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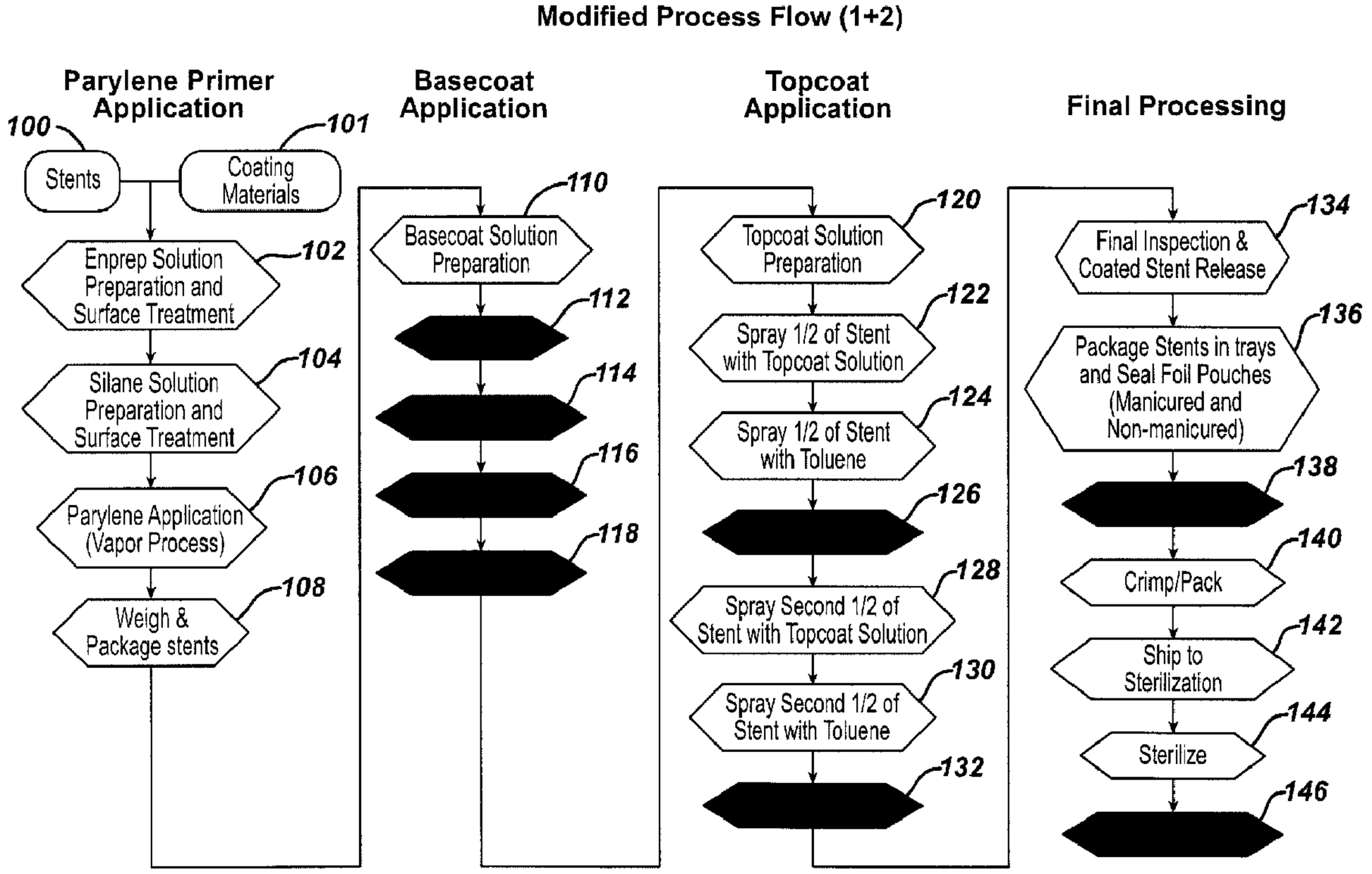
(54) **Titre : PROCEDE DE REVETEMENT DES ENDOPROTHESES POUR AMELIORER LA STABILITE DE_L'AGENT THERAPEUTIQUE CONTENU DANS CELLES-CI**

(54) **Title: METHOD OF COATING STENTS TO IMPROVE THE STABILITY OF THE THERAPEUTIC AGENT CONTAINED THEREIN**

Modified Process Flow (1+2)



(57) **Abrégé/Abstract:**
Processes for coating implantable medical devices that improve the stability of therapeutic agents contained within the coating. In one embodiment, the process comprises: applying a primer coating on the implantable medical device; preparing a basecoat

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solution comprising polymers and a therapeutic agent and applying the basecoat solution to the implantable medical devices; preparing a topcoat solution comprising at least one polymer and applying the topcoat solution to the implantable medical devices coated with the basecoat solution; applying a solvent to partially redissolve the topcoat and basecoat while altering the surface finish and dissolution properties of the therapeutic agent; and final processing the implantable medical devices, including inspecting, packaging and sterilizing the coated medical devices.

