents, migraine remedies, mineral products, otologicals, anti parkinson agents, thyroid therapeutic agents, spasmolytics, platelet aggregation inhibitors, vitamins, cytostatics and metastasis inhibitors, phytopharmaceuticals, chemotherapeutic agents and amino acids. Examples of suitable active ingredients are acarbose, antigens, beta-receptor blockers, non-steroidal antiinflammatory drugs {NSAIDs], cardiac glycosides, acetylsalicylic acid, virustatics, aclarubicin, acyclovir, cisplatin, actinomycin, alpha- and beta-sympatomimetics, (dmeprazole, allopurinol, alprostadil, prostaglandins, amantadine, ambroxol, amlodipine, methotrexate, S-aminosalicylic acid, amitriptyline, amoxicillin, anastrozole, atenolol, azathioprine, balsalazide, beclomethasone, betahistine, bezafibrate, bicalutamide, diazepam and diazepam derivatives, budesonide, bufexamac, buprenorphine, methadone, calcium salts, potassium salts, magnesium salts, candesartan, carbamazepine, captopril, cefalosporins, cetirizine, chenodeoxycholic acid, ursodeoxycholic acid, theophylline and theophylline derivatives, trypsins, cimetidine, clarithromycin, clavulanic acid, clindamycin, clobutinol, clonidine, cotrimoxazole, codeine, caffeine, vitamin D and derivatives of vitamin D, colestyramine, cromoglicic acid, coumarin and coumarin derivatives, cysteine, cytarabine, cyclophosphamide, ciclosporin, cyproterone, cytabarine, dapiprazole, desogestrel, desonide, dihydralazine, diltiazem, ergot alkaloids, dimenhydrinate, dimethyl sulphoxide, dimeticone, domperidone and domperidan derivatives, dopamine, doxazosin, doxorubizin, doxylamine, dapiprazole, benzodiazepines, diclofenac, glycoside antibiotics, desipramine, econazole, ACE inhibitors, enalapril, ephedrine, epinephrine, epoetin and epoetin derivatives, morphinans, calcium antagonists, irinotecan, modafinil, orlistat, peptide antibiotics, phenytoin, riluzoles, risedronate, sildenafil, topiramate, macrolide antibiotics, oestrogen and oestrogen derivatives, progestogen and progestogen derivatives, testosterone and testosterone derivatives, androgen and androgen derivatives, ethenzamide, etofenamate, etofibrate, fenofibrate, etofylline, etoposide, famciclovir, famotidine, felodipine, fenofibrate, fentanyl, fenticonazole, gyrase inhibitors, fluconazole, fludarabine, fluarizine, fluorouracil, fluoxetine, flurbiprofen, ibuprofen, flutamide, fluvastatin, follitropin, formoterol, fosfomicin, furosemide, fusidic acid, gallopamil, ganciclovir, gemfibrozil, gentamicin, ginkgo, Saint John's wort, glibenclamide, urea derivatives as oral antidiabetics, glucagon, glucosamine and glucosamine derivatives, glutathione, glycerol and glycerol derivatives, hypothalamus hormones, goserelin, gyrase inhibitors, guanethidine, halofantrine, haloperidol, heparin and heparin derivatives, hyaluronic acid, hydralazine, hydrochlorothiazide and hydrochlorothiazide derivatives, salicylates,

hydroxyzine, idarubicin, ifosfamide, imipramine, indometacin, indoramine, insulin, interferons, iodine and iodine derivatives, isoconazole, isoprenaline, glucitol and glucitol derivatives, itraconazole, ketoconazole, ketoprofen, ketotifen, lacidipine, lansoprazole, levodopa, levomethadone, thyroid hormones, lipoic acid and lipoic acid derivatives, lisinopril, lisuride, lofepramine, lomustine, loperamide, loratadine, maprotiline, mebendazole, mebeverine, meclozine, mefenamic acid, mefloquine, meloxicam, mepindolol, meprobamate, meropenem, mesalazine, mesuximide, metamizole, metformin, methotrexate, methylphenidate, methylprednisolone, metixene, metoclopramide, metoprolol, metronidazole, mianserin, miconazole, minocycline, minoxidil, misoprostol, mitomycin, mizolastine, moexipril, morphine and morphine derivatives, evening primrose, nalbuphine, naloxone, tilidine, naproxen, narcotine, natamycin, neostigmine, nicergoline, nicethamide, nifedipine, niflumic acid, nimodipine, nimorazole, nimustine, nisoldipine, adrenaline and adrenaline derivatives, norfloxacin, novamine sulfone, noscapine, nystatin, ofloxacin, olanzapine, olsalazine, omeprazole, omoconazole, ondansetron, oxaceprol, oxacillin, oxiconazole, oxymetazoline, pantoprazole, paracetamol, paroxetine, penciclovir, oral penicillins, pentazocine, pentifylline, pentoxifylline, perphenazine, pethidine, plant extracts, phenazone, pheniramine, barbituric acid derivatives, phenylbutazone, phenytoin, pimozide, pindolol, piperazine, piracetam, pirenzepine, piribedil, piroxicam, pramipexole, pravastatin, prazosin, procaine, promazine, propiverine, propranolol, propyphenazone, prostaglandins, protionamide, proxyphylline, quetiapine, quinapril, quinaprilat, ramipril, ranitidine, reproterol, reserpine, ribavirin, rifampicin, risperidone, ritonavir, ropinirole, roxatidine, roxithromycin, ruscogenin, rutoside and rutoside derivatives, sabadilla, salbutamol, salmeterol, scopolamine, selegiline, sertaconazole, sertindole, sertralion, silicates, sildenafil, simvastatin, sitosterol, sotalol, spaglumic acid, sparfloxacin, spectinomycin, spiramycin, spirapril, spironolactone, stavudine, streptomycin, sucralfate, sufentanil, sulbactam, sulphonamides, sulfasalazine, sulpiride, sultamicillin, sultiam, sumatriptan, suxamethonium chloride, tacrine, tacrolimus, taliolol, tamoxifen, taurolidine, tazarotene, temazepam, teniposide, tenoxicam, terazosin, terbinafine, terbutaline, terfenadine, terlipressin, tertatolol, tetracyclins, teryzoline, theobromine, theophylline, butizine, thiamazole, phenothiazines, thiotepa, tiagabine, tiapride, propionic acid derivatives, ticlopidine, timolol, tinidazole, tioconazole, tioguanine, tioxolone, tiropramide, tizanidine, tolazoline, tolbutamide, tolcapone, tolnaftate, tolperisone, topotecan, torasemide, antioestrogens, tramadol, tramazoline, trandolapril, tranylcypromine, trapidil, trazodone, triamcinolone and triamcinolone derivatives, triamterene, trifluperidol, trifluridine, trimethoprim, trimipramine, tripelennamine, triprolidine, trifosfamide, tromantadine,

trometamol, tropalpin, troxerutine, tulobuterol, tyramine, tyrothricin, urapidil, ursodeoxycholic acid, chenodeoxycholic acid, valaciclovir, valproic acid, vancomycin, vecuronium chloride, Viagra, venlafaxine, verapamil, vidarabine, vigabatrin, viloazine, vinblastine, vincamine, vincristine, vindesine, vinorelbine, vinpocetine, viquidil, warfarin, xantinol nicotinate, xipamide, zafirlukast, zalcitabine, zidovudine, zolmitriptan, zolpidem, zoplicone, zotipine and the like. See, e.g., US Patent No. 6,897,205; see also US Patent No. 6,838,528; US Patent No. 6,497,729.

[0055] Examples of therapeutic agents employed in conjunction with the invention include, rapamycin, 40-O-(2-Hydroxyethyl)rapamycin (everolimus), 40-O-Benzyl-rapamycin, 40-O-(4'-Hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin, 40-O-Allyl-rapamycin, 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2':E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin 40-O-(2-Hydroxy)ethoxycar-bonylmethyl-rapamycin, 40-O-(3-Hydroxy)propyl-rapamycin 4O-O-(6-Hydroxy)hexyl-rapamycin 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin 4O-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin, 4O-O-(2-Acetoxy)ethyl-rapamycin 4O-O-(2-Nicotinoyloxy)ethyl-rapamycin, 4O-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin 4O-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 28-O-Methyl-rapamycin, 4O-O-(2-Aminoethyl)-rapamycin, 4O-O-(2-Acetaminoethyl)-rapamycin 4O-O-(2-Nicotinamidoethyl)-rapamycin, 4O-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 4O-O-(2-Ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-Tolylsulfonamidoethyl)-rapamycin, 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin, 42-Epi-(tetrazolyl)rapamycin (tacrolimus), and 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus).

[0056] The active ingredients may, if desired, also be used in the form of their pharmaceutically acceptable salts or derivatives (meaning salts which retain the biological effectiveness and properties of the compounds of this invention and which are not biologically or otherwise undesirable), and in the case of chiral active ingredients it is possible to employ both optically active isomers and racemates or mixtures of diastereoisomers.

[0057] "Stability" as used herein in refers to the stability of the drug in a polymer coating deposited on a substrate in its final product form (e.g., stability of the drug in a coated stent). The term stability will define 5% or less degradation of the drug in the final product form.

[0058] "Active biological agent" as used herein refers to a substance, originally produced by living organisms, that can be used to prevent or treat a disease (meaning any treatment of a disease in a mammal, including preventing the disease, i.e. causing the clinical symptoms of the disease not to develop; inhibiting the disease, i.e. arresting the development of clinical symptoms; and/or relieving the disease, i.e. causing the regression of clinical symptoms). It is possible that the active biological agents of the invention may also comprise two or more active biological agents or an active biological agent combined with a pharmaceutical agent, a stabilizing agent or chemical or biological entity. Although the active biological agent may have been originally produced by living organisms, those of the present invention may also have been synthetically prepared, or by methods combining biological isolation and synthetic modification. By way of a non-limiting example, a nucleic acid could be isolated form from a biological source, or prepared by traditional techniques, known to those skilled in the art of nucleic acid synthesis. Furthermore, the nucleic acid may be further modified to contain non-naturally occurring moieties. Non-limiting examples of active biological agents include peptides, proteins, enzymes, glycoproteins, nucleic acids (including deoxyribonucleotide or ribonucleotide polymers in either single or double stranded form, and unless otherwise limited, encompasses known analogues of natural nucleotides that hybridize to nucleic acids in a manner similar to naturally occurring nucleotides), antisense nucleic acids, fatty acids, antimicrobials, vitamins, hormones, steroids, lipids, polysaccharides, carbohydrates and the like. They further include, but are not limited to, antirestenotic agents, antidiabetics, analgesics, antiinflammatory agents, antirheumatics, antihypotensive agents, antihypertensive agents, psychoactive drugs, tranquillizers, antiemetics, muscle relaxants, glucocorticoids, agents for treating ulcerative colitis or Crohn's disease, antiallergics, antibiotics, antiepileptics, anticoagulants, antimycotics, antitussives, arteriosclerosis remedies, diuretics, proteins, peptides, enzymes, enzyme inhibitors, gout remedies, hormones and inhibitors thereof, cardiac glycosides, immunotherapeutic agents and cytokines, laxatives, lipid-lowering agents, migraine remedies, mineral products, otologicals, anti parkinson agents, thyroid therapeutic agents, spasmolytics, platelet aggregation inhibitors, vitamins, cytostatics and metastasis inhibitors, phytopharmaceuticals and chemotherapeutic agents. Preferably, the active biological agent is a peptide, protein or enzyme, including derivatives and analogs of natural peptides, proteins and enzymes.

[0059] "Activity" as used herein refers to the ability of a pharmaceutical or active biological agent to prevent or treat a disease (meaning any treatment of a disease in a mammal, including preventing the disease, i.e. causing the clinical symptoms of the disease not to develop;

inhibiting the disease, i.e. arresting the development of clinical symptoms; and/or relieving the disease, i.e. causing the regression of clinical symptoms). Thus the activity of a pharmaceutical or active biological agent should be of therapeutic or prophylactic value.

