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(54) Title: DRUG ELUTING BIORESORBABLE POLYMER MESH COVERED EMBOLIC PROTECTION IMPLANTABLE DEVICE

(57) Abstract: The invention discloses drug eluting bioresorbable polymer mesh covered embolic protection stents that are suitable for implantation into a patient's body lumen, such as a blood vessel or coronary artery, to maintain the patency thereof.



**“DRUG ELUTING BIORESORBABLE POLYMER MESH COVERED
EMBOLIC PROTECTION IMPLANTABLE DEVICE”**

Technical field:

This invention relates to embolic protection device. More particularly, the invention relates to drug eluting bioresorbable polymer mesh covered embolic protection stents that are suitable for implantation into a patient's body lumen, such as a blood vessel or coronary artery, to maintain the patency thereof.

Background and prior art:

Vascular stents are particularly useful in the treatment of atherosclerotic stenosis in arteries and blood vessels. Stenting is a routine procedure for the patients suffering with ischemic heart disease or coronary heart disease, to open up the clogged artery that caused the attack. Standard stents are not engineered for patients with acute coronary syndrome which is also known as myocardial infarction (MI) or acute heart attack patients. They are designed for treating stable angina patients whose occlusion is different from that of an occlusion in a heart attack patient. In acute heart attack patients the plaque or thrombus is unstable and often breaks up causing downstream blockages, some of which can be fatal in a significant portion of heart attack patients. Thrombus embolization, during percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), continues to be a major drawback leading to micro vascular obstruction and diminishing myocardial perfusion, leading to increase infarct size, reduces the recovery of ventricular function, and thus increases mortality.

Attempts to improve the safety of carotid artery stenting (CAS) have focused on mechanisms to reduce procedure-related atheroembolism and periprocedural stroke. In this regard, a variety of embolic protection devices (EPDs) have been developed to address this issue, which includes a) a distal occlusion balloon; b) distal filter devices; and c) proximal protection devices with and without flow

reversal. Accordingly, a wide array of embolic protection devices (EPDs) such as proximal protection devices and distal protection devices has been introduced in the last decade to address this clinical problem. Although the use of distal embolic-protection devices has previously been demonstrated to reduce major adverse cardiovascular events associated with percutaneous coronary intervention (PCI) in these patients, however, all the currently used EPDs suffer from considerable shortcomings.

The disadvantages of distal protection devices are requirement of distal “landing zone,” imperfect deliverability, suboptimal protection, lack of adjacent (between the target lesion and the EPD) side branch protection, device clogging, impaired flow, and device-related vessel spasm or injury.

Filters, although, easier to use by less experienced operators, are only “partially” protective, allowing particles smaller than their pore sizes to pass through them and to the brain. Further, these filters can occasionally be difficult to retrieve, and also, if the filter becomes full, the overflowing debris must be removed or aspirated separately to avoid spilling the contents of the filter during retrieval.

Similarly, the disadvantages associated with the proximal protection devices require a proximal “landing zone,” which results in a “working area” that is neither perfuse nor visualized, and can potentially cause proximal injury or proximal embolization involving side branches emerging between the EPD and the target lesion. The efficacy of proximal EPDs is dependent on the absence of such side branches or collateral vessels between the EPD and the target lesion, which is often not the case.

The prior art further suggest the use of embolic protection mesh device. Embolic protective mesh device comprises small apertures, which is often deployed with a stent to prevent restenosis through the larger metal stent apertures. While often

preventing restenosis, mesh covered stents cause a significant increase in other life-threatening hazards.

Critical blood component such as platelets are sticky, irregularly shaped, that promote blood clotting and readily sense, aggregate around, and stick to, clumps of free floating endothelial cells. An embolism of aggregated platelets and endothelial cells presents a health threat that can form at any time following mesh covered stent implantation (nondrug implant), causing an estimated 10 % of all mesh covered stent recipients to eventually develop necrosis of vital organs and lead to the death of the recipient.