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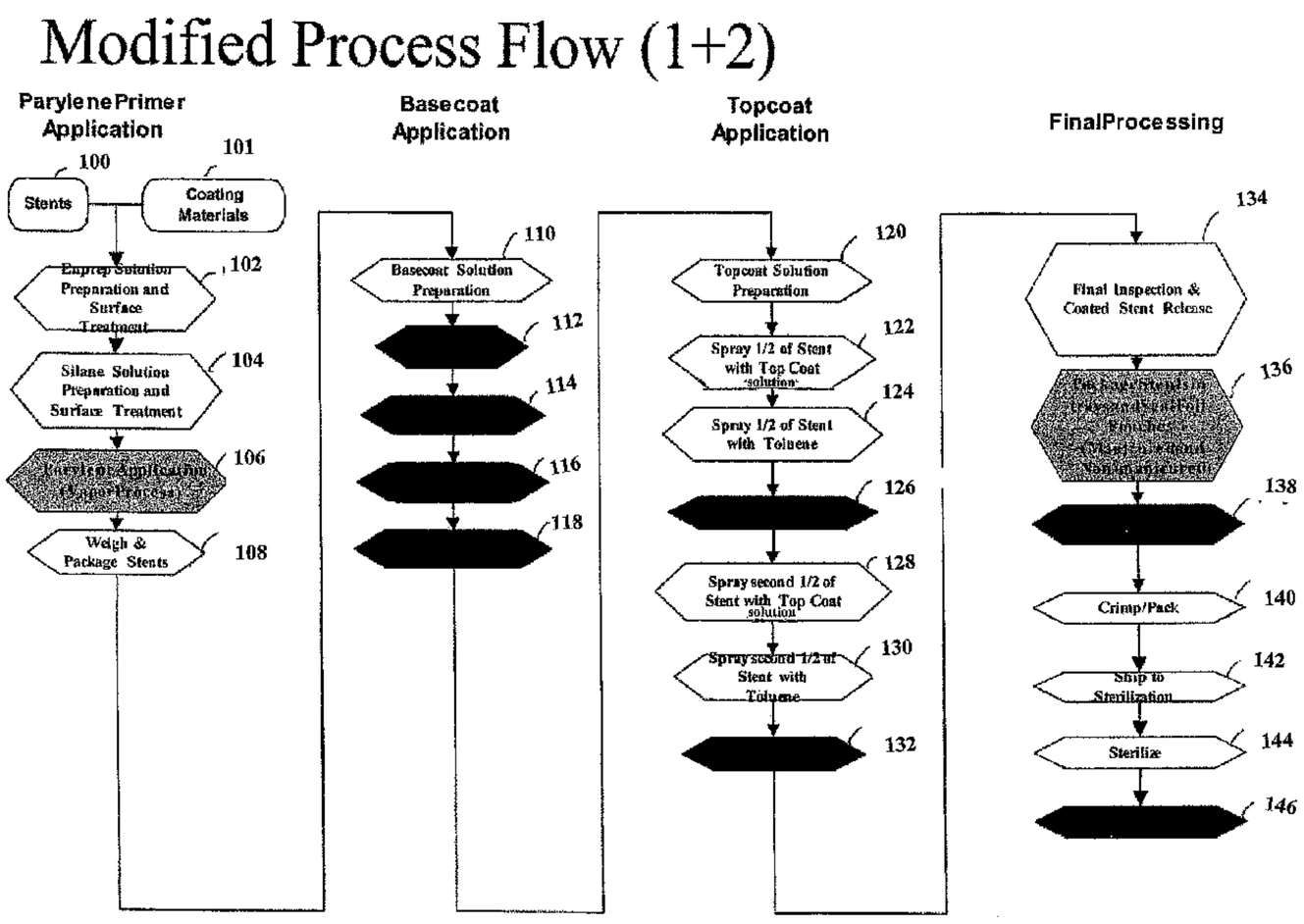
(54) Title: METHOD OF COATING MEDICAL DEVICES



(57) Abstract: Processes for coating implantable medical devices that improve the stability of therapeutic agents contained within the coating. In one embodiment, the process comprises: applying a primer coating on the implantable medical device; preparing a basecoat solution comprising polymers and a therapeutic agent and applying the basecoat solution to the implantable medical devices; preparing a topcoat solution comprising at least one polymer and applying the topcoat solution to the implantable medical devices coated with the basecoat solution; applying a solvent to partially redissolve the topcoat and basecoat while altering the surface finish and dissolution properties of the therapeutic agent; and final processing the implantable medical devices, including inspecting, packaging and sterilizing the coated medical devices.

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METHOD OF COATING STENTS TO IMPROVE THE STABILITY OF THE THERAPEUTIC AGENT CONTAINED THEREIN

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to methods for coating stents, and more particularly to methods for coating stents with therapeutic agents.

2. Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that profuse the heart and other major organs. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is 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 percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel, which may occur immediately after the procedure and restenosis, which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the smooth muscle cells and is rich in heparin-like glycosylaminoglycans, which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985, Phenotypic Modulation of Smooth Cells in Primary Culture", (Table of Contents), Chapter 2, Volume 1, pp. 39-52).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, basic fibroblast growth factor, epidermal growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke a proliferative and migratory response in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days' post-injury and peaks several days thereafter (Campbell and Campbell, Cell Biology of Smooth Muscle in Culture: Implications for

Atherogenesis", Inter. Angio, 6 pp. 73 (1987); CLOWES, A.W.et al., "Kinetics of Cellular Proliferation after Arterial Injury", Laboratory Investigation, Vol. 52, No. 6, pp. 611-616, 1985); SCHWARTZ, S.M. et al., Significance of Quiescent Smooth Muscle Migration in the Injured Rat Carotid Artery, Circ. Res., 56, 1985, pp. 139-145.

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells adhere to the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., Sustained Activation of Vascular Cells and Leukocytes in the Rabbit Aorta after Balloon Injury", Circulation Vol. 88 p. 1788 (1993); Edelman et al., "Pathobiologic Responses to Stenting", American Journal of Cardiology Vol. 91, Issue 7, Suppl. 1 (April 1998) pp. 4E-6E). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A.W. and Karnovsky M., Nature 265: 25-26, 1977; Guyton, J.R. et al., Circ. Res., 46: 625-634,

1980; Clowes, A.W. and Clowes, M.M., Lab. Invest. 52: 611-616, 1985; Clowes, A.W. and Clowes, M.M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ. Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J.W. et al., Circ. 80: 11-66, 1989), taxol (Sollot, S.J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J.S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C.F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G.A.A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G.M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M.W. et al., Circ. 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G.K. and Holm, J., Circ. 84: 1266-1272, 1991), rapamycin (Marx, S.O. et al., Circ. Res. 76: 412-417, 1995), steroids (Colburn, M.D. et al., J. Vasc. Surg. 15: 510-518, 1992), see also Berk, B.C. et al., J. Am. Coll. Cardiol. 17: 111B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligionucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M.W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative action on smooth muscle cells *in vitro* has been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligionucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been

effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, Clinical Trials to Prevent Restenosis after Percutaneous Coronary Revascularization, Annals New York Academy of Sciences, 1997, pp. 255-288; "Clinical Trials to Prevent Restenosis after Percutaneous Coronary Revascularization", Department of Cardiolog, Cleveland Clinical Foundation, Ohio p. 255 (1991); Lang et al., Effects of Okadaic Acid and ATPyS on Cell Length and Ca2+ Channel Currents Recorded in Single Smooth Muscle Cells of the Guinea-pig Taenia Caeci, Br. J. Pharmacol., 104, 1991, pp. 331-336; Popma et al., "Clinical Trials of Restenosis After Coronary Angioplasty", Journal of the American Heart Association (Circulation), 84:1426-1436 (1991). The platelet GP II_b/III_a receptor, antagonist, Reopro® is still under study but Reopro® has not shown definitive results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, Clinical Trials to Prevent Restenosis after Percutaneous Coronary Revascularization, Annals New York Academy of Sciences, 1997, pp. 255-288; Lang et al., Effects of Okadaic Acid and ATPyS on Cell Length and Ca2+ Channel Currents Recorded in Single Smooth Muscle Cells of the Guinea-pig Taenia Caeci, Br. J. Pharmacol., 104, 1991, pp. 331-336; Popma et al., Clinical Trials of Restenosis After Coronary Angioplasty", Journal of the American Heart Association (Circulation), 84:1426-1436 (1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering

agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, Clinical Trials to Prevent Restenosis after Percutaneous Coronary Revascularization, Annals New York Academy of Sciences, 1997, pp. 255-288; Franklin and Faxon, "Pharmacologic Prevention of Restenosis After Coronary Angioplasty: Review of the Randomized Clinical Trials", Coronary Artery Disease, Vol. 4, No. 3 (March 1993) Serruys, P.W. et al., Evaluation of Ketanserin in the Prevention of Restenosis after Percutaneous Transluminal Coronary Angioplasty. A Multicenter Randomized Double-blind Placebo-controlled Trial, Circulation, 88, 1993, pp. 1588-1601); SERRUYS, P.W. et al., Heparin-Coated Palmaz-Schatz Stents in Human Coronary Arteries: Early Outcome of the Benestent-II Pilot Study, Circulation, Vol. 93(3), 1996, pp. 412-422. Recent observations suggest that the antilipid/antioxident agent, probucol, may be useful in preventing restenosis but this work requires confirmation (Tardif et al., "Probucol and Multivitamins in the Prevention of Restenosis After Coronary Angioplasty", New England Journal of Medicine, Volume 337:365-372 (1997); Yokoi, et al., "Effectiveness of an Antioxidant in Preventing Restenosis After Percutaneous Transluminal Coronary Angioplasty: The Probucol Angioplasty Restenosis Trial", JACC, Vol. 30, No. 4 p. 855 (1997). Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., "Catheter-Based Radiotherapy to Inhibit Restenosis after Coronary Stenting", New England Journal of Medicine, Vol. 336, p. 1679 (1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven useful in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., "A Comparison of Balloon-Expandable-Stent Implantation with Balloon Angioplasty in Patients with Coronary Artery Disease", New England Journal of Medicine, Volume 331:489-495 (1994); Fischman et al., A Randomized Comparison of Coronary-Stent Placement and Balloon Angioplasty in the Treatment of Coronary Artery Disease", The New England Journal of Medicine, Volume 331:496-501 (1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., Heparin-Coated Palmaz-Schatz Stents in Human Coronary Arteries: Early Outcome of the Benestent-II Pilot Study, Circulation, Vol. 93(3), 1996, pp. 412-422). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

As stated above, the use of heparin coated stents demonstrates the feasibility and clinical usefulness of local drug delivery; however, the manner in which the particular drug or drug combination is affixed to the local delivery device will play a role in the efficacy of this type of treatment. For example, the processes and materials utilized to affix the drug/drug combinations to the local delivery device should not interfere with the

operations of the drug/drug combinations. In addition, the processes and materials utilized should be biocompatible and maintain the drug/drug combinations on the local device through delivery and over a given period of time. For example, removal of the drug/drug combination during delivery of the local delivery device may potentially cause failure of the device.

Accordingly, there exists a need for drug/drug combinations and associated local delivery devices for the prevention and treatment of vascular injury causing intimal thickening which is either biologically induced, for example, atherosclerosis, or mechanically induced, for example, through percutaneous transluminal coronary angioplasty. In addition, there exists a need for maintaining the drug/drug combinations on the local delivery device through delivery and positioning as well as ensuring that the drug/drug combination is released in therapeutic dosages over a given period of time.

A variety of stent coatings and compositions have been proposed for the prevention and treatment of injury causing intimal thickening. The coatings may be capable themselves of reducing the stimulus the stent provides to the injured lumen wall, thus reducing the tendency towards thrombosis or restenosis. Alternately, the coating may deliver a pharmaceutical/therapeutic agent or drug to the lumen that reduces smooth muscle tissue proliferation or restenosis. The mechanism for delivery of the agent is through diffusion of the agent through either a bulk polymer or through pores that are created in the polymer structure, or by erosion of a biodegradable coating.

Both bioabsorbable and biostable compositions have been reported as coatings for stents. They generally have been polymeric coatings that either encapsulate a pharmaceutical/therapeutic agent or drug, e.g. rapamycin, taxol etc., or bind such an agent to the surface, e.g. heparin-coated stents. These coatings are applied to the stent in a number of

ways, including, though not limited to, dip, spray, or spin coating processes.

While the selection of an appropriate therapeutic agent and an appropriate coating in which to incorporate the therapeutic agent is important, maintaining the stability of the agent is also important. Accordingly, there

exists a need for developing a process for coating the implantable medical device that incorporates steps to stabilize the therapeutic agent.

SUMMARY OF THE INVENTION

The process of the present invention provides a means for overcoming the difficulties associated with the coating of implantable medical devices with therapeutic agents.

In accordance with one aspect, the present invention is directed to a process for coating implantable medical devices. The method comprises applying a primer coating on the implantable medical devices, including the application of a parylene layer and annealing the parylene layer to reduce autoxidation initiators, preparing a basecoat solution comprising polymers and a therapeutic agent and applying the basecoat solution to the implantable medical devices coated with parylene, the basecoat solution being prepared with and applied utilizing a process to reduce the presence and exposure of the basecoat solution to oxygen, raising the glass transition temperature of the therapeutic agent and creating a coating morphology to protect the therapeutic agent from autoxidation, preparing a topcoat solution comprising at least one polymer and applying the topcoat solution to the implantable medical devices coated with the basecoat solution, the topcoat solution being prepared with and applied utilizing a process to reduce the presence and exposure of the topcoat solution to oxygen, raising the glass transition temperature of the therapeutic agent

and creating a coating morphology to protect the therapeutic agent from autoxidation and finally processing the implantable medical devices, including inspecting, packaging and sterilizing the coated medical devices, the final processing including protecting the therapeutic agent from autoxidation, reducing the presence of and exposure of all materials to free radicals and reducing the presence of and exposure of all materials to oxygen.