[0060] "Secondary, tertiary and quaternary structure " as used herein are defined as follows. The active biological agents of the present invention will typically possess some degree of secondary, tertiary and/or quaternary structure, upon which the activity of the agent depends. As an illustrative, non-limiting example, proteins possess secondary, tertiary and quaternary structure. Secondary structure refers to the spatial arrangement of amino acid residues that are near one another in the linear sequence. The α-helix and the β-strand are elements of secondary structure. Tertiary structure refers to the spatial arrangement of amino acid residues that are far apart in the linear sequence and to the pattern of disulfide bonds. Proteins containing more than one polypeptide chain exhibit an additional level of structural organization. Each polypeptide chain in such a protein is called a subunit. Quaternary structure refers to the spatial arrangement of subunits and the nature of their contacts. For example hemoglobin consists of two α and two β chains. It is well known that protein function arises from its conformation or three dimensional arrangement of atoms (a stretched out polypeptide chain is devoid of activity). Thus one aspect of the present invention is to manipulate active biological agents, while being careful to maintain their conformation, so as not to lose their therapeutic activity.

[0061] "Polymer" as used herein, refers to a series of repeating monomeric units that have been cross-linked or polymerized. Any suitable polymer can be used to carry out the present invention. It is possible that the polymers of the invention may also comprise two, three, four or more different polymers. In some embodiments, of the invention only one polymer is used. In some preferred embodiments a combination of two polymers are used. Combinations of polymers can be in varying ratios, to provide coatings with differing properties. Those of skill in the art of polymer chemistry will be familiar with the different properties of polymeric compounds.

[0062] "Therapeutically desirable morphology" as used herein refers to the gross form and structure of the pharmaceutical agent, once deposited on the substrate, so as to provide for optimal conditions of ex vivo storage, in vivo preservation and/or in vivo release. Such optimal conditions may include, but are not limited to increased shelf life, increased in vivo stability, good biocompatibility, good bioavailability or modified release rates. Typically, for the present invention, the desired morphology of a pharmaceutical agent would be crystalline or semi-crystalline or amorphous, although this may vary widely depending on many factors

including, but not limited to, the nature of the pharmaceutical agent, the disease to be treated/prevented, the intended storage conditions for the substrate prior to use or the location within the body of any biomedical implant. Preferably at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the pharmaceutical agent is in crystalline or semi-crystalline form.

[0063] "Stabilizing agent" as used herein refers to any substance that maintains or enhances the stability of the biological agent. Ideally these stabilizing agents are classified as Generally Regarded As Safe (GRAS) materials by the US Food and Drug Administration (FDA). Examples of stabilizing agents include, but are not limited to carrier proteins, such as albumin, gelatin, metals or inorganic salts. Pharmaceutically acceptable excipient that may be present can further be found in the relevant literature, for example in the Handbook of Pharmaceutical Additives: An International Guide to More Than 6000 Products by Trade Name, Chemical, Function, and Manufacturer; Michael and Irene Ash (Eds.); Gower Publishing Ltd.; Aldershot, Hampshire, England, 1995.

[0064] "Compressed fluid" as used herein refers to a fluid of appreciable density (e.g., >0.2 g/cc) that is a gas at standard temperature and pressure. "Supercritical fluid", "near-critical fluid", "near-supercritical fluid", "critical fluid", "densified fluid" or "densified gas" as used herein refers to a compressed fluid under conditions wherein the temperature is at least 80% of the critical temperature of the fluid and the pressure is at least 50% of the critical pressure of the fluid.

[0065] Examples of substances that demonstrate supercritical or near critical behavior suitable for the present invention include, but are not limited to carbon dioxide, isobutylene, ammonia, water, methanol, ethanol, ethane, propane, butane, pentane, dimethyl ether, xenon, sulfur hexafluoride, halogenated and partially halogenated materials such as chlorofluorocarbons, hydrochlorofluorocarbons, hydrofluorocarbons, perfluorocarbons (such as perfluoromethane and perfuoropropane, chloroform, trichloro-fluoromethane, dichloro-difluoromethane, dichloro-tetrafluoroethane) and mixtures thereof.

[0066] "Sintering" as used herein refers to the process by which parts of the matrix or the entire polymer matrix becomes continuous (e.g., formation of a continuous polymer film). As discussed below, the sintering process is controlled to produce a fully conformal continuous matrix (complete sintering) or to produce regions or domains of continuous coating while producing voids (discontinuities) in the matrix. As well, the sintering process is controlled such that some phase separation is obtained between polymer different polymers (e.g., polymers A and B) and/or to produce phase separation between discrete polymer particles.

Through the sintering process, the adhesions properties of the coating are improved to reduce flaking of detachment of the coating from the substrate during manipulation in use. As described below, in some embodiments, the sintering process is controlled to provide incomplete sintering of the polymer matrix. In embodiments involving incomplete sintering, a polymer matrix is formed with continuous domains, and voids, gaps, cavities, pores, channels or, interstices that provide space for sequestering a therapeutic agent which is released under controlled conditions. Depending on the nature of the polymer, the size of polymer particles and/or other polymer properties, a compressed gas, a densified gas, a near critical fluid or a super-critical fluid may be employed. In one example, carbon dioxide is used to treat a substrate that has been coated with a polymer and a drug, using dry powder and RESS electrostatic coating processes. In another example, isobutylene is employed in the sintering process. In other examples a mixture of carbon dioxide and isobutylene is employed.

[0067] When an amorphous material is heated to a temperature above its glass transition temperature, or when a crystalline material is heated to a temperature above a phase transition temperature, the molecules comprising the material are more mobile, which in turn means that they are more active and thus more prone to reactions such as oxidation. However, when an amorphous material is maintained at a temperature below its glass transition temperature, its molecules are substantially immobilized and thus less prone to reactions. Likewise, when a crystalline material is maintained at a temperature below its phase transition temperature, its molecules are substantially immobilized and thus less prone to reactions. Accordingly, processing drug components at mild conditions, such as the deposition and sintering conditions described herein, minimizes cross-reactions and degradation of the drug component. One type of reaction that is minimized by the processes of the invention relates to the ability to avoid conventional solvents which in turn minimizes autoxidation of drug, whether in amorphous, semi-crystalline, or crystalline form, by reducing exposure thereof to free radicals, residual solvents and autoxidation initiators.

[0068] "Rapid Expansion of Supercritical Solutions" or "RESS" as used herein involves the dissolution of a polymer into a compressed fluid, typically a supercritical fluid, followed by rapid expansion into a chamber at lower pressure, typically near atmospheric conditions. The rapid expansion of the supercritical fluid solution through a small opening, with its accompanying decrease in density, reduces the dissolution capacity of the fluid and results in the nucleation and growth of polymer particles. The atmosphere of the chamber is maintained in an electrically neutral state by maintaining an isolating "cloud" of gas in the chamber.

Carbon dioxide or other appropriate gas is employed to prevent electrical charge is transferred from the substrate to the surrounding environment.

[0069] "Bulk properties" properties of a coating including a pharmaceutical or a biological agent that can be enhanced through the methods of the invention include for example: adhesion, smoothness, conformality, thickness, and compositional mixing.

[0070] "Electrostatically charged" or "electrical potential" or "electrostatic capture" as used herein refers to the collection of the spray-produced particles upon a substrate that has a different electrostatic potential than the sprayed particles. Thus, the substrate is at an attractive electronic potential with respect to the particles exiting, which results in the capture of the particles upon the substrate. i.e. the substrate and particles are oppositely charged, and the particles transport through the fluid medium of the capture vessel onto the surface of the substrate is enhanced via electrostatic attraction. This may be achieved by charging the particles and grounding the substrate or conversely charging the substrate and grounding the particles, or by some other process, which would be easily envisaged by one of skill in the art of electrostatic capture.

[0071] Means for creating the bioabsorbable polymer(s) + drug (s) matrix on the stent-form – forming the final device:

- Spray coat the stent-form with drug and polymer as is done in Micell process (e-RESS, e-DPC, compressed-gas sintering).
- Perform multiple and sequential coating–sintering steps where different materials may be deposited in each step, thus creating a laminated structure with a multitude of thin layers of drug(s), polymer(s) or drug+polymer that build the final stent.
- Perform the deposition of polymer(s) + drug(s) laminates with the inclusion of a mask on the inner (luminal) surface of the stent. Such a mask could be as simple as a non-conductive mandrel inserted through the internal diameter of the stent form. This masking could take place prior to any layers being added, or be purposefully inserted after several layers are deposited continuously around the entire stent-form.

[0072] Another advantage of the present invention is the ability to create a stent with a controlled (dialed-in) drug-elution profile. Via the ability to have different materials in each layer of the laminate structure and the ability to control the location of drug(s) independently in these layers, the method enables a stent that could release drugs at very specific elution profiles, programmed sequential and/or parallel elution profiles. Also, the present invention allows controlled elution of one drug without affecting the elution of a second drug (or different doses of the same drug).

[0073] The embodiments incorporating a stent form or framework provide the ability to radiographically monitor the stent in deployment. In an alternative embodiment, the inner-

diameter of the stent can be masked (e.g. by a non-conductive mandrel). Such masking would prevent additional layers from being on the interior diameter (abluminal) surface of the stent. The resulting configuration may be desirable to provide preferential elution of the drug toward the vessel wall (luminal surface of the stent) where the therapeutic effect of anti-restenosis is desired, without providing the same antiproliferative drug(s) on the abluminal surface, where they may retard healing, which in turn is suspected to be a cause of late-stage safety problems with current DESs.

[0074] The present invention provides numerous advantages. The invention is advantageous allows for employing a platform combining layer formation methods based on compressed fluid technologies; electrostatic capture and sintering methods. The platform results in drug eluting stents having enhanced therapeutic and mechanical properties. The invention is particularly advantageous in that it employs optimized laminate polymer technology. In particular, the present invention allows the formation of discrete layers of specific drug platforms.

[0075] Conventional processes for spray coating stents require that drug and polymer be dissolved in solvent or mutual solvent before spray coating can occur. The platform provided herein the drugs and polymers are coated on the stent framework in discrete steps, which can be carried out simultaneously or alternately. This allows discrete deposition of the active agent (e.g.; a drug) within a polymer matrix thereby allowing the placement of more than one drug on a single medical device with or without an intervening polymer layer. For example, the present platform provides a dual drug eluting stent.

[0076] Some of the advantages provided by the subject invention include employing compressed fluids (e.g., supercritical fluids, for example E-RESS based methods); solvent free deposition methodology; a platform that allows processing at lower temperatures thereby preserving the qualities of the active agent and the polymer matrix; the ability to incorporate two, three or more drugs while minimizing deleterious effects from direct interactions between the various drugs and/or their excipients during the fabrication and/or storage of the drug eluting stents; a dry deposition; enhanced adhesion and mechanical properties of the layers on the stent framework; precision deposition and rapid batch processing; and ability to form intricate structures.

[0077] In one embodiment, the present invention provides a multi-drug delivery platform which produces strong, resilient and flexible drug eluting stents including an anti-restenosis drug (e.g.; a limus or taxol) and anti-thrombosis drug (e.g.; heparin or an analog thereof) and well characterized bioabsorbable polymers. The drug eluting stents provided herein minimize

potential for thrombosis, in part, by reducing or totally eliminating thrombogenic polymers and reducing or totally eliminating residual drugs that could inhibit healing.

[0078] The platform provides optimized delivery of multiple drug therapies for example for early stage treatment (restenosis) and late-stage (thrombosis).

[0079] The platform also provides an adherent coating which enables access through tortuous lesions without the risk of the coating being compromised.

[0080] Another advantage of the present platform is the ability to provide highly desirable eluting profiles (e.g., the profile illustrated in Figures 14-17).

[0081] Advantages of the invention include the ability to reduce or completely eliminate potentially thrombogenic polymers as well as possibly residual drugs that may inhibit long term healing. As well, the invention provides advantageous stents having optimized strength and resilience if coatings which in turn allows access to complex lesions and reduces or completely eliminates delamination. Laminated layers of bioabsorbable polymers allow controlled elution of one or more drugs.