Emboic protective filter implant device causes neo-intimal hyperplasia due to vessel wall injury and also the absence of anti-proliferative drug causes restenosis same as a bare metal vascular implant. Even with drug eluting vascular implant, the problem of late thrombosis in the absence of longer anti-platelet drug therapy still exists.

In the light of the foregoing, it is evident that the drug-eluting bioresorbable polymer mesh covered stent although reduces restenosis more than the non-eluting mesh covered stents, however, may pose even greater threat of embolic death than the nondrug-eluting stents.

To solve the foregoing problems, bioresorbable/Bioabsorbable vascular implants are invented in the prior art, however, with restrictive radial strength.

In the light of the above, there remains a need in the art to develop an embolic protection device that can overcome the above mentioned disadvantages by maintaining the safety & patency of coronary or carotid artery stenting (CAS) so as to reduce procedure-related atheroembolism and periprocedural stroke.

Therefore, the objective of the invention is to develop drug eluting bioresorbable polymer mesh Covered Embolic Protection Stent that will eliminate the disadvantages associated with the current embolic protection devices in the market.

Summary of the invention:

In line with the above objective, the instant invention provides drug eluting bioresorbable polymer mesh covered embolic protective Stent that has the potential of serving as a “built-in” and temporary EPD till the revascularization with enhanced bioavailability of therapeutic agents and bio absorption of Embolic protective mesh. The biocompatible/bioresorbable/biodegradable materials as referred herein means and include the materials that dissolve in the body once their purpose has been served.

Accordingly, the invention provides a drug eluting embolic protection device which comprises;

- a) a metallic stent configured to be positioned in body lumen; and
- b) bioresorbable polymer mesh cover, to be placed over the stent co-axially, fabricated from an oriented bioresorbable polymeric monofilament of diameter in the range of 15 to 50 μ m, knitted into expandable mesh structure having longitudinal aperture from 100 to 300 μ m with transverse aperture from 100 to 250 μ m,

Wherein, the polymeric mesh cover is coated abuminmusly with at least one drug selected from the group consisting of antiproliferative drug; antithrombin and antiplatelet dispersed in polymeric matrix to provide sustained release and to prevent plaque dislodgement and blocks debris (Emboli shower) from entering the bloodstream during and post stenting procedure.

A new strategy has been developed in with respect to current invention to reduce the risk of distal embolization, restenosis & late thrombosis during percutaneous

intervention. We designed the system using a hybrid shell design cobalt chromium-metal stent covered with an ultrathin flexible drug eluting bioresorbable polymeric mesh that is anchored to the external surface of the struts. During stent deployment, the mesh stretches and slides over the expanded stent struts, traps the thromboembolic debris underneath the fiber net and isolates the plaque/prothrombotic intimal components from the blood stream. The bioresorbable polymer mesh having capability to sustain the elute of antiproliferative drug used to prevent restenosis and elute antiplatelet drug to eliminate late thrombosis. The platform of the therapeutic agent is designed to degrade as and when revascularisation occurs. These characteristics make this device very attractive for any intervention where thromboembolic complications might affect procedural success.

Description of drawings

Figure 1 depicts hybrid design of the stent

Figure 2 shows the flowchart depicting construction of bioresorbable mesh fiber monofilament using the combination of PLA and PCL polymers

Figure 3 shows proprietary dedicated mandrel

Figures 4 and 5 depicts SEM images of drug eluting mesh covered stent

Figure 6 depicts in vitro analysis of drug eluting bioresorbable polymer mesh covered stent which includes drug release study of antiproliferative drug and antiplatelet drugs along with in-vitro degradation of bioresorbable polymer mesh and radial strength of device.

Detailed description of the invention

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be fully understood and appreciated.