The process of the present invention incorporates a number of steps to increase the stability of the therapeutic agent, including protecting the therapeutic agent from autoxidation by increasing the glass transition temperature of the agent, reducing the presence of and/or exposure of various materials utilized to free radicals and autoxidation initiators and reducing the presence of and/or exposure of the various materials to oxygen.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

Figure 1 is a flow chart of a first exemplary embodiment of a process for coating stents in accordance with the present invention.

Figure 2 is a flow chart of a second exemplary embodiment of a process for coating stents in accordance with the present invention.

Figure 3 is a flow chart of a third exemplary embodiment of a process for coating stents in accordance with the present invention.

Figure 4 is a flow chart of a fourth exemplary embodiment of a process for coating stents in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is directed to a process for coating stents or other implantable medical devices with one or more therapeutic agents, such as a rapamycin. One exemplary process is set forth in the flow chart of Figure 1. The first part of the process comprises the primer application. In the exemplary embodiment, the first step in the process is surface preparation and treatment, step 102. This step involves utilizing a cleaning solution to remove endotoxins from the stents to be coated. The cleaning solution may comprise any number of cleaning solutions, for example, a high pH solution such as a potassium hydroxide solution containing silicates. The next step is also a surface preparation and treatment step, step 104. In this step a silane solution is utilized to prepare the surfaces of the stents for the deposition of a primer layer. The next step is the application of the primer itself, step 106. In this exemplary embodiment, parylene is applied to the stents utilizing a vapor deposition process. Once the parylene is applied, the stents are packaged and weighed, step 108. Once the stents are weighed, they are placed in containers or vials. The vials may be formed from any number of suitable materials. In the exemplary embodiment, the vials are formed from polypropylene.

The second part of the process comprises the basecoat application. The first step in the second part of the process is the preparation of the basecoat, step 110. The basecoat may comprise any suitable biocompatible polymers and therapeutic agents. The therapeutic agents and polymers should preferably be compatible. In the exemplary embodiment, the basecoat solution comprises polyethylene co-vinylacetate, polybutylmethacrylate and a rapamycin, such as sirolimus. The solution is prepared in a standard reactor. The solution is decanted into smaller containers for the next step. The next step is the coating of the stents, step 112. In this step, the stents are coated with the basecoat solution. The stents may be coated in any suitable manner. In the exemplary embodiment, the stents are coated utilizing a spray coating

technique. Nitrogen is utilized as the carrier gas for the basecoat solution. In step 112, one half of the stent is coated and then air dried in step 114. The half coated stents are dried at a relative humidity of about thirty to about fifty-five percent for about thirty minutes. The air temperature is held at about room temperature. The air in the drying chamber is continuously recirculated. Upon completion of the drying step 114, the second half of the stent is coated, step 116 and then dried again in step 118. Steps 116 and 118 are identical to steps 112 and 114.

The third part of the process comprises the topcoat application. The first step in the third part of the process is the preparation of the topcoat solution, step 120. The preparation of the topcoat comprises preparing a solution of polybutylmethacrylate. Once the solution is prepared and decanted into a spraying container, one-half of the stent is coated, step 122. The next step of the process is another coating step, step 124. In this coating step, the half of the stents that have been topcoated are sprayed with toluene. The spraying of toluene has a polishing effect on the topcoat and also facilitates elution control of the therapeutic agent from the polymeric coating. Once step 124 is complete, the stents are air dried, step 126, under the same conditions as in steps 114 and 118. Steps 128, 130 and 132 are the same as steps 122, 124 and 126 but for the second half of the stents.

The fourth and final part of the exemplary process comprises the final processing. The first step in the fourth part of the process is final inspection and coated stent release, step 134. Each of the stents is inspected for defects. Various inspection techniques such as microscopy may be utilized to determine if the stents meet various rigorous standards. The next step in the process is packaging, step 136. The stents are put into trays and sealed in pouches. In this exemplary embodiment, the trays are PETG trays. Once the stents are packaged, they are refrigerated, step 138. The stents are maintained at a temperature from about five degrees centigrade to about eight degrees centigrade. Wider ranges may be

utilized. The next step in the process is the crimping and packaging of each of the stents, step 140. In this step, the stents are positioned on the delivery device and crimped to the desired size. Once positioned on the delivery devices, the whole system is packaged and shipped to a location for sterilization, steps 142 and 144. The systems are sterilized utilizing ethylene oxide, but other suitable sterilization processes may be utilized. The final step of the process is final packaging, step 146.

A number of process modifications may be utilized to address autoxidation. Autoxidation occurs when there is a fuel, in this case the therapeutic agent, an ignition of the fuel, in this case radicals, and finally, there is oxygen or oxygen containing compounds. The first process modification includes protecting the active pharmaceutic ingredient or therapeutic agent, sirolimus, from autoxidation. One way in which to protect the active pharmaceutic ingredient is to raise its glass transition temperture, tg. A higher glass transition temperature leads to a more stable therapeutic agent at room temperature. Amorphous substances act like sponges and will pick up other compounds such as solvents. Sirolimus is an amorphous therapeutic agent. Accordingly, in order to make an amorphous therapeutic agent more stable, one has to raise its glass transition temperature and since solvents lower the glass transition temperature, the minimization of exposure to residual solvents is required. Ways in which to reduce or minimize exposure to residual solvents include keeping extraneous solvents away from the coating, for example, cleaning agents and solvent bottles, and storing stents in an environment that is substantially solvent free, for example, away from freshly coated stents and/or from solutions. Preferably, the therapeutic agents or stents coated with therapeutic agents are stored in stability chambers. In addition, a higher glass transition temperature may be achieved by increasing the removal of residual solvents post coating. This may be accomplished by allowing more time for residual solvent removal post coating, by applying vacuum conditions and heat to enhance residual solvent removal and by allowing short-term moisture exchange (presence of humidity) to enhance

residual solvent removal. The long-term exposure to relative humidity is preferably controlled because humidity may act as a plasticizer. Vacuum packaging and packaging under inert gas of the finished goods addresses this concern. Also, the three domain coating morphology, i.e., three different zones of polymer and therapeutic agent offers only some protection of the therapeutic agent from oxygen. Accordingly, the spraying conditions may be modified to control or affect the coating morphology, for example, low humidity and spray head distance. The steps of the process that may be modified to accomplish these improvements include steps 112, 114, 116, 118, 126, 132, 138 and 146 as illustrated in Figure 2.