[0082] The platform provided herein reduces or completely eliminates shortcoming that have been associated with conventional drug eluting stents. For example, the platform provided herein allows for much better tuning of the period of time for the active agent to elute and the period of time necessary for the polymer matrix to resorb thereby minimizing thrombosis and other deleterious effects associate with poorly controlled drug release.

[0083] The present invention provides several advantages which overcome or attenuate the limitations of current technology for bioabsorbable stents. Fro example, an inherent limitation of conventional bioabsorbable polymeric materials relates to the difficulty in forming to a strong, flexible, deformable (e.g. balloon deployable) stent with low profile. The polymers generally lack the strength of high-performance metals. The present invention overcomes these limitations by creating a laminate structure in the essentially polymeric stent. Without wishing to be bound by any specific theory or analogy, the increased strength provided by the stents of the invention can be understood by comparing the strength of plywood vs. the strength of a thin sheet of wood.

[0084] Embodiments of the invention involving a thin metallic stent-framework provide advantages including the ability to overcome the inherent elasticity of most polymers. It is generally difficult to obtain a high rate (e.g., 100%) of plastic deformation in polymers (compared to elastic deformation where the materials have some 'spring back' to the original shape). Again, without wishing to be bound by any theory, the central metal stent framework

(that would be too small and weak to serve as a stent itself) would act like wires inside of a plastic, deformable stent, basically overcoming any 'elastic memory' of the polymer.

Examples

[0085] The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Example.

[0086] In this example illustrates embodiments that provide a coated coronary stent, comprising: a stent framework and a rapamycin-polymer coating wherein at least part of rapamycin is in crystalline form and the rapamycin-polymer coating comprises one or more resorbable polymers.

[0087] In these experiments two different polymers were emplyed:

Polymer A: - 50:50 PLGA-Ester End Group, MW~90kD, degradation rate ~70 days

Polymer B: - 50:50 PLGA-Carboxylate End Group, MW~29kD, degradation rate ~28 days

[0088] Metal stents were coated as follows:

AS1: Polymer A/Rapamycin/Polymer A/Rapamycin/Polymer A

AS2: Polymer A/Rapamycin/Polymer A/Rapamycin/Polymer B

AS1 (B): Polymer B/Rapamycin/Polymer B/Rapamycin/Polymer B

AS1b: Polymer A/Rapamycin/Polymer A/Rapamycin/Polymer A

AS2b: Polymer A/Rapamycin/Polymer A/Rapamycin/Polymer B

[0089] Elution results are illustrated in Figures 13-17.

[0090] The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. While embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS:

1. A method of preparing a coronary stent comprising:
    a. providing a stent framework;
    b. depositing a plurality of layers on said stent framework to form said coronary stent; wherein at least one of said layers comprises a drug-polymer coating wherein at least part of the drug is in crystalline form and the polymer is a bioabsorbable polymer.
2. The method of Claim 1, wherein the drug and polymer are in the same layer; in separate layers or in overlapping layers.
3. The method of Claim 1, wherein the stent framework is made of stainless steel.
4. The method of Claim 1 wherein the stent framework is formed from a metal alloy.
5. The method of Claim 1 wherein the stent framework is formed from a cobalt chromium alloy.
6. The method of Claim 1 wherein the stent framework is formed from a material comprising the following percentages by weight: 0.05-0.15 C, 1.00-2.00 Mn, 0.040 Si, 0.030 P, 0.3 S, 19.00-21.00 Cr, 9.00-11.00 Ni, 14.00-16.00 W, 3.00 Fe, and Bal. Co.
7. The method of Claim 1 wherein the stent framework is formed from a material comprising at most the following percentages by weight: about 0.025 maximum C, 0.15 maximum Mn, 0.15 maximum Si, 0.015 maximum P, 0.01 maximum S, 19.00-21.00 maximum Cr, 33-37 Ni, 9.0-10.5 Mo, 1.0 maximum Fe, 1.0 maximum Ti, and Bal. Co.
8. The method of Claim 1, wherein the stent framework has a thickness of about 50% or less of a thickness of the coronary stent.
9. The method of Claim 1, wherein the stent framework has a thickness of about 100 μm or less.
10. The method of Claim 1, wherein said bioabsorbable polymer is selected from PGA poly(glycolide), LPLA poly(l-lactide), DLPLA poly(dl-lactide), PCL poly(e-caprolactone) PDO, poly(dioxolane) PGA-TMC, 85/15 DLPLG p(dl-lactide-co-glycolide), 75/25 DLPL, 65/35 DLPLG, 50/50 DLPLG, TMC poly(trimethylcarbonate), p(CPP:SA) poly(1,3-bis-p-(carboxyphenoxy)propane-co-sebacic acid).
11. The method of Claim 1 comprising depositing 4 or more layers.

12. The method of Claim 1 comprising depositing 10, 20, 50, or 100 layers.

13. The method of Claim 1 wherein said layers comprise alternate drug and polymer layers.

14. The method of Claim 13, wherein the drug layers are substantially free of polymer and the polymer layers are substantially free of drug.

15. The method of Claim 14, wherein said one or more active agents comprise a macrolide immunosuppressive (limus) drug.

16. The method of Claim 15, wherein the macrolide immunosuppressive drug comprises one or more of rapamycin, 40-O-(2-Hydroxyethyl)rapamycin (everolimus), 40-O-Benzyl-rapamycin, 40-O-(4'-Hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin, 40-O-Allyl-rapamycin, 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2':E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin 40-O-(2-Hydroxy)ethoxycar-bonylmethyl-rapamycin, 40-O-(3-Hydroxy)propyl-rapamycin 4O-O-(6-Hydroxy)hexyl-rapamycin 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin 4O-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin, 4O-O-(2-Acetoxy)ethyl-rapamycin 4O-O-(2-Nicotinoyloxy)ethyl-rapamycin, 4O-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin 4O-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 28-O-Methyl-rapamycin, 4O-O-(2-Aminoethyl)-rapamycin, 4O-O-(2-Acetaminoethyl)-rapamycin 4O-O-(2-Nicotinamidoethyl)-rapamycin, 4O-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 4O-O-(2-Ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-Tolylsulfonamidoethyl)-rapamycin, 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin, 42-Epi-(tetrazolyl)rapamycin (tacrolimus), and 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus).

17. The method of Claim 15, wherein said macrolide immunosuppressive drug is at least 50% crystalline.

18. The method of Claim 1, wherein depositing a plurality of layers on said stent framework to form said coronary stent comprises depositing polymer particles on said framework by an RESS process.

19. The method of Claim 1, wherein depositing a plurality of layers on said stent framework to form said coronary stent comprises depositing polymer particles on said framework in dry powder form.

20. A coronary stent prepared by the method of Claim 1.

21. A laminate coronary stent comprising

a. a stent framework;

b. a plurality of layers deposited on said stent framework to form said coronary stent; wherein at least one of said layers comprises a bioabsorbable polymer and at least one of said layers comprises one or more active agents; wherein at least part of the active agent is in crystalline form.

22. The stent of Claim 1, wherein the active agent and polymer are in the same layer; in separate layers or form overlapping layers.

23. A coronary stent comprising

a. a stent framework;

b. a plurality of layers deposited on said stent framework to form said coronary stent; wherein at least one of said layers comprises a PLGA bioabsorbable polymer and at least one of said layers comprises rapamycin; wherein at least part of rapamycin is in crystalline form.

24. The stent of Claim 23, wherein the rapamycin and polymer are in the same layer; in separate layers or form overlapping layers.

25. The coronary stent of Claim 23 wherein the plurality of layers comprise five layers deposited as follows: a first polymer layer, a first rapamycin layer, a second polymer layer, a second rapamycin layer and a third polymer layer.

26. The coronary stent of Claim 23 wherein the PLGA polymer has a molecular weight of about 90 kD.

27. The coronary stent of Claim 23 wherein the PLGA polymer has a molecular weight of about 29 kD.

28. The stent of Claim 23 wherein the stent framework is formed from a material comprising the following percentages by weight: 0.05-0.15 C, 1.00-2.00 Mn, 0.040 Si, 0.030 P, 0.3 S, 19.00-21.00 Cr, 9.00-11.00 Ni, 14.00-16.00 W, 3.00 Fe, and Bal. Co.

29. The stent of Claim 23 wherein the stent framework is formed from a material comprising at most the following percentages by weight: about 0.025 maximum C, 0.15 maximum Mn, 0.15 maximum Si, 0.015 maximum P, 0.01 maximum S, 19.00-21.00 maximum Cr, 33-37 Ni, 9.0-10.5 Mo, 1.0 maximum Fe, 1.0 maximum Ti, and Bal. Co

30. A method of preparing a coronary stent comprising:

a. providing a stent framework;

b. depositing a plurality of layers on said stent framework to form said coronary stent; wherein at least one of said layers comprises a bioabsorbable polymer; wherein depositing each layer of said plurality of layers on said stent framework comprises the following steps:

discharging at least one pharmaceutical agent and/or at least one active biological agent in dry powder form through a first orifice;

discharging the at least one polymer in dry powder form through said first orifice or through a second orifice;

depositing the polymer and pharmaceutical agent and/or active biological agent particles onto said framework, wherein an electrical potential is maintained between the framework and the polymer and pharmaceutical agent and/or active biological agent particles, thereby forming said layer; and

sintering said layer under conditions that do not substantially modify the morphology of said pharmaceutical agent and/or the activity of said biological agent.

31. A method of preparing a coronary stent comprising:

a. providing a stent framework;

b. depositing a plurality of layers on said stent framework to form said coronary stent; wherein at least one of said layers comprises a bioabsorbable polymer; at least one pharmaceutical agent in a therapeutically desirable morphology and/or at least one active biological

agent; wherein depositing each layer of said plurality of layers on said stent framework comprises the following steps:

i. discharging the at least one pharmaceutical agent and/or at least one active biological agent in dry powder form through a first orifice;

ii. forming a supercritical or near supercritical fluid solution comprising at least one supercritical fluid solvent and at least one polymer and discharging said supercritical or near supercritical fluid solution through a second orifice under conditions sufficient to form solid particles of the polymer;

iii. depositing the polymer and pharmaceutical agent and/or active biological agent particles onto said framework, wherein an electrical potential is maintained between the framework and the polymer and pharmaceutical agent and/or active biological agent particles, thereby forming said layer; and

iv. sintering said layer under conditions that do not substantially modify the morphology of said pharmaceutical agent and/or the activity of said biological agent.

32. A method of preparing a coronary stent comprising:

a. providing a stent framework;

b. depositing a plurality of layers on said stent framework to form said coronary stent; wherein at least one of said layers comprises a bioabsorbable polymer; at least one pharmaceutical agent in a therapeutically desirable morphology and/or at least one active biological agent; wherein depositing each layer of said plurality of layers on said stent framework comprises the following steps:

i. forming a supercritical or near supercritical fluid solution comprising at least one supercritical fluid solvent and one or more pharmaceutical agents and/or at least one active biological agent discharging said supercritical or near supercritical fluid solution through a first orifice under conditions sufficient to form solid

particles of said one or more pharmaceutical agents and/or at least one active biological agent;

ii. forming a supercritical or near supercritical fluid solution comprising at least one supercritical fluid solvent and at least one polymer and discharging said supercritical or near supercritical fluid solution through said first orifice or through a second orifice under conditions sufficient to form solid particles of the polymer;

iii. depositing the polymer and pharmaceutical agent and/or active biological agent particles onto said framework, wherein an electrical potential is maintained between the framework and the polymer and pharmaceutical agent and/or active biological agent particles, thereby forming said layer; and

iv. sintering said layer under conditions that do not substantially modify the morphology of said pharmaceutical agent and/or the activity of said biological agent.

33. The method of claims 30-32, further comprising discharging a third dry powder comprising a second pharmaceutical agent in a therapeutically desirable morphology in dry powder form and/or active biological agent whereby a layer comprising at least two different pharmaceutical agents and/or active biological agents is deposited on said framework or at least two layers each comprising one of two different pharmaceutical agents and/or active biological agents are deposited on said framework.