In accordance with the above, the invention describes drug eluting bioresorbable polymer mesh covered embolic protective Stent that has the potential of serving as

a “built-in” and temporary EPD till the revascularization with enhanced bioavailability of therapeutic agents and bio absorption of Embolic protective mesh.

According to a preferred embodiment, the invention provides a drug eluting embolic protection device which comprises;

- a) a metallic stent configured to be positioned in body lumen; and
- b) bioresorbable polymer mesh cover, to be placed over the stent co-axially, fabricated from an oriented bioresorbable polymeric monofilament of diameter in the range of 15 to 50 μ m, knitted into expandable mesh structure having longitudinal aperture from 100 to 300 μ m with transverse aperture from 100 to 250 μ m,

Wherein, the polymeric mesh cover is coated abuminmusly with at least one drug selected from the group consisting of antiproliferative drug; antithrombin and antiplatelet dispersed in polymeric matrix to provide sustained release and to prevent plaque dislodgement and blocks debris (Emboli shower) from entering the bloodstream during and post stenting procedure.

In another embodiment, the invention provides unique dual mechanism that comprises sustained delivery of anti-proliferative drug, anti-thrombic and anti-platelet drug coupled with trapping the embolic debris beneath the micro level bioresorbable mesh. The drug eluting embolic protective mesh minimizes body response; promote revascularization and eliminates the prothrombotic intima or embolic components from the blood stream makes it an attractive device for any intervention where embolic complications can affect procedural and clinical success.

Drug Eluting Bioresorbable Polymer mesh covered stent system according to the invention comprises a novel combination of a drug eluting Bioresorbable polymer mesh covered coronary stent which is designed to prevent plaque dislodgement

and blocks debris (Emboli shower) from entering the bloodstream during and post procedure.

The stent material can be selected from the group consisting of Stainless Steel, CoCr, Nitinol or Bioresorbable polymer.

In one preferred embodiment, the stent with a hybrid design having partial closed cells at top and bottom has been provided to facilitate ease in attaching a drug eluting polymeric mesh. Normally stent design comprises either open cell or closed cell. A metal stent having partial closed cells design with multiple connectors is provided for uniform expansion of the stent. Further, optimum cell size and shape are provided to minimize the vessel wall injury which normally occurs due to intracellular balloon protrusion; better vessel wall coverage, lower strut thickness to minimize local mechanical injury to endothelium. The hybrid design of the stent according to the invention is shown in figure 1. The stents with other designs can also be used to attach the drug eluting polymeric mesh provided according to the invention.

The bioresorbable and bio-compatible polymer materials used in the preparation of micro mesh may be one or more polymers from selected from the group consisting of PLA or any other degradable co-polymeric combination, such as poly lactic-co-polyglycolic ("PLGA"), polycaprolactone ("PCL"), polygluconate, polylactic acid-polyethylene oxide copolymers, poly(hydroxybutyrate), polyanhydride, poly-phosphoester, poly(amino acids), poly-L-lactide, poly-D-lactide, polyglycolide, poly(alpha-hydroxy acid) and combinations thereof.

In another embodiment, the micro mesh as provided in the present invention can also be of other biodegradable and non-biodegradable polymers.

A bioresorbable mesh covered stent in accordance with present invention comprises either natural fiber monofilaments or an injection moulded or extruded

fenestrated tube formed from the blends of at least two bioresorbable, bio-compatible polymers. These polymers may include, but are not limited to poly-L-lactide (PLLA), poly-D, L-lactide (PDLA) and poly- ϵ -caprolactone (PCL).

In one preferred embodiment, the Drug Eluting Bioresorbable Polymer mesh covered stent system comprises an ultra-thin bioresorbable polymer mesh (emboli protective mesh), wrapped around the Cobalt Chromium (Co-Cr) L605 stent. The Embolic protective mesh is composed of a micron-level-fiber knitted mesh of Bioresorbable oriented polymer "PLA", engineered in an optimal geometric configuration and designed for utmost flexibility while retaining strength characteristics of the fiber material. The mesh is designed to expand seamlessly & uniformly when the stent is deployed radially, without affecting the structural integrity of the stent; thereby prevents plaque detachment during and post procedure of stenting.