Another process modification comprises reducing the presence of and/or exposure to free radicals and, autoxidation initiators. This may be accomplished by utilizing materials with minimal free radicals, for example, polypropylene vials may be utilized rather than PETG trays, and utilizing tools to assist in the crimping and packaging stage that are fabricated from inert materials. This may also be accomplished by parylene annealing to reduce parylene radicals. The steps of the process that may be modified to accomplish these improvements include steps 104 and 136 as illustrated in Figure 3.

Yet another process modification comprises reducing the presence of and/or exposure to oxygen. This may be accomplished by having improved controls of raw materials, improved coating solution mixing and handling, and improved coatings. Improved control of raw materials includes solvents such as THF with low hydroperoxides and an active pharmaceutic ingredient with minimal handling. Improved coating solution mixing and handling includes inert gas blanketing to reduce dissolved oxygen and the minimization of all decanting steps. Improved coating includes spraying in a nitrogen rich environment, vacuum oven, purging with inert gas after annealing and vacuum packaging, and/or packaging under inert gas of works in progress and finished goods. The steps of the

process that may be modified to accomplish these improvements include steps 101, 110, 112, 116, 120, 136 and 146 as illustrated in Figure 4.

It is important to note that although stents are discussed in detail herein, the local delivery of drug/drug combinations 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. For example, intraocular lenses, placed to restore vision after cataract surgery is often compromised by the formation of a secondary cataract. The latter is often a result of cellular overgrowth on the lens surface and can be potentially minimized by combining a drug or drugs with the device. Other medical devices which often fail due to tissue in-growth or accumulation of proteinaceous material in, on and around the device, such as shunts for hydrocephalus, dialysis grafts, colostomy bag attachment devices, ear drainage tubes, leads for pace makers and implantable defibrillators can also benefit from the device-drug combination approach. Devices which serve to improve the structure and function of tissue or organ may also show benefits when combined with the appropriate agent or agents. For example, improved osteointegration of orthopedic devices to enhance stabilization of the implanted device could potentially be achieved by combining it with agents such as bone-morphogenic protein. Similarly other surgical devices, sutures, staples, anastomosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, vascular implants, tissue adhesives and sealants, tissue scaffolds, various types of dressings, bone substitutes, intraluminal devices, and vascular supports could also provide enhanced patient benefit using this drug-device combination approach. Essentially, any type of medical device may be coated in some fashion with a drug or drug combination which enhances treatment over use of the singular use of the device or pharmaceutical agent.

In addition to various medical devices, the coatings on these devices may be used to deliver therapeutic and pharmaceutic agents

including: antiproliferative/antimitotic agents including natural products such as vinca alkaloids (i.e. vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (i.e. etoposide, teniposide), antibiotics (dactinomycin (actinomycin D) daunorubicin, doxorubicin and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin, enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents such as G(GP) II_b/III_a inhibitors and vitronectin receptor antagonists; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), triazenes – dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs (fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine {cladribine}); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (i.e. estrogen); anticoagulants (heparin, synthetic

heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory; antisecretory (breveldin); anti-inflammatory: such as adrenocortical steroids (cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6α-methylprednisolone, triamcinolone, betamethasone, and dexamethasone), non-steroidal agents (salicylic acid derivatives i.e. aspirin; para-aminophenol derivatives i.e. acetominophen; indole and indene acetic acids (indomethacin, sulindac, and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and

oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate); immunosuppressives: (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); angiogenic agents: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF); angiotensin receptor blockers; nitric oxide donors; anti-sense oligionucleotides and combinations thereof; cell cycle inhibitors, mTOR inhibitors, and growth factor receptor signal transduction kinase inhibitors; retenoids; cyclin/CDK inhibitors; HMG co-enzyme reductase inhibitors (statins); and protease inhibitors.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for coating implantable medical devices comprising:

(a) applying a primer coating on the implantable medical devices, comprising the application of a parylene layer and annealing the parylene layer to reduce autoxidation initiators;

(b) preparing a basecoat solution comprising polymers and a therapeutic agent and applying the basecoat solution to the implantable medical devices coated with parylene, the basecoat solution being prepared with and applied utilizing a process to reduce the presence and exposure of the basecoat solution to oxygen;

(c) preparing a topcoat solution comprising at least one polymer and applying the topcoat solution to the implantable medical devices coated with the basecoat solution, the topcoat solution being prepared with and applied utilizing a process to reduce the presence and exposure of the topcoat solution to oxygen;

(d) applying a solvent that has the potential to redissolve the coating components and alter the surface finish and the dissolution properties of the therapeutic agent;

(e) reducing the solvent content thereby raising the glass transition temperature of the therapeutic agent and creating a coating morphology to protect the therapeutic agent from autoxidation; and

(f) finally processing the implantable medical devices, including inspecting, packaging and sterilizing the coated medical devices, the final processing including protecting the therapeutic agent from autoxidation, reducing the presence of and exposure of all materials to radicals and reducing the presence of and exposure of all materials to oxygen.

2. The process according to claim 1, further comprising providing higher glass transition temperatures by minimizing exposure to solvents after drying.

3. The process according to claim 1, further comprising storing the medical devices in a solvent-free environment.

4. The process according to claim 1, further comprising increasing removal of residual solvents by allowing more time for removal thereof post-coating.

5. The process according to claim 1, further comprising applying vacuum and heat to enhance residual solvent removal.

6. The process according to claim 1, further comprising increasing removal of residual solvents by allowing short-term moisture exchange.

7. The process according to claim 1, wherein final processing further comprises vacuum packaging under inert gas.

8. The process according to claim 1, further comprising minimizing the presence or exposure to free radicals and autoxidation initiators by using materials with minimal free radicals.

9. The process according to claim 8, further comprising using tools comprised of inert materials.

10. The process according to claim 8, further comprising minimizing the presence or exposure to oxygen by using raw materials without free radicals or radical initiators and solvents with low hydroperoxide content.