34. The method of claims 30-32, wherein the framework is electrostatically charged.

35. The method of claims 30-32, wherein said framework is biodegradable.

36. The method of claims 30-32, wherein the therapeutically desirable morphology of said pharmaceutical agent is crystalline or semi-crystalline.

37. The method of claims 30-32, wherein at least 50% of said pharmaceutical agent in powder form is crystalline or semicrystalline.

38. The method of claims 30-32, wherein said pharmaceutical agent comprises at least one drug.

39. The method of claims 30-32, wherein the at least one drug is selected from the group consisting of antirestenotic agents, antidiabetics, analgesics, antiinflammatory agents, antirheumatics, antihypotensive agents, antihypertensive agents.

40. The method of claims 30-32, wherein the activity of said active biological agent is of therapeutic or prophylactic value.

41. The method of claims 30-32, wherein said biological agent is selected from the group comprising peptides, proteins, enzymes, nucleic acids, antisense nucleic acids, antimicrobials, vitamins, hormones, steroids, lipids, polysaccharides and carbohydrates.

42. The method of claims 30-32, wherein the activity of said active biological agent is influenced by the secondary, tertiary or quaternary structure of said active biological agent.

43. The method of claim 30-32, wherein said active biological agent possesses a secondary, tertiary or quaternary structure which is not substantially changed after the step of sintering said layer.

44. The method of claims 30-32, wherein said active biological agent further comprises a stabilizing agent.

45. The method of claims 30-32, wherein said sintering comprises treating said layer with a compressed gas, compressed liquid or supercritical fluid that is a non-solvent for both the polymer and the pharmaceutical and/or biological agents.

46. The method of claim 45, wherein said compressed gas, compressed liquid or supercritical fluid comprises carbon dioxide, isobutylene or a mixture thereof.

47. The method of claim 46, wherein said layer comprises a microstructure.

48. The method of claim 47, wherein said microstructure comprises microchannels, micropores and/or microcavities.

49. The method of claim 48, wherein the particles of said pharmaceutical agent and/or active biological agent are sequestered or encapsulated within said microstructure.

50. The method of claim 48, where said microstructure is selected to allow controlled release of said pharmaceutical agent and/or active biological agent.

51. The method of claim 48, where said microstructure is selected to allow sustained release of said pharmaceutical agent and/or active biological agent.

52. The method of claim 48, where said microstructure is selected to allow continuous release of said pharmaceutical agent and/or active biological agent.

53. The method of claim 48, where said microstructure is selected to allow pulsatile release of said pharmaceutical agent and/or active biological agent.

54. The method of Claims 30-32, wherein said bioabsorbable polymer is selected from PGA poly(glycolide), LPLA poly(l-lactide), DLPLA poly(dl-lactide), PCL poly(e-caprolactone) PDO, poly(dioxolane) PGA-TMC, 85/15 DLPLG p(dl-lactide-co-glycolide), 75/25 DLPL,

65/35 DLPLG, 50/50 DLPLG, TMC poly(trimethylcarbonate), p(CPP:SA) poly(1,3-bis-p-(carboxyphenoxy)propane-co-sebacic acid).

55. The method of Claims 30-32 comprising depositing 4 or more layers.

56. The method of Claims 30-32 comprising depositing 10, 20, 50, or 100 layers.

57. The method of Claims 30-32 wherein said layers comprise alternate drug and polymer layers.

58. The method of Claim 57, wherein the drug layers are substantially free of polymer and the polymer layers are substantially free of drug.

59. The method of Claims 30-32, wherein said one or more active agents comprise a macrolide immunosuppressive (limus) drug.

60. The method of Claim 59, wherein the macrolide immunosuppressive drug comprises one or more of rapamycin, 40-O-(2-Hydroxyethyl)rapamycin (everolimus), 40-O-Benzyl-rapamycin, 40-O-(4'-Hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin, 40-O-Allyl-rapamycin, 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2':E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin 40-O-(2-Hydroxy)ethoxycar-bonylmethyl-rapamycin, 40-O-(3-Hydroxy)propyl-rapamycin 4O-O-(6-Hydroxy)hexyl-rapamycin 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin 4O-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin, 4O-O-(2-Acetoxy)ethyl-rapamycin 4O-O-(2-Nicotinoyloxy)ethyl-rapamycin, 4O-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin 4O-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 28-O-Methyl-rapamycin, 4O-O-(2-Aminoethyl)-rapamycin, 4O-O-(2-Acetaminoethyl)-rapamycin 4O-O-(2-Nicotinamidoethyl)-rapamycin, 4O-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 4O-O-(2-Ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-Tolylsulfonamidoethyl)-rapamycin, 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin, 42-Epi-(tetrazolyl)rapamycin (tacrolimus), and 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus).

61. A coated coronary stent, comprising:

a stent framework; and

a rapamycin-polymer coating wherein at least part of rapamycin is in crystalline form and the rapamycin-polymer coating comprises one or more resorbable polymers.

62. The coated coronary stent of Claim 61, wherein said rapamycin-polymer coating has substantially uniform thickness and rapamycin in the coating is substantially uniformly dispersed within the rapamycin-polymer coating.

63. The coated coronary stent of Claim 61 wherein the one or more resorbable polymers are selected from PLGA (poly(lactide-co-glycolide); DLPLA — poly(dl-lactide); LPLA — poly(l-lactide); PGA — polyglycolide; PDO — poly(dioxanone); PGA-TMC — poly(glycolide-co-trimethylene carbonate); PGA-LPLA — poly(l-lactide-co-glycolide); PGA-DLPLA — poly(dl-lactide-co-glycolide); LPLA-DLPLA — poly(l-lactide-co-dl-lactide); PDO-PGA-TMC — poly(glycolide-co-trimethylene carbonate-co-dioxanone) and combinations thereof.

64. The coronary stent of Claim 61 wherein the polymer is 50/50 PLGA.

65. The coated coronary stent of Claim 61, wherein at least part of said rapamycin forms a phase separate from one or more phases formed by said polymer.

66. The coated coronary stent of Claim 61, wherein said rapamycin is at least 50% crystalline.

67. The coated coronary stent of Claim 61, wherein said rapamycin is at least 75% crystalline.

68. The coated coronary stent of Claim 61, wherein said rapamycin is at least 90% crystalline.

69. The coated coronary stent of Claim 61, wherein said rapamycin is at least 95% crystalline.

70. The coated coronary stent of Claim 61, wherein said rapamycin is at least 99% crystalline.

71. The coated coronary stent of Claim 1, wherein said polymer is a mixture of two or more polymers.

72. The coated coronary stent of Claim 71, wherein said mixture of polymers forms a continuous film around particles of rapamycin.

73. The coated coronary stent of Claim 71, wherein said two or more polymers are intimately mixed.

74. The coated coronary stent of Claim 73, wherein said mixture comprises no single polymer domain larger than about 20 nm.

75. The coated coronary stent of Claim 71, wherein each polymer in said mixture comprises a discrete phase.

76. The coated coronary stent of Claim 75, wherein discrete phases formed by said polymers in said mixture are larger than about 10nm.

77. The coated coronary stent of Claim 75, wherein discrete phases formed by said polymers in said mixture are larger than about 50nm.

78. The coated coronary stent of Claim 61, wherein rapamycin in said stent has a shelf stability of at least 3 months.

79. The coated coronary stent of Claim 61, wherein rapamycin in said stent has a shelf stability of at least 6 months.

80. The coated coronary stent of Claim 61, wherein rapamycin in said stent has a shelf stability of at least 12 months.

81. The coated cornoray stent of Claim 61 wherein said coating is substantially conformal.

82. The coated coronary stent of Claim 61, wherein said stent provides an elution profile wherein about 10% to about 50% of rapamycin is eluted at week 1 after the composite is implanted in a subject under physiological conditions, about 25% to about 75% of rapamycin is eluted at week 2 and about 50% to about 100% of rapamycin is eluted at week 6.

83. The coated coronary stent of Claim 61, wherein said stent provides an elution profile wherein about 10% to about 50% of rapamycin is eluted at week 1 after the composite is implanted in a subject under physiological conditions, about 20% to about 75% of rapamycin is eluted at week 2 and about 50% to about 100% of rapamycin is eluted at week 10.

84. The coated stent of Claim 61, wherein the stent framework is a stainless steel framework.

85. A coated coronary stent, comprising:

a stent framework; and

a rapamycin-polymer coating wherein at least part of rapamycin is in crystalline form and wherein the polymer is bioabsorbable.

86. A coated coronary stent, comprising:

a stent framework; and

a macrolide immunosuppressive (limus) drug-polymer coating wherein at least part of the drug is in crystalline form and the polymer is bioabsorbable.

87. The coated stent of Claim 85, wherein the macrolide immunosuppressive drug comprises one or more of rapamycin, 40-O-(2-Hydroxyethyl)rapamycin (everolimus), 40-O-Benzyl-rapamycin, 40-O-(4'-Hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin, 40-O-Allyl-rapamycin, 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2':E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin 40-O-(2-Hydroxy)ethoxycar-bonylmethyl-rapamycin, 40-O-(3-Hydroxy)propyl-rapamycin 4O-O-(6-Hydroxy)hexyl-rapamycin 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin 4O-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin, 4O-O-(2-Acetoxy)ethyl-rapamycin 4O-O-(2-Nicotinoyloxy)ethyl-rapamycin, 4O-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin 4O-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 28-O-Methyl-rapamycin, 4O-O-(2-Aminoethyl)-rapamycin, 4O-O-(2-Acetaminoethyl)-rapamycin 4O-O-(2-Nicotinamidoethyl)-rapamycin, 4O-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 4O-O-(2-Ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-Tolylsulfonamidoethyl)-rapamycin, 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin, 42-Epi-(tetrazolyl)rapamycin (tacrolimus), and 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus).

88. The coated coronary stent of Claim 85, wherein said macrolide immunosuppressive drug is at least 50% crystalline.

89. A method for preparing a coated coronary stent comprising the following steps:

providing a stainless or cobalt –chromium stent framework;

forming a macrolide immunosuppressive (limus) drug-polymer coating on the stent framework wherein at least part of the drug is in crystalline form and the polymer is bioabsorbable.

90. The method of Claim 89 wherein the macrolide is deposited in dry powder form.

91. The method of Claim 89 wherein the bioabsorbable polymer is deposited in dry powder form.

92. The method of Claim 89 wherein the polymer is deposited by an e-SEDS process.

93. The method of Claim 89 wherein the polymer is deposited by an e-RESS process.

94. The method of Claim 89 further comprising sintering said coating under conditions that do not substantially modify the morphology of said macrolide.

95. The method of Claim 89, wherein the macrolide immunosuppressive drug comprises one or more of rapamycin, 40-O-(2-Hydroxyethyl)rapamycin (everolimus), 40-O-Benzyl-rapamycin, 40-O-(4'-Hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin, 40-O-Allyl-rapamycin, 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2':E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin 40-O-(2-Hydroxy)ethoxycar-bonylmethyl-rapamycin, 40-O-(3-Hydroxy)propyl-rapamycin 4O-O-(6-Hydroxy)hexyl-rapamycin 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin 4O-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin, 4O-O-(2-Acetoxy)ethyl-rapamycin 4O-O-(2-Nicotinoyloxy)ethyl-rapamycin, 4O-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin 4O-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 28-O-Methyl-rapamycin, 4O-O-(2-Aminoethyl)-rapamycin, 4O-O-(2-Acetaminoethyl)-rapamycin 4O-O-(2-Nicotinamidoethyl)-rapamycin, 4O-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 4O-O-(2-Ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-Tolylsulfonamidoethyl)-rapamycin, 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin, 42-Epi-(tetrazolyl)rapamycin (tacrolimus), and 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus).