In another aspect, the Embolic Protective mesh is fabricated from an oriented PLA monofilament as a pre patterned micro knit fabric by circular micro knitting technology. The oriented PLA monofilament has diameter in the range from 15 to 50 μm . The tolerance diameter of monofilament will be $\pm 2 \mu\text{m}$ (0.002 mm).

The PLA monofilament is fabricated from medical grade PLA polymer granule through micro extrusion system and orientation is performed by heating under oven, stretching & heating process.

An expansible stent, operatively associated with the stent mesh, wherein, the diameter of bioresorbable fiber has a property of forming a substantially stable layer covering endothelial cells, thus reducing platelet aggregation.

In another preferred embodiment, the construction of bioresorbable mesh fiber monofilament using the combination of PLA and PCL polymers is described in figure 2. According to the construction, the PLA and PCL polymers are first dry blended under an inert atmosphere, then extruded in a rod form. In a preferred

embodiment of the present invention, granules of PLA and PCL are dry-blended with a PLA/PCL ratio of 90:10 to 99.1:0.9.

The blended PLA and PCL polymer rod is pelletized and then dried. The dried polymer pellets are then extruded to form a coarse monofilament which is quenched into a final monofilament with an average diameter from approximately 0.05 mm to 1 mm which is further proceed to make high tensile monofilament fiber having the diameter of 0.015 to 0.050 mm (+/- 0.002).

In another embodiment, the invention provides a method of fabricating monofilament using oriented monofilament fabrication accessory in conjunction with 20mm extruder.

Monofilament head & die mounted onto extruder output flange for downward extrusion through die assembly with one hole of suitable diameter to produce 30-35 μ m thickness monofilaments. The formed monofilament is passed through quench tank made of SS, having the measurements 250 mm wide x 250 mm deep x 500 mm long. Monofilament moves to the first godet (taken up) set up comprise 3 godet rolls with one rubberized pressure roll (pneumatically operated) provided for conveying monofilament at a constant speed. The rolls are driven by 0.37 kW AC geared motor, 3 phase, 50 cycles with frequency inverter control to reduce the diameter of monofilament. The monofilament is then entered into first orientation oven having the measurements 1000 mm long x 200 mm wide, fully insulated hot air oven mounted on steel frame having steel sheathed electrical resistance air heaters, and 1 No. high-velocity blower fitted with 0.18 kW AC motor, 2880 rpm, 3 phase, 50 cycles to assist stretching of the monofilament.

The monofilament is then entered into second godet (stretching) which comprises 5 godet rolls with pneumatically controlled pressure rolls on 1st and the 5th roll of godet assembly, driven by 0.75 kW AC geared motor, 3 phase, 50 cycles with frequency inverter control.

The monofilament is then entered into second orientation Oven which is having measurements 1000 mm long x 200 mm wide, fully insulated hot air oven mounted on steel frame having steel sheathed electrical resistance air heaters, and 1 No. high-velocity blower fitted with 0.18 kW AC motor, 2880 rpm, 3 phase, 50 cycles to assist stretching of the monofilament.

The monofilament is then finally entered into third Godet (Take-Off) which comprises 3 godet rolls with one rubberized pressure roll (pneumatically operated) provided for conveying monofilament at a constant speed. The rolls are driven by 0.75 kW AC geared motor, 3 phase, 50 cycles with frequency inverter control. Lastly, the monofilament enters into Winder, which is Single station bobbin, driven by 0.09 kW torque motor to wind oriented monofilament on a spool.