11. The process according to claim 10, further comprising minimizing decanting of coating solutions and solvents.

12. The process according to claim 11, further comprising blanketing with inert gas to reduce dissolved oxygen.

13. The process according to claim 12, further comprising decreasing levels of oxygen by processing in a nitrogen rich environment.

14. The process according to claim 13, further comprising packaging under inert gas.

15. The process of claim 1, wherein the solvent is toluene.

16. The process of claim 1, wherein the basecoat is applied to the medical device at once.

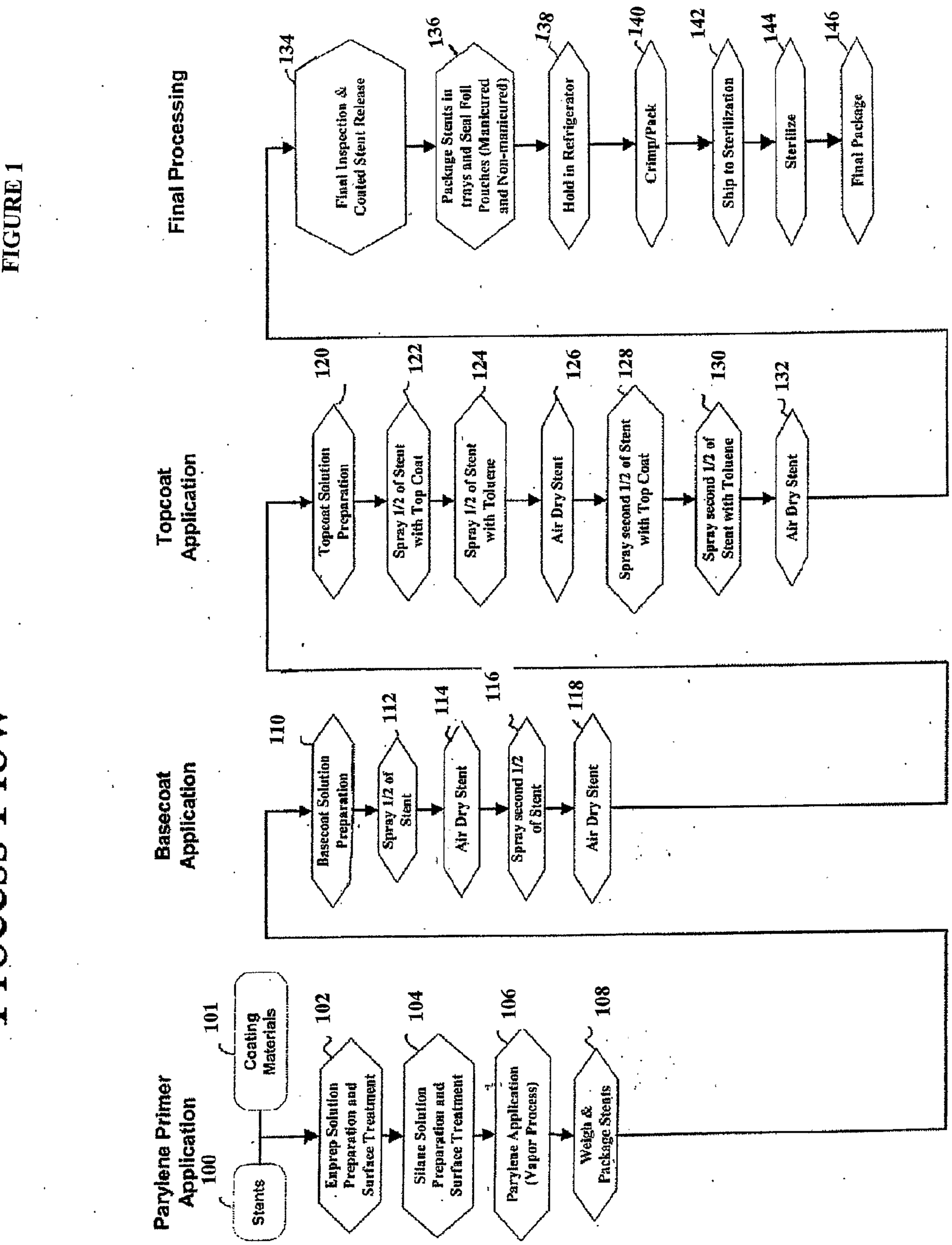
17. The process of claim 1, wherein the basecoat is applied to the medical device incrementally.