96. The method of Claim 89 wherein one or more resorbable polymers are selected from PLGA (poly(lactide-co-glycolide); DLPLA — poly(dl-lactide); LPLA — poly(l-lactide); PGA — polyglycolide; PDO — poly(dioxanone); PGA-TMC — poly(glycolide-co-trimethylene carbonate); PGA-LPLA — poly(l-lactide-co-glycolide); PGA-DLPLA — poly(dl-lactide-co-glycolide); LPLA-DLPLA — poly(l-lactide-co-dl-lactide); PDO-PGA-TMC — poly(glycolide-co-trimethylene carbonate-co-dioxanone).

97. A coated coronary stent, comprising:

a stent framework;

a first layer of bioabsorbable polymer; and

a rapamycin-polymer coating comprising rapamycin and a second bioabsorbable polymer wherein at least part of rapamycin is in crystalline form and wherein

the first polymer is a slow absorbing polymer and the second polymer is a fast absorbing polymer.

98. The stent of Claim 97 wherein the fast absorbing polymer is PLGA copolymer with a ratio of about 40:60 to about 60:40 and the slow absorbing polymer is a PLGA copolymer with a ration of about 70:30 to about 90:10.

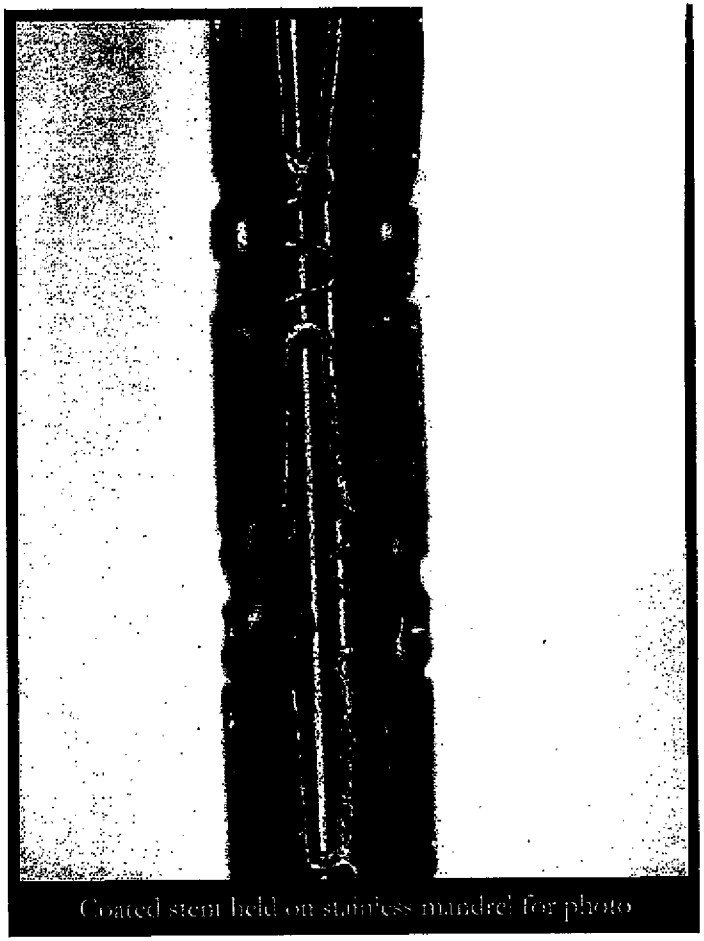
Technology

Utilizing supercritical fluids (E-RESS)

- Solvent-free
- Low temperature
- Multiple drugs
- "Dry": no bleeding of layers
- Excellent adhesion of layers and mechanical properties
- Excellent *precision of layers* and enables rapid batch processing

Capable of making novel devices

- Enables laminate structure
- Forming intricate, novel devices
- Unique laminate structure provides structural control without introducing new materials or new delivery system
- Demonstrated for drug-eluting coatings and coated membranes



Coated stent held on stainless mandrel for photo

Process Technology

Step One

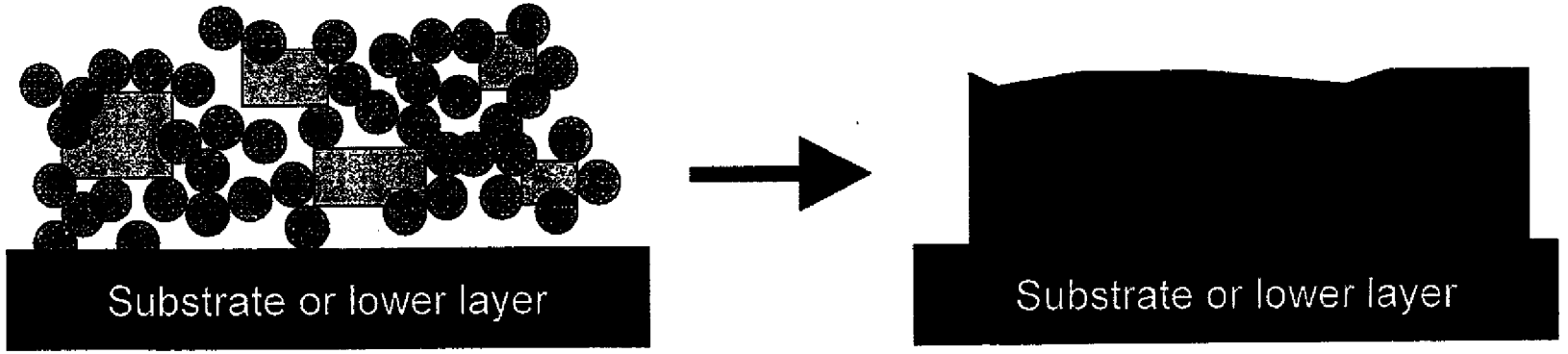
CritiCoat™: Electrostatic Coating

Nano and microparticles of polymer(s) and drug(s) are electrostatically captured, dry, upon a stent form

Step Two

CritiFlo™: Sintering

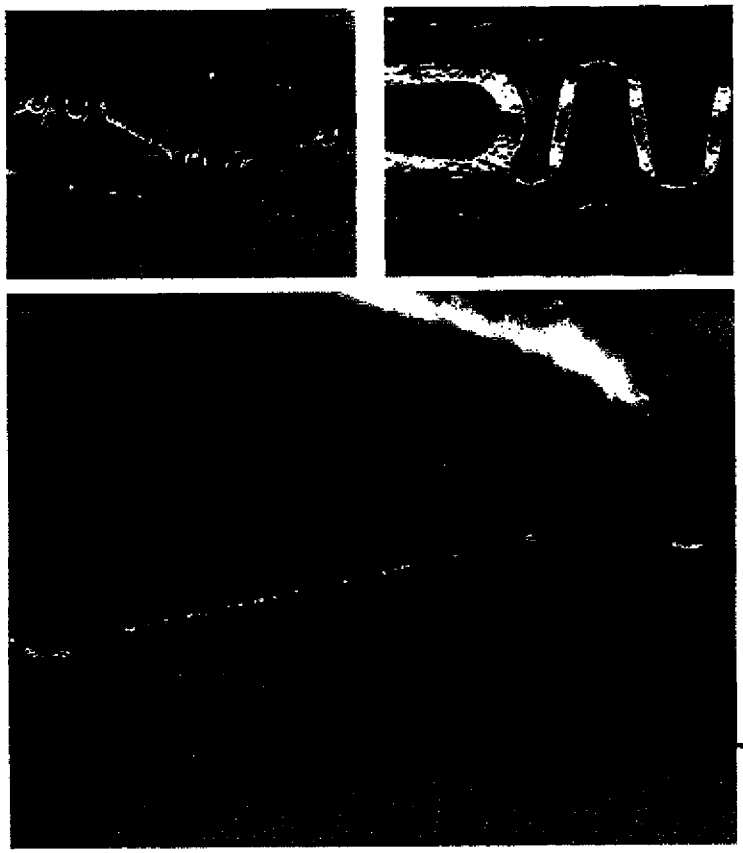
Polymer nanoparticles fused via SCF: No solvents or high temperatures



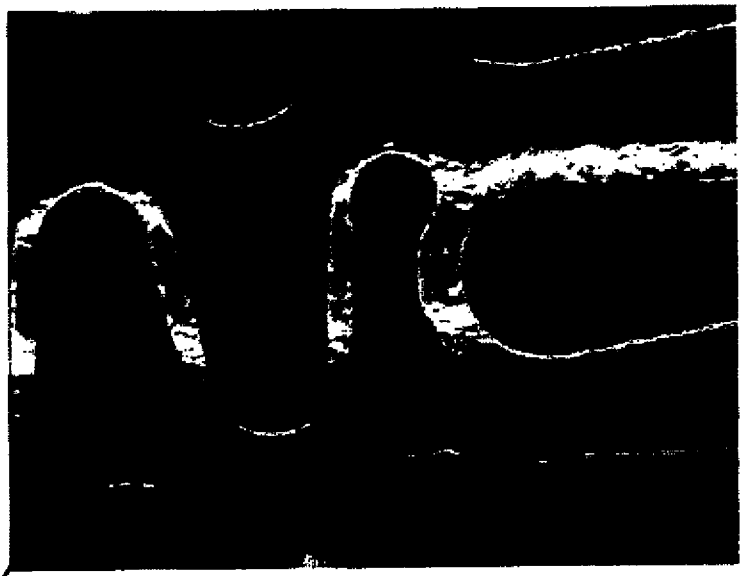
The final material provides a smooth, adherently laminated layer with precise control over location of drug(s)

Mechanically Effective

Coating With and Without Parylene Base-coat



Without paralyene base-coat



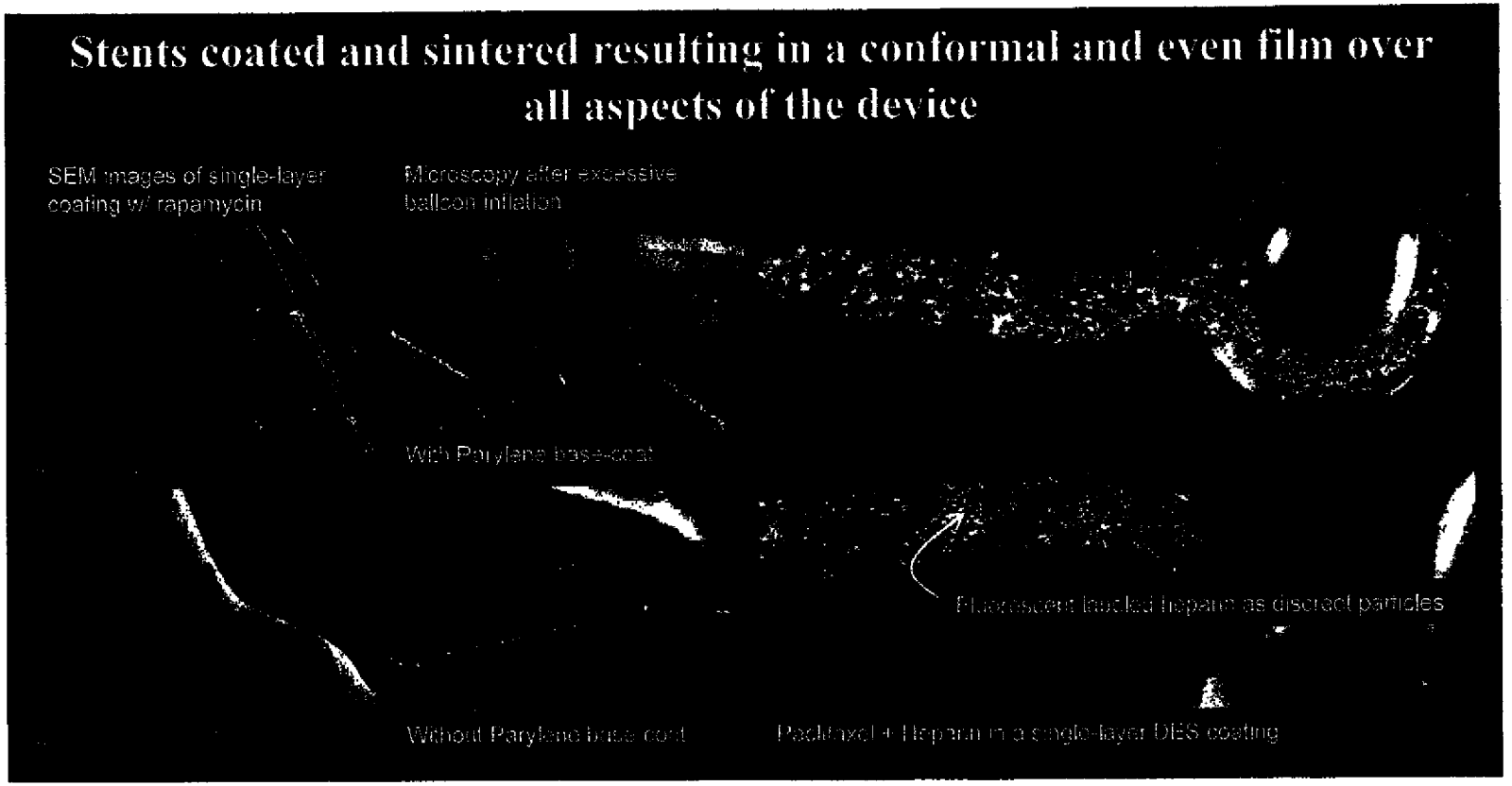
With paralyene base-coat

Balloon expanded coated stents

Attributes

In a Single Layer For:

- ✓ Smooth, conformal and mechanically adherent coating on different stent substrates
- ✓ Wide range of drugs (rapamycin, paclitaxel, heparin, small molecules, etc.)
- ✓ Multiple and dissimilar drugs (paclitaxel + heparin) in the same coating

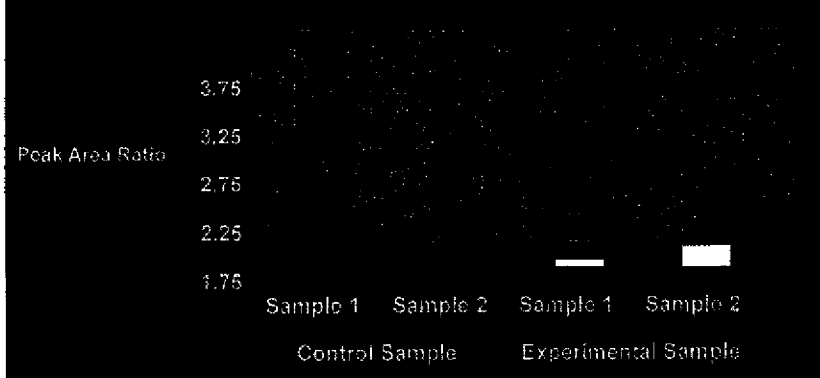


Attributes

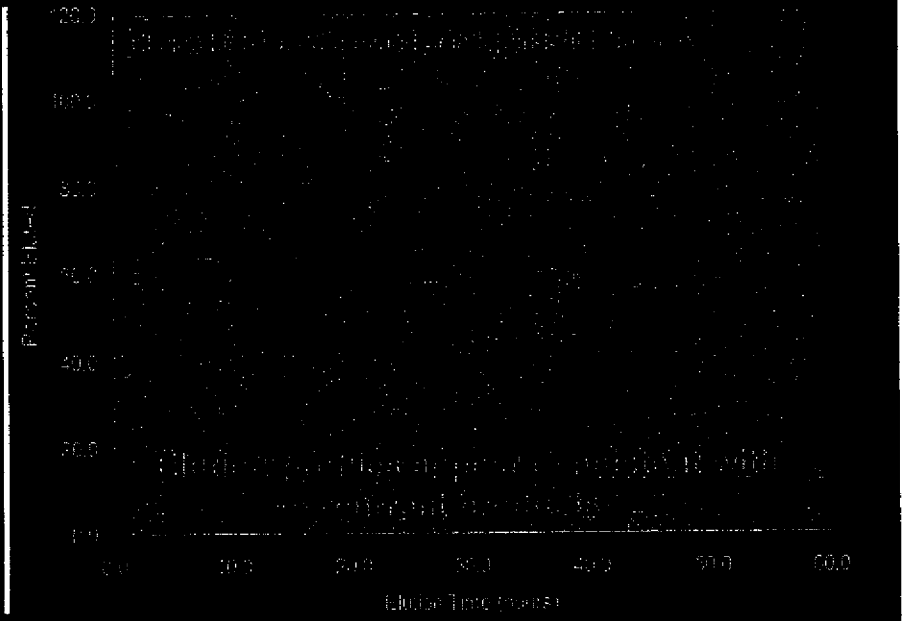
In a Single Layer For:

- ✓ Control over drug morphology: crystalline or amorphous
- ✓ Maintain drug stability
- ✓ No effect on elution vs. commercial analogs

Rapamycin DES coating with drug maintained in crystalline morphology

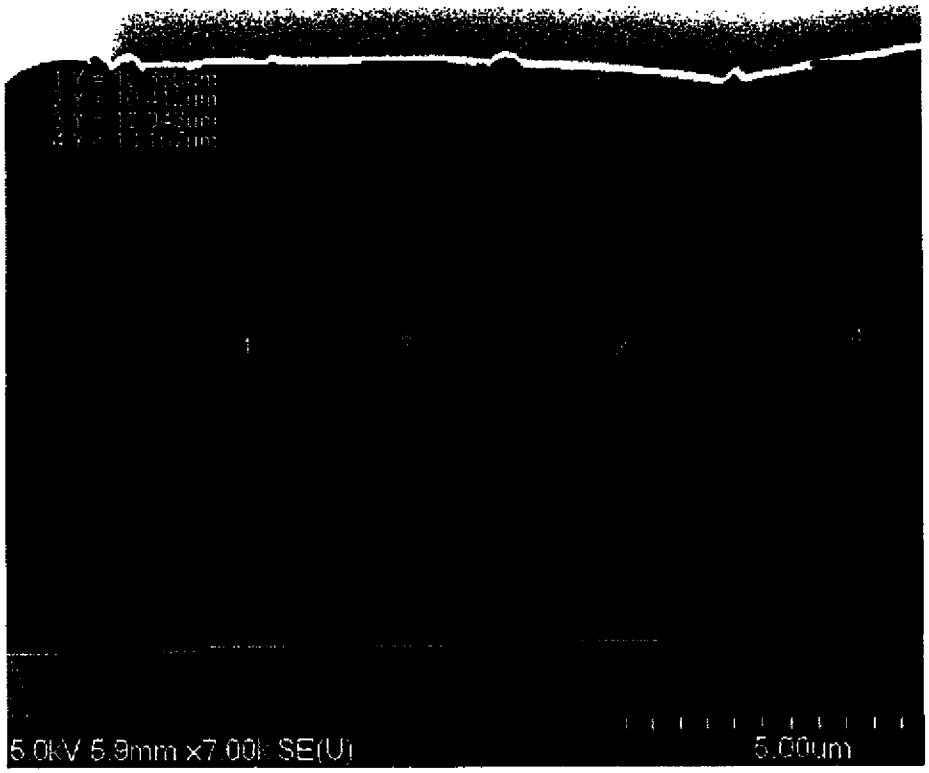


Peak area ratio between the control samples (left two bars) and the Micell processed materials (right two bars) indicate no difference in the rate of rapamycin degradation.



Attributes

Thin, conformal, defect-free coatings at target thickness



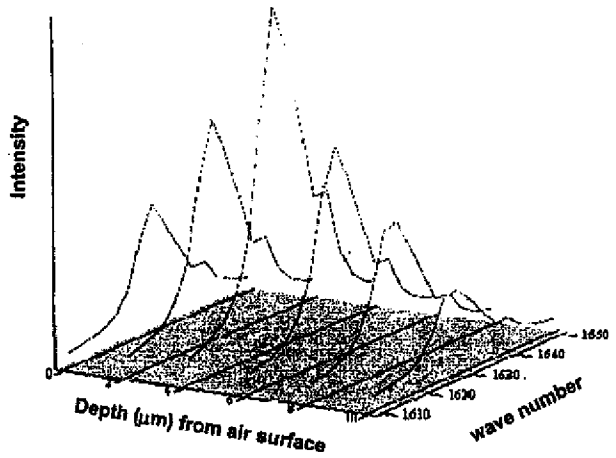
Mean Coating Thickness:
10.2 ± 0.2 µm

Attributes

Controlled Drug Placement

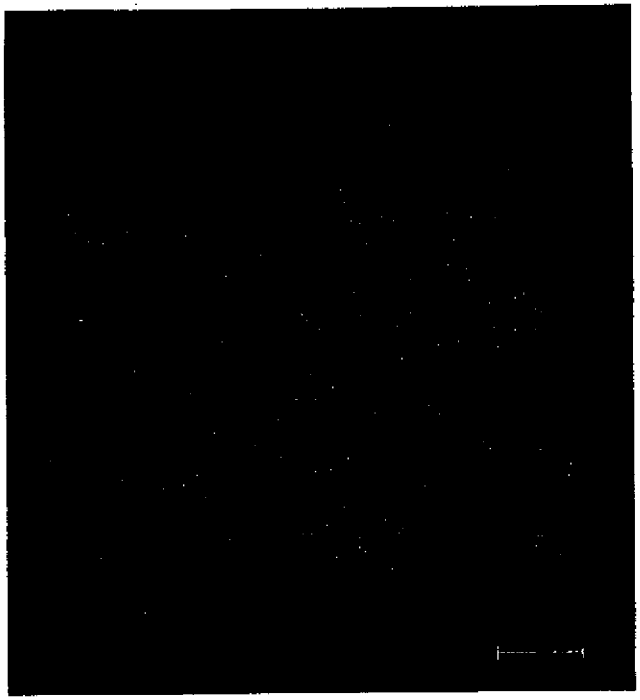
Drug loaded purposefully in the center of the 10µm DES coating

Drug peak ~1620



Confocal Raman spectra

Drug loaded equally throughout the 10µm DES coating and evident in the surface



SIMS of DES coating surface

Drug-Polymer coated coronary stent

(a) immediately after deposition,

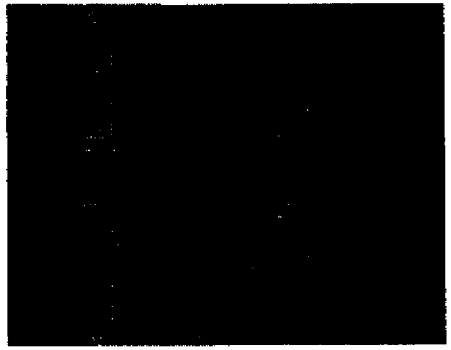
(b) after annealing in a dense carbon dioxide environment at 40°C