The blends of PCL, PLA, PLLA, and PDLLA used for the preparation of the mesh in accordance with the present invention have been found to provide improved process ability and stability when compared to co-polymerization process. Without intending to be bound by this theory, one possible explanation for the improvements in process ability and stability can be attributed to the difference in physical states in which the individual polymers exist once combined. Typically, co-polymers are mostly amorphous compositions, but blends of PLA and PCL may exist as different size and shape of semi-crystalline domains of each polymer with a greater percentage of PCL at the surface. Morphology of both domains may be manipulated by thermal treatments. This increased concentration of PCL at the surface is believed to contribute to the blended composition's increased resistance to hydrolytic attack. Control over the morphology of the final polymer blend is an advantage in providing the improved physical and biological properties of the mesh.

Mesh fabricated by Circular Knitting technologies and their significance in properties of microfiber resorbable mesh.

Circular Knit structures come in two general forms; wefts knit and warp knit. Mesh construction can be dramatically different between the two structures, but the concept of using intermeshing loops of yarn is the same for both. The properties of a weft knitted structure are largely dependent on the interaction of each stitch with its neighbouring stitches in the course and wale directions. The course is the cross direction to the fabric production, while the wale is the parallel direction to the fabric production.

The simple weft knit structure is formed by loops created by needles knitting fiber across the width of the fabric with each loop being created by pulling it through the previous loop in the same direction bellow figure. Needle movements are simply up and down and are controlled by a camera. When the needles are in the up position, each weft fiber is fed at an angle to the direction of fabric formation, solitary or multiple ends of fiber can be fed into the mesh at one time but each end knits has the same pattern with no overlap or variation. At a cross-sectional view of the structure, all the loops are bent into the third dimension due to the manner in which loops are pulled through each other. The simplicity of the circular weft knit structure with minimal cross-over points between courses and wales makes it strong in burst strength, extremely porous, highly droppable, and highly elastic. However, the greatest obstacle for the weft knit construction in use for medical applications is that they easily run from their edges, especially when cut.

Edge disruption can be prevented through trimming process which is removal of unwanted fiber thread generated after cutting the micro knitted mesh in to required length of pieces. It can be done by plastic welding or soldering to fuse the extended thread after cutting.

In an embodiment, the proprietary manual trimming process is developed that can prevent disruption from mesh edges at the time of cutting weft knitted bioresorbable mesh. In an embodiment, the mesh is cut with sharp knife, screened the monofilament from which whole mesh is formed. The unwanted fiber filament

is flushed using medical grade nitrogen or inert gases. Identical end of both meshes is fixed through notch. The whole trimming process is carried out under stereo-microscope beneath laminar air flow environment.

Weft knitting of micro-porous mesh structure is performed by circular knitting machine head having 15 to 40 needles, preferably 22 and 30 needles. The aperture size of mesh depends on configuration of knitting head speed (RPM), mesh traction speed (frequency) & fiber initial tension.

Sr. No.	Traction Speed Frequency	Knitting Head Speed (RPM)	Transverse Aperture size (mm)	Longitudinal size (mm)	Mesh Diameter (mm)
1	0.249	74	0.230	0.100	1.70
2	0.333	102	0.386	0.107	2.02
3	0.361	120	0.335	0.120	2.13
4	0.444	124	0.190	0.110	1.70
5	0.472	140	0.210	0.120	1.9

Accordingly, in a preferred embodiment, the single oriented monofilament having a diameter of 15 to 50 μm is knitted into expandable mesh structure with longitudinal aperture from 100 to 300 μm while transverse aperture from 100 to 250 μm , to be mounted on a stent frame structure to prevent embolic debris dislodgment as well as reducing a chance of endothelial cells breaking free as a result of natural pulsatile blood flow.

An exemplary embodiment, using the above components and techniques, a porous structure with 35-40 courses per cm is manufactured.