18. The process according to claim 1, wherein the topcoat is applied to the medical device at once.

19. The process according to claim 1, wherein the topcoat is applied to the medical device incrementally.

FIGURE 1

Process Flow



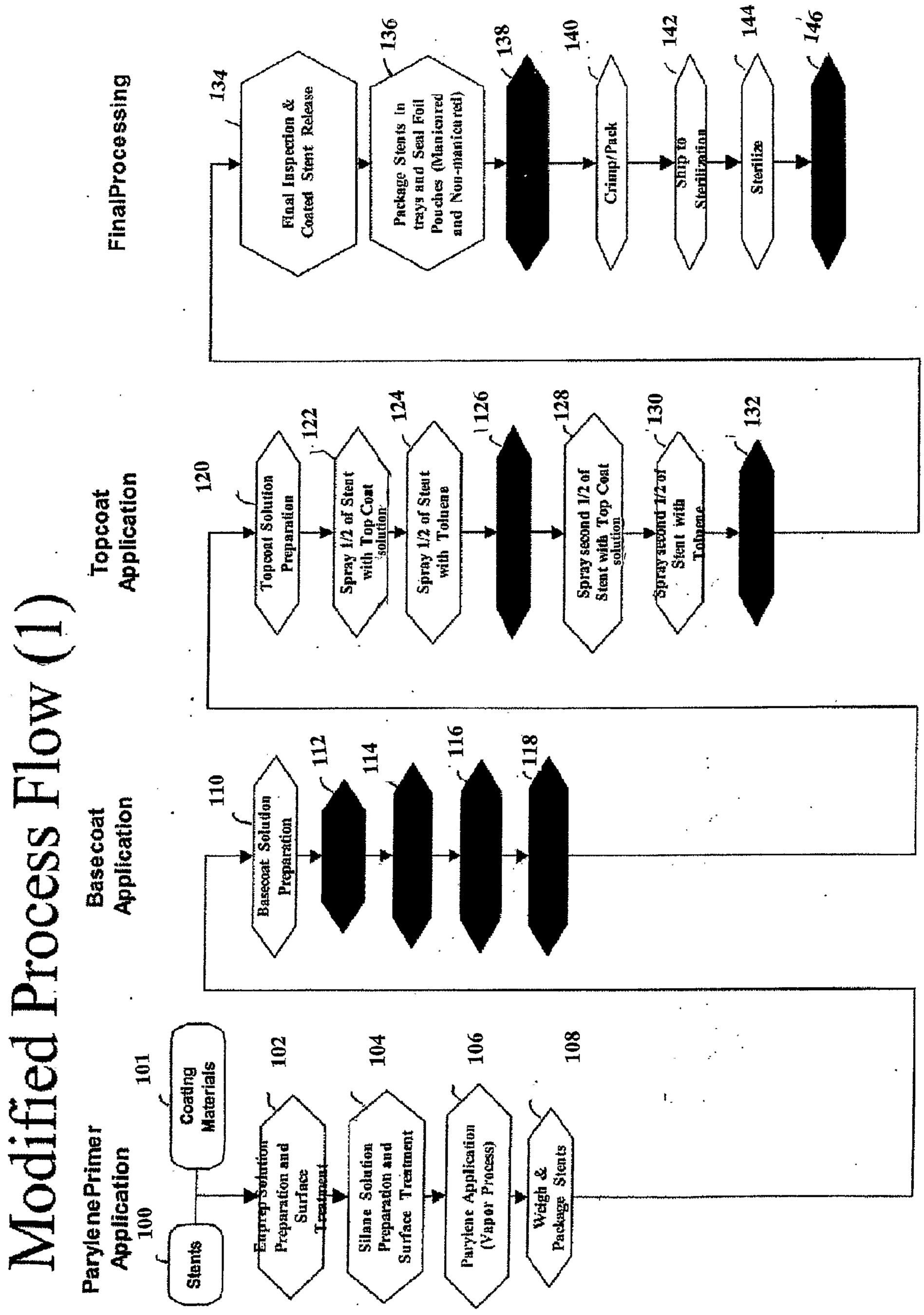

Process Flow (1)
Modified
Parylene Primer Application
100
Stents
101
Coating Materials
Enprep Solution Preparation and Surface Treatment
102
Silane Solution Preparation and Surface Treatment
104
Parylene Application (Vapor Process)
106
Weigh & Package Stents
108
Basecoat Application
110
Basecoat Solution Preparation
112
114
116
118
Topcoat Application
120
Topcoat Solution Preparation
122
Spray 1/2 of Stent with Top Coat solution
124
Spray 1/2 of Stent with Toluene
126
Spray second 1/2 of Stent with Top Coat solution
128
Spray second 1/2 of Stent with Toluene
130
132
Final Processing
134
Final Inspection & Coated Stent Release
136
Package Stents in trays and Seal Foil Pouches (Manicured and Non-manicured)
138
140
Crimp/Pack
142
Ship to Sterilization
144
Sterilize
146