Optical Microscopy of Rapamycin/PEVA/PBMA Coated Stents

(a) Powder coated before sintering

Outside Surface

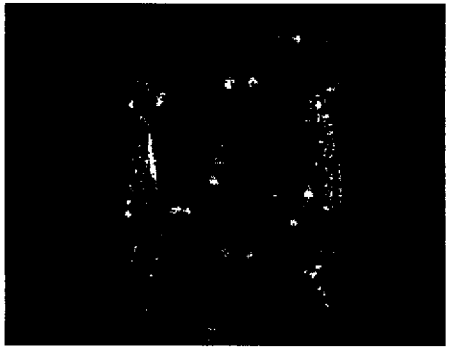
Edge Surface



Inside Surface

(b) Powder coated after sintering

Outside Surface

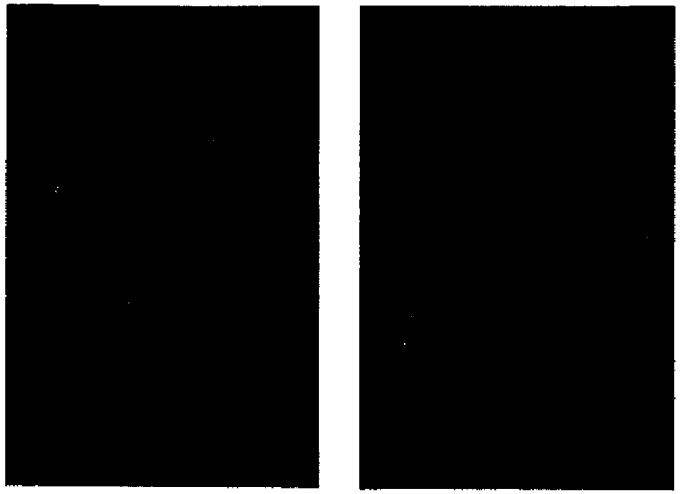


Edge Surface

Inside Surface

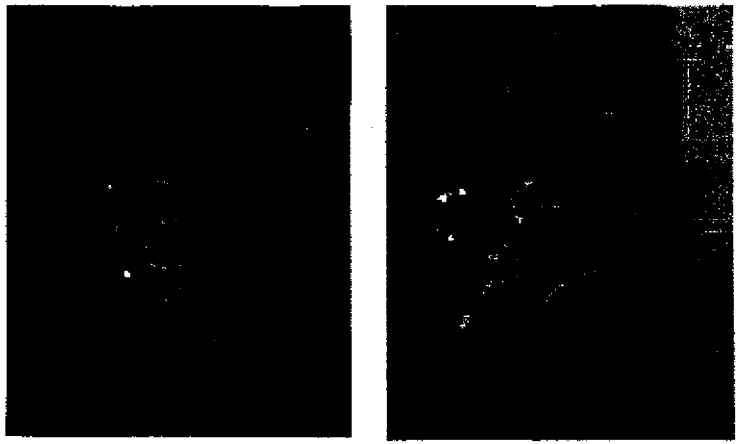
Optical Microscopy of Rapamycin/PEVA/PBMA Coated Stents

(a) Powder coated before sintering



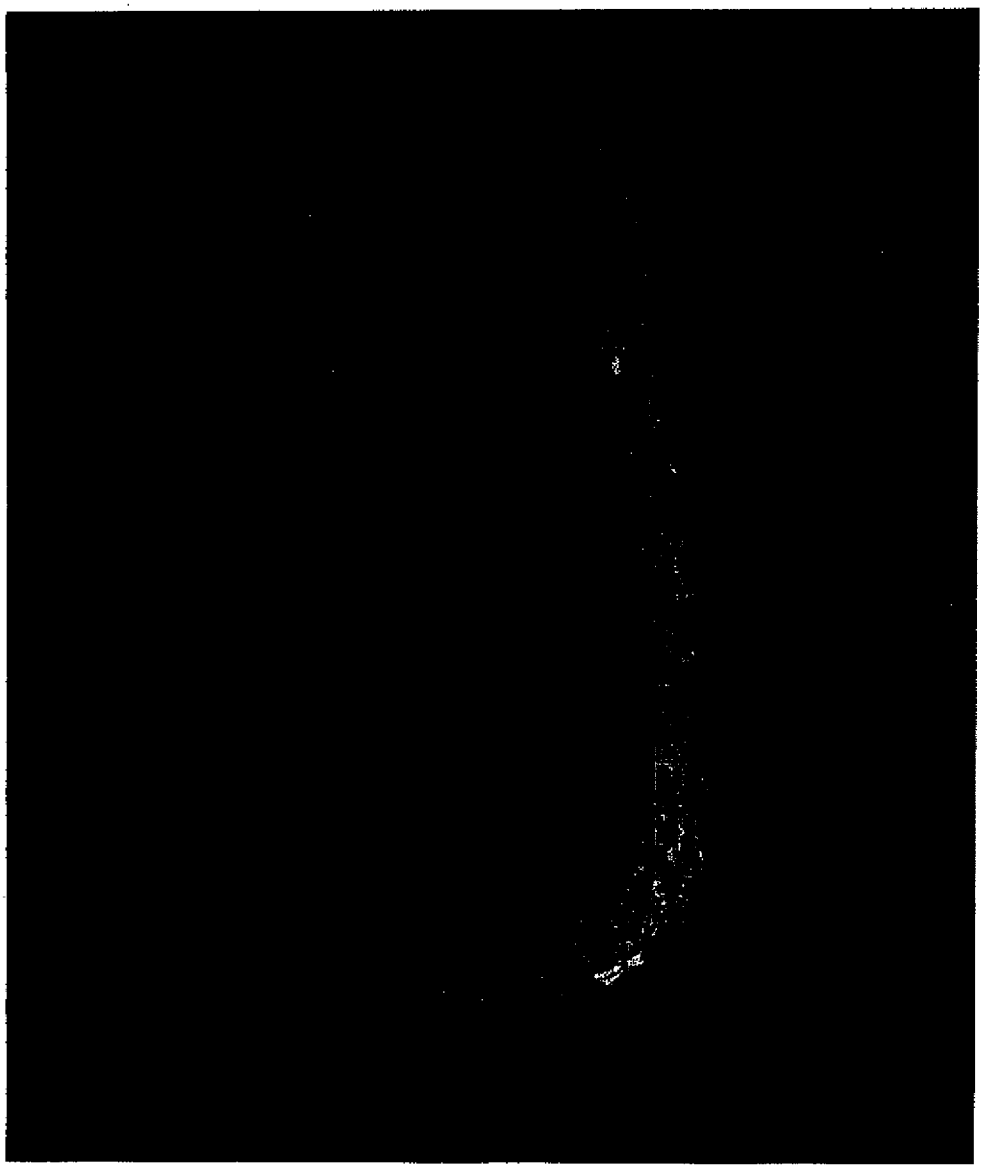
Outside Surface Inside Surface

(b) Powder coated after sintering



Outside Surface Inside Surface

Optical Microscopy of Rapamycin/PEVA/PBMA Coated Stents After Sintering at 100X magnification