The bioresorbable fiber is treated by means of plasma surface modification to promote bio-absorption and sustained release of therapeutics substance. Tailoring the interface interactions between a Bioabsorbable embolic protective mesh and the surrounding tissue is a capital aspect to consider for the design of medical

devices. Bioabsorbable polymer fiber presents suitable mechanical properties for various biological substitutes; however the lack of cell adhesion on their surface is often a problem. The common approach is to incorporate bio-molecules, either by blending or by coupling. But these modifications disrupt polymer intra- and intermolecular interactions leading therefore to a loss of its original mechanical properties.

Accordingly, in the present invention, surface modification by glow discharge plasma, technique is adopted which is known to modify only the surface without altering the bulk properties. This technique has been investigated to promote cell attachment on PLA substrates. N₂/H₂ microwave plasma treatment has been performed, and the chemical composition of PLA surface has been investigated for the wettability. Plasma modification of the oriented monofilament by amination as above induces an increase in the PLA surface wettability with no significant change in surface roughness. Thus plasma amination of PLA is a promising approach to improve cell behaviour on contact with bioresorbable fiber for vessel implant. Similarly, monofilaments of other bioresorbable polymers can also be subjected to plasma amination to improve the surface wettability.

In preferred embodiment, the polymer fiber is elastic, biocompatible and hemocompatible

In another embodiment, the micro mesh as provided in the present invention can also be of other biodegradable and non-biodegradable polymers.

In one embodiment, the pharmaceutical agent is eluted from the bioresorbable mesh. The active pharmaceutical agent is eluted from a bioresorbable mesh. In a further aspect, the bioresorbable mesh is coated using dip coating, micro spray coating techniques through drug polymer matrix comprising biodegradable polymers.

In dip coating, porous structure is coated using a biocompatible, hemocompatible, bio-stable and/or biodegradable polymer dissolved in an organic solvent to create stable uniform therapeutic layer over the bioresorbable polymer mesh.

In one embodiment, the bioresorbable polymer mesh is coated abluminusly with proprietary formulation of drug/polymer matrix. The abluminus coating provides better safety than fully coated bioresorbable mesh.

In spray coating, porous structure is mounted on mandrel and micro droplet of therapeutic agent is sprayed upon the porous structure using a biocompatible, hemocompatible, bio-stable and/or biodegradable polymer dissolved in an organic solvent to create stable uniform therapeutic agent layer on bioresorbable mesh.

In an embodiment, the dose of therapeutic agents are reduced in contrast to normal drug eluting stent because the 'drug eluting mesh' provides more surface area in contact to vessel wall thereby enabling more tissue uptake and thus increases bioavailability with reduced therapeutic dose.

In an embodiment, the thickness of the drug loaded bioresorbable polymer mesh ranges from about 15 to 50 μm .

In an embodiment, the invention provides sustained delivery of anti-proliferative drug (Sirolimus), anti-thrombic (Argatroban) & anti-platelet drug (sarpogralate) formulated with biodegradable polymer matrix to target site using bioresorbable mesh cover to be placed on a stent as a drug delivery platform. The sustained drug release is obtained in such a way to inhibit vascular intimal hyperplasia, platelet deposition & platelet aggregation.

In a further embodiment, the pharmaceutical agents such as anti-proliferative Drug (Sirolimus) as well anti-thrombic& anti-platelet drug (Argatroban & sarpogralate) along with polymer matrix are coated only on abluminus surface of

bioresorbable mesh which is stent expansible and in contact with vessel lumen to give better bioavailability.

The bioresorbable mesh is coated on abluminus surface with proprietary drug polymer matrix layer by layer to achieve endothelial coverage, target drug release and reduced systemic exposure of therapeutic agents. The drug polymer matrix comprises biodegradable polymer, therapeutic agent and vaporizable solvent.

The following example illustrates a method for forming different layers of bioresorbable polymeric mesh.

A bioresorbable mesh is coated abluminously in three different layers. The method for formulation of bioresorbable mesh will now be described in detail herein below.