FIGURE 2

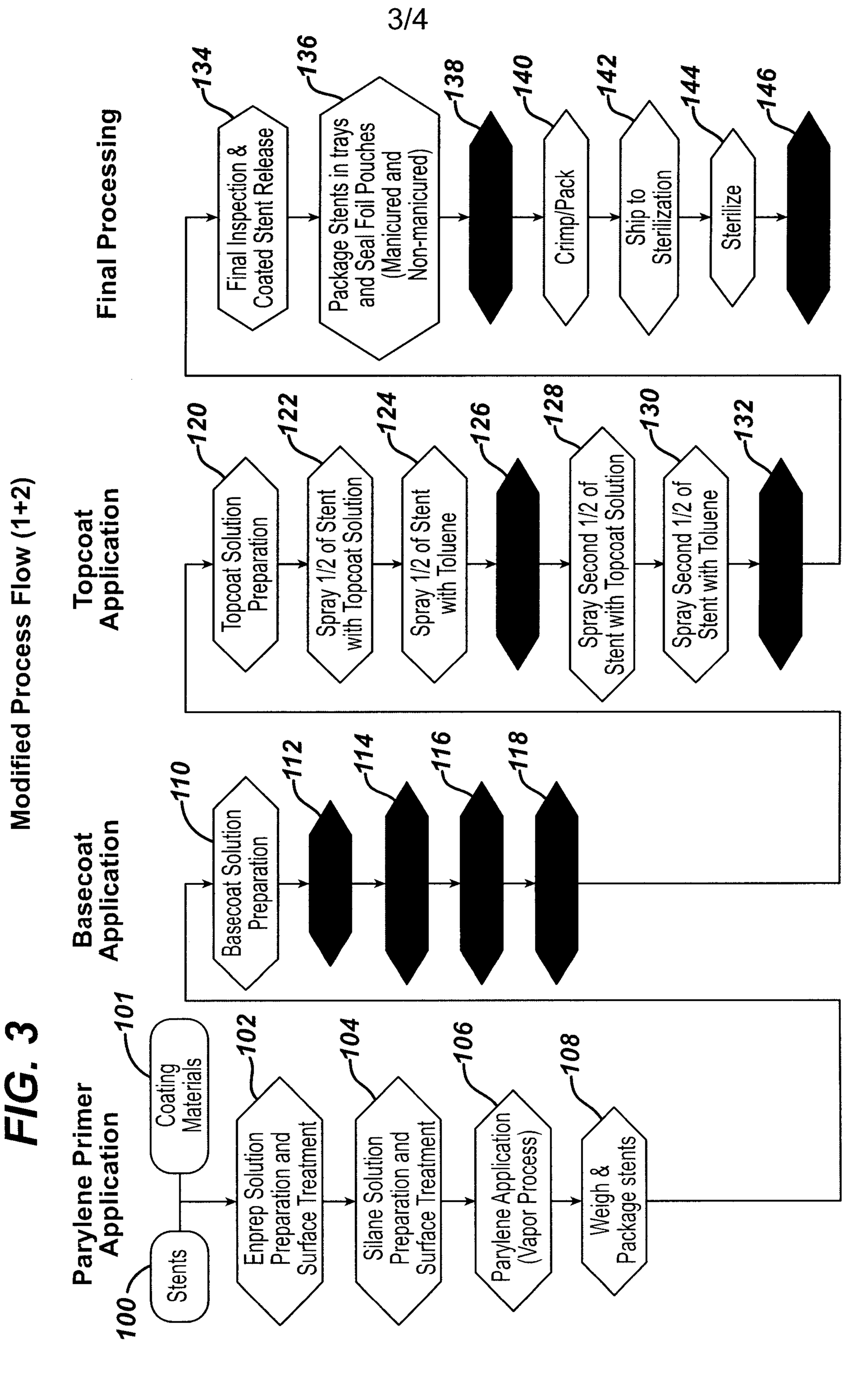
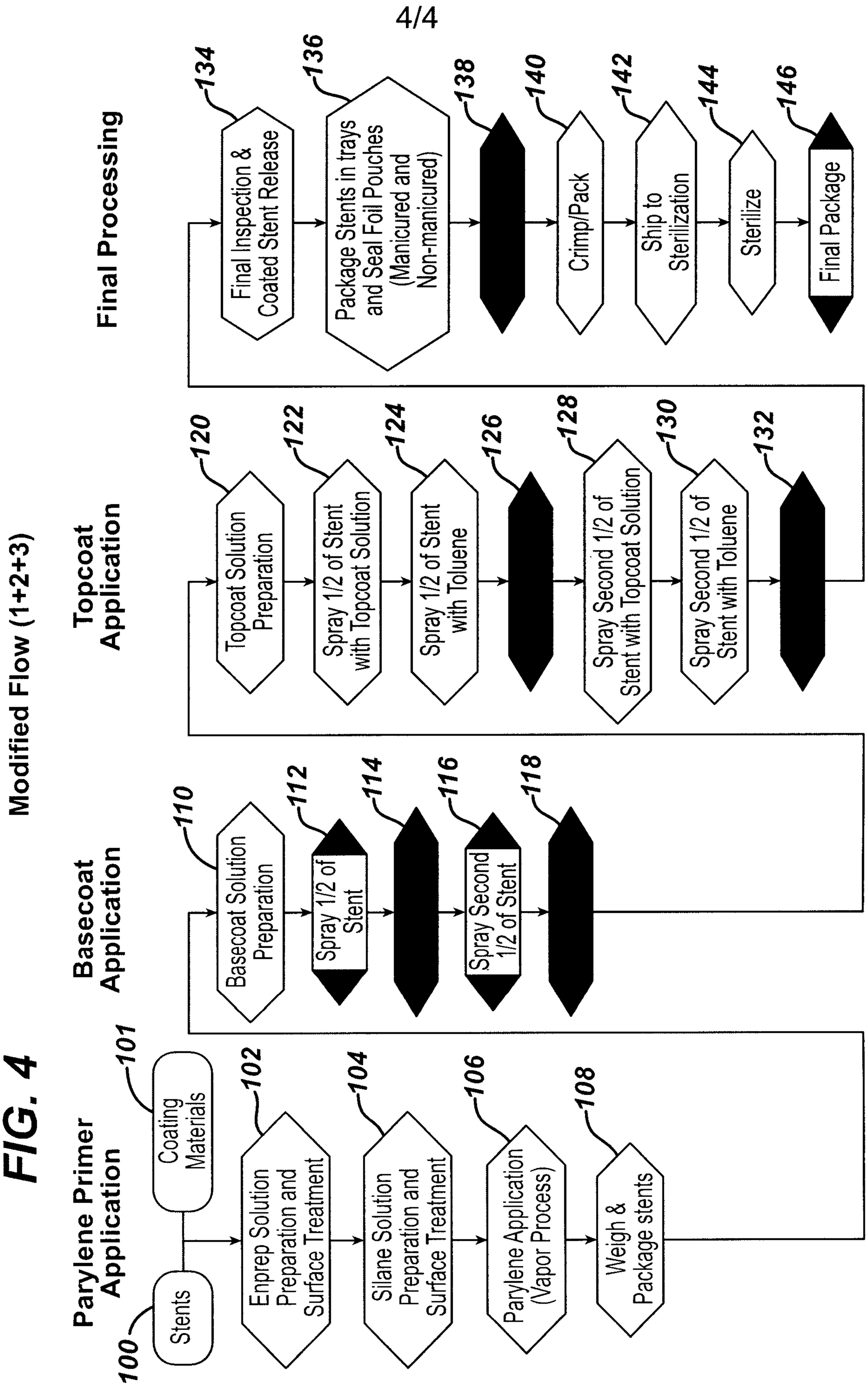

Modified Process Flow (1+2)
Parylene Primer Application
100
Stents
101
Coating Materials
102
Enprep Solution Preparation and Surface Treatment
104
Silane Solution Preparation and Surface Treatment
106
Parylene Application (Vapor Process)
108
Weigh & Package stents
Basecoat Application
110
Basecoat Solution Preparation
112
114
116
118
Topcoat Application
120
Topcoat Solution Preparation
122
Spray 1/2 of Stent with Topcoat Solution
124
Spray 1/2 of Stent with Toluene
126
128
Spray Second 1/2 of Stent with Topcoat Solution
130
Spray Second 1/2 of Stent with Toluene
132
Final Processing
134
Final Inspection & Coated Stent Release
136
Package Stents in trays and Seal Foil Pouches (Manicured and Non-manicured)
138
140
Crimp/Pack
142
Ship to Sterilization
144
Sterilize
146

FIG. 3

FIG. 4


Parylene Primer Application
100
Stents
101
Coating Materials
Enprep Solution Preparation and Surface Treatment
102
Silane Solution Preparation and Surface Treatment
104
Parylene Application (Vapor Process)
106
Weigh & Package stents
108
Modified Flow (1+2+3)
Basecoat Application
110
Basecoat Solution Preparation
112
Spray 1/2 of Stent
114
Spray Second 1/2 of Stent
116
118
Topcoat Application
120
Topcoat Solution Preparation
122
Spray 1/2 of Stent with Topcoat Solution
124
Spray 1/2 of Stent with Toluene
126
Spray Second 1/2 of Stent with Topcoat Solution
128
Spray Second 1/2 of Stent with Toluene
130
132
Final Processing
134
Final Inspection & Coated Stent Release
136
Package Stents in trays and Seal Foil Pouches (Manicured and Non-manicured)
138
140
Crimp/Pack
142
Ship to Sterilization
144
Sterilize
146
Final Package

Modified Process Flow (1+2)