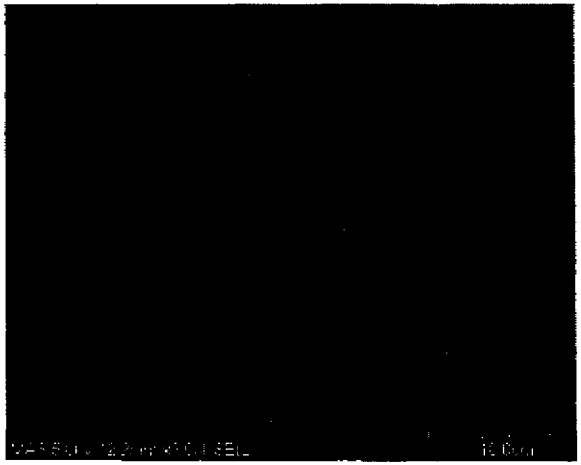


Scanning Electron Microscope Images of Rapamycin/PEVA/PBMA Coated Stents

(a) x30 magnification

(b) x250 magnification

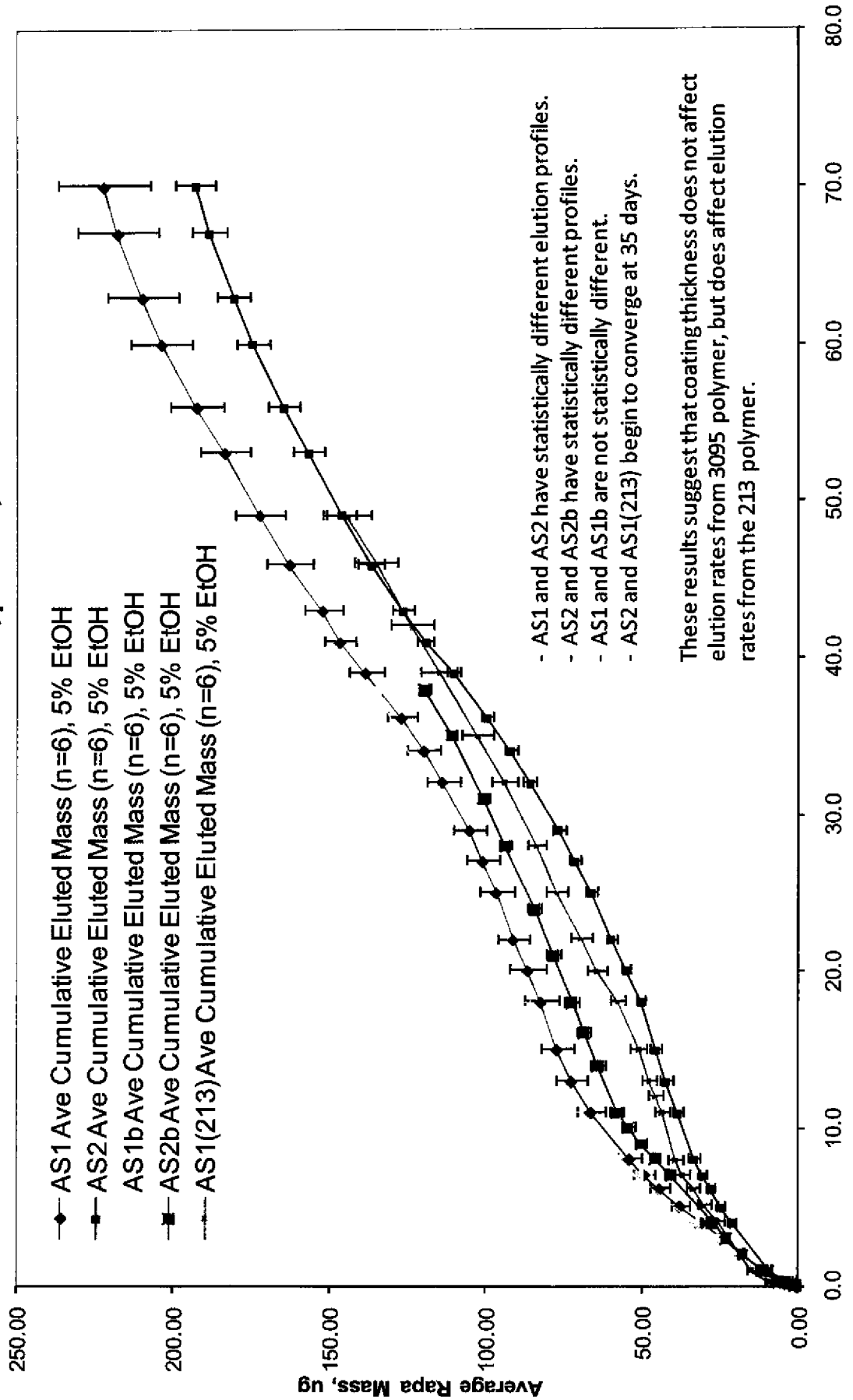
(c) x1000 magnification

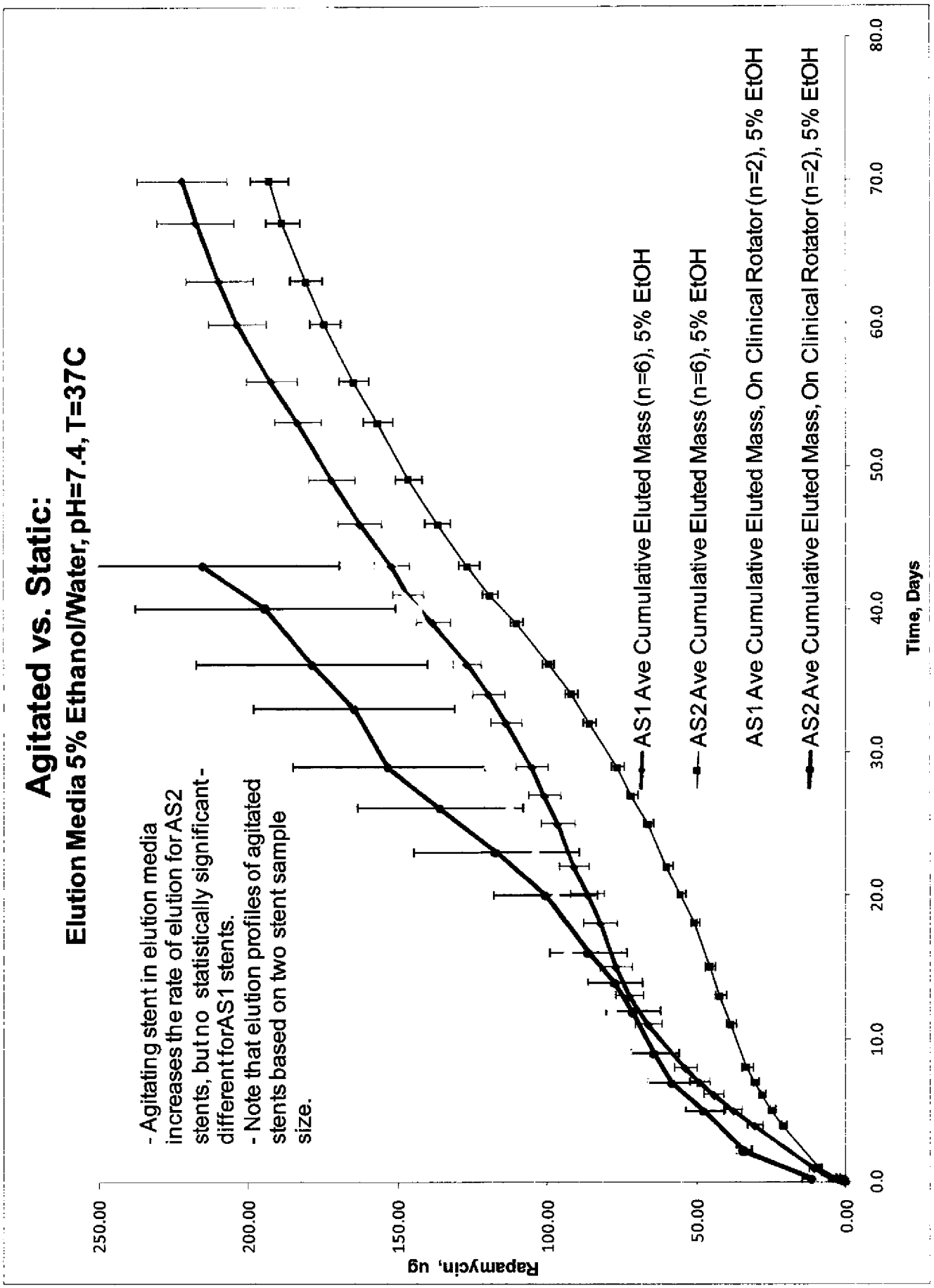


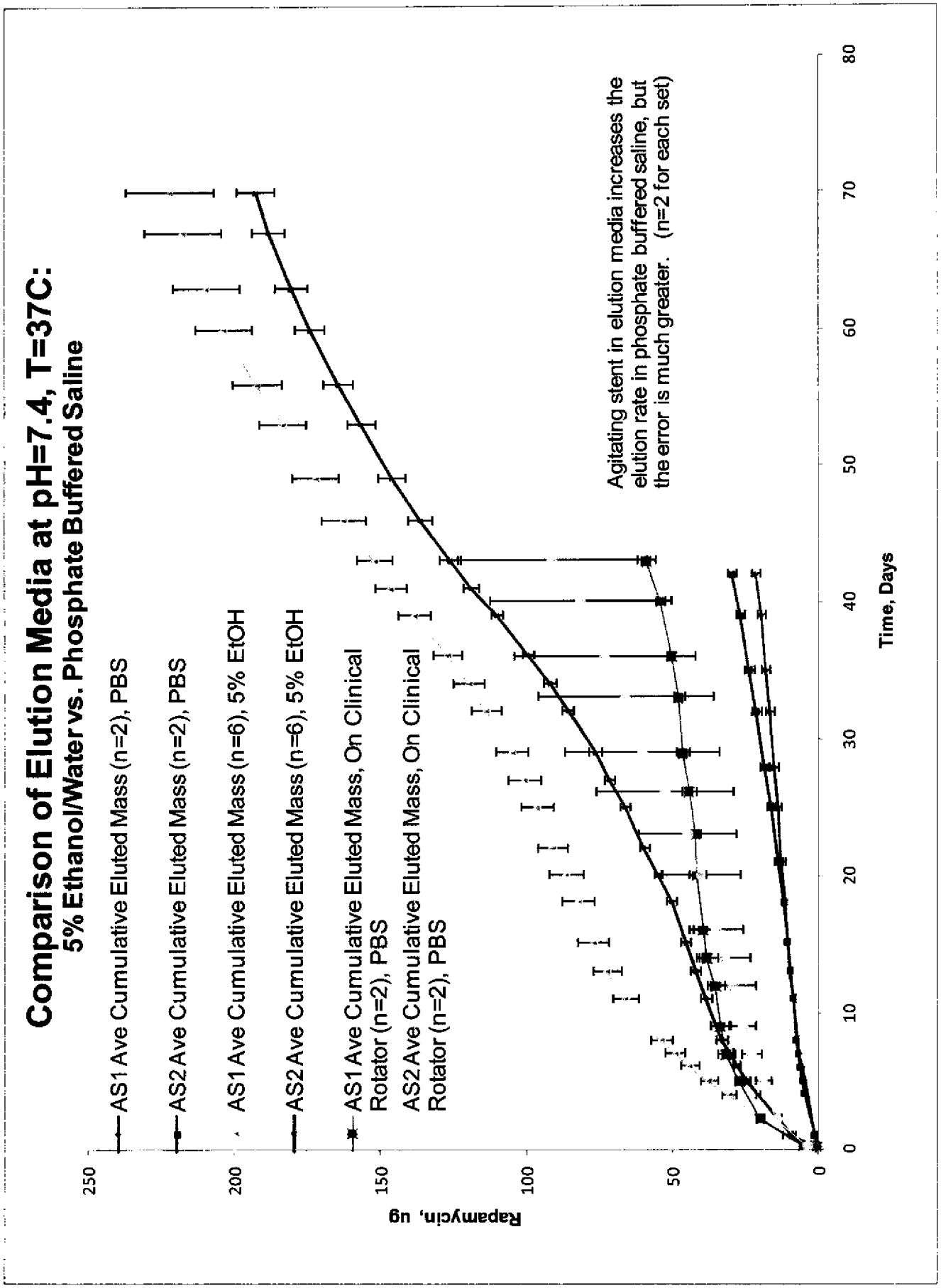
(d) x3000 magnification

Average Coating Masses

Stent Coating	Ave. Rapamycin, ug	Ave. Polymer, ug	Ave. Total Mass, ug
AS1	175		
AS2	153	717	870
AS1(B)	224	737	961
AS1b	171	322	493
AS2b	167	380	547


Comparison of Stent Polymer Coatings
Elution Media 5% Ethanol/Water, pH=7.4, T=37C Static
AS1 Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS2 Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS1b Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS2b Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS1(213) Ave Cumulative Eluted Mass (n=6), 5% EtOH
- AS1 and AS2 have statistically different elution profiles.
- AS2 and AS2b have statistically different profiles.
- AS1 and AS1b are not statistically different.
- AS2 and AS1(213) begin to converge at 35 days.
These results suggest that coating thickness does not affect elution rates from 3095 polymer, but does affect elution rates from the 213 polymer.
Average Rapa Mass, ug
Time, days
0.00
50.00
100.00
150.00
200.00
250.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0


Agitated vs. Static:
Elution Media 5% Ethanol/Water, pH=7.4, T=37C
- Agitating stent in elution media increases the rate of elution for AS2 stents, but no statistically significant-different for AS1 stents.
- Note that elution profiles of agitated stents based on two stent sample size.
Rapamycin, ug
Time, Days
AS1 Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS2 Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS1 Ave Cumulative Eluted Mass, On Clinical Rotator (n=2), 5% EtOH
AS2 Ave Cumulative Eluted Mass, On Clinical Rotator (n=2), 5% EtOH
250.00
200.00
150.00
100.00
50.00
0.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0


Comparison of Elution Media at pH=7.4, T=37C:
5% Ethanol/Water vs. Phosphate Buffered Saline
AS1 Ave Cumulative Eluted Mass (n=2), PBS
AS2 Ave Cumulative Eluted Mass (n=2), PBS
AS1 Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS2 Ave Cumulative Eluted Mass (n=6), 5% EtOH
AS1 Ave Cumulative Eluted Mass, On Clinical Rotator (n=2), PBS
AS2 Ave Cumulative Eluted Mass, On Clinical Rotator (n=2), PBS
Agitating stent in elution media increases the elution rate in phosphate buffered saline, but the error is much greater. (n=2 for each set)
Rapamycin, ug
Time, Days
0
50
100
150
200
250
0
10
20
30
40
50
60
70
80

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/60671

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61L 33/00; A61F 2/00 (2008.04)
USPC - 427/2.24; 424/423
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)
USPC - 427/2.24; 424/423

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 427/2.1,2.24,214,224,212,470; 428/323,407; 623/23.760,23.260,23.160,1.46; 525/149,419; 118/621; 424/423 (text search - see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,OC,EPAB,JPAB); DialogPro (General Research); Google Scholar
Coronary, vascular, stent, implant, coat, layer, film, drug, polymer, bioabsorb, resorb, crystalline, steel, cobalt, chromium, thick, PLGA, kD, alternate, limus, rapamycin, RESS, SEDS, dry, powder, sinter, 50/50, mix, discrete, phase, life, elutio

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0009564 A1 (MCCLAIN et al.) 11 January 2007 (11.01.2007), abstract, para [0001]-[0003], [0008], [0017]-[0029], [0033], [0039]-[0042] and [0049].	1-4, 10, 15-17, 20-24, 61, 63, 65-77, 81, 84-89, 95 and 96
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Y		5-9, 11-14, 18, 19, 25-32, 62, 64, 78-80, 82, 83, 90-94, 97 and 98
Y	US 2006/0222756 A1 (DAVILA et al.) 05 October 2006 (05.10.2006), abstract, Fig. 25, para [0015]-[0019], [0022], [0023], [0028], [0035]-[0038], [0066]-[0070], [0085], [0086], [0100]-[0103] and [0109].	5, 11, 13, 14 and 25
Y	US 7,163,715 B1 (KRAMER) 16 January 2007 (16.01.2007), abstract, col 1,ln 14-65, , col 2,ln 13-27, col 3,ln 4-18, col 5, ln 26-38, col 6, ln 38-56, col 10, ln 44 - col 11, ln 5, col 15, ln 31-49, col 15, ln 66 - col 16, ln 13 and col 16, ln 29-42.	6-9, 28 and 29
Y	US 2006/0198868 A1 (DEWITT et al.) 07 September 2006 (07.09.2006), abstract, para [0002], [0012]-[0019], [0028], [0053]-[0058], [0193], [0195], [0197], [0202]-[0204], [0206], [0209]-[0215], [0229], [0230], [0263], [0276], [0279], [0284] and [0285].	12 , 78-80, 82, 83, 97 and 98
Y	US 2005/0191491 A1 (WANG et al.) 01 September 2005 (01.09.2005), abstract, para [0003]-[0005], [0013]-[0015], [0018], [0025]-[0028], [0094], [0118], [0119], [0143] and [0190].	18, 19, 30-32, 62, 64, 90-94 and 98
Y	US 2003/0180376 A1 (DALAL et al.) 25 September 2003 (25.09.2003), para [0166], [0167] and claim 24.	26 and 27

☒ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2008 (27.08.2008)	SEPTEMBER 5, 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/60671

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/0288481 A1 (DESNOYER et al.) 29 December 2005 (29.12.2005), abstract, para [0013]-[0015], [0035]-[0037] and [0043].	6, 7, 28 and 29
A	US 2005/0216075 A1 (WANG et al.) 29 September 2005 (29.09.2005), entire document.	11, 13, 14, 97 and 98
A	US 2005/0019747 A1 (ANDERSON et al.) 27 January 2005 (27.01.2005), entire document.	12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/60671

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 33-60
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.