Layer 1(base layer) is made up of PLLA, Argatroban and Sarpogrelate hydrochloride, which were weighed in mentioned amount in table 1 and dissolved in 70 ml HFIP + 30 ml DCM by blending at inert atmosphere then extruded in a rod form. Here the polymer v/s drug ratio is 69:31. PLLA as carrier polymer; Argatroban act as anticoagulant (thrombin inhibitor) and Sarpogrelate Hydrochloride (avoid platelet aggregation).

Layer 2 (top layer) made up of PLLA and 50:50 PLGA polymers mixture (49:21); Argatroban which act as an anticoagulant (thrombin inhibitor), Sarpogrelate Hydrochloride (avoid platelet aggregation) and limus family drug (antiproliferative agent). Dissolving it in 70 ml Hexafluoro-isopropanol HFIP + 30 ml DCM. Here polymer v/s drug ratio is 70:30.

Layer 3 is made up of Shellac polymer which is coated on a mesh by dissolving it in 100 ml of DCM.

Formulation content:

Coat	Content	Ratio (Drug Polymer)		Gm	Solvent
Layer-1	PLLA	69	69	0.098	70 ml HFIP+ 30 ml DCM
	Argatroban	31	7.75	0.011	
	Sarpogrelate Hydrochloride		23.25	0.033	
Layer-2	PLLA	70	49	0.098	70 ml HFIP+ 30 ml DCM
	50:50 PLGA		21	0.042	
	Argatroban	30	5	0.010	
	Sarpogrelate Hydrochloride		12.5	0.025	
	Sirolimus		12.5	0.025	
Layer-3	Protective layer				

The Embolic Protective mesh is coated with anti-proliferative Drug (Sirolimus) as well anti-thrombic& anti-platelet drug (Argatroban& sarpogrelate) dispersed in a polymer matrix. The anti-proliferative drug selectively stops cell growth, by blocking cell-cycle progression and eventually inhibits Cell Proliferation and the restenosis. The antithrombotic drug prevents deposition, aggregation, activation of platelet at the site of treatment and thrombin formation. The synergistic effects of the drugs along with embolic protective mesh minimize Restenosis and thrombosis compared to any other DES currently available in the market.

The drug eluting bioresorbable embolic protective mesh is designed to prevent distal embolization by reducing thrombus and plaque fragments released during and post percutaneous coronary intervention (PCI). The objective of this invention is to establish the clinical feasibility, safety and performance during primary PCI for ST-segment elevation myocardial infarction (STEMI), saphenous vein graft (SVG) and coronary artery bypass graft surgery (CABG).

The main advantage of this invention lies in coating of micron thickness mesh with therapeutic agents. The present inventors have designed proprietary dedicated mandrel as shown in figure 3 that can hold the knitted mesh with ease

and mountable on the coating machine. Accordingly, the bioresorbable polymer mesh mounted on a mandrel using the hypodermic needle. The mandrel is inflated with inflation device so that mesh can hold on the mandrel at the time of coating. The mandrel pressure is locked and mounted the mandrel on the coating machine stage and adjusted nitrogen pressure, flow rate and angle of the micro-spray gun. Once coating process completed the mesh is removed carefully from the mandrel by applying negative pressure to the mandrel. The coating surface integrity is checked under a stereoscopic microscope and the coated mesh is stored in a vial and the vial is placed in a vacuum oven for the removal of residual solvent. The therapeutic agent content is determined by HPLC loading method with respect to loading requirement.

In a further aspect, the micro spray coating technique is used to coat the drug dissolved in polymer matrix, layer by layer. The base layer comprises anti-platelet & anti-thrombic drug polymer matrix having capability to prevent platelet deposition and promote healing of vessel endothelial cell. The top layer comprises combination of drugs such as anti-proliferative, anti-thrombic as well as anti-platelet category. The drug dose for base layer is from 0.4 to 0.7 $\mu\text{g}/\text{mm}^2$ & top layer dose 0.5 to 0.8 $\mu\text{g}/\text{mm}^2$. The formulation of drug polymer matrix is designed to give sustained drug release in such a way that prevents vascular intimal hyperplasia, platelet deposition & aggregation.

According to the invention, the Drug eluting bioresorbable mesh is in coaxial association with the stent by wrapped around the stent structure and attached to an outside of the stent structure by bioresorbable micro fiber threading technique.

In another embodiment, the coaxial association includes the knitted stent jacket being sewed, adhered, glued, folded, or sutured to the stent.

In another preferred embodiment, the combination of PLA and PCL polymeric mesh wrapped around cobalt chromium stent according to the invention which

helps to diffuse the stent pressure and reduces injury to the vessel wall and lower the likelihood of restenosis.

The Embolic Protective mesh as provided in the present invention starts hydrolytic degradation after endothelialisation of lumen and generates soluble monomer (e.g., L-lactate), which is converted into pyruvate and eventually enters the Krebs cycle and is further converted into carbon dioxide and water. These final products are excreted from the body through the kidneys or lungs, which results in complete bioresorption of the drug coated mesh.

The metal stent as used in the invention has circumferential closed cells design with multiple connectors for uniform expansion; Optimum cell size and shape result in minimum vessel wall injury due to intra cellular balloon protrusion, better vessel wall coverage, and lower strut thickness to minimize local mechanical injury to endothelium.

In a further embodiment, the drug coated Bioresorbable Polymer mesh covered stent provided according to the invention is crimped onto the PTCA or PTA Balloon Delivery catheter. It provides the means for carrying the stent through the coronary vasculature and for proper positioning of the stent at site of intervention. The drug coated Bioresorbable Polymer mesh covered stent according to the invention can be delivered using rapid exchange delivery system or over the wire delivery system.

The anti-proliferative drugs used for coating the mesh can be selected from Sirolimus, Everolimus, Paclitaxel, actinomycin D (ActD), taxol, 5-FU, daunomycin, mitomycin and dexamethasone.

The anti-platelet and anti-thrombic drugs can be direct acting drugs like Argatroban, sarpograte. The other anti-platelet and anti-thrombic drugs which include sodium heparin, low molecular weight heparin, hirudin, recombinant

hirudin, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-argchloromethylketone, dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist and thrombin inhibitor.

In a preferred embodiment, the anti-proliferative drug (Sirolimus), anti-thrombic (Argatroban) & anti-platelet drug (sarpogralate) are formulated in biodegradable polymer matrix as a drug delivery platform, coated on bioresorbable mesh placed over the stent, so as to deliver the drugs in sustained manner at target site. The sustained drug release is obtained in such a way to inhibit vascular intimal hyperplasia, platelet deposition & platelet aggregation.

The drug eluting bioresorbable mesh covered stent according to the invention is provided with an anti-proliferative agent to minimize restenosis as well as risk of target lesion revascularization (TLR) and anti-platelet as well as anti-thrombic agents which are released in a sustained manner for a time period of not less than 3 month.

The sustained drug release is purely based on nature of therapeutic substance and carrier polymer. The encapsulation capacity of anti-thrombin & anti platelet drug is poor due to hydrophilic nature; however, the release of both the drugs is very fast. For providing the sustained release of anti-proliferative drug (Hydrophobic) & anti-thrombic / anti-platelet drug (Hydrophilic), the polymers like PVB [poly (vinyl acetyl-co-vinyl alcohol-co vinyl acetate)] alone or with PLLA, PLGA, PCL, PDLA polymer matrix can be used.

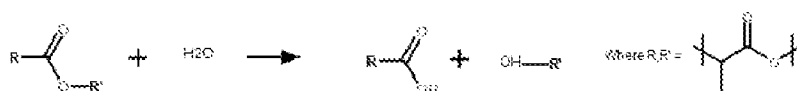
The optional primer layer of PVB can be applied on the mesh surface to improve the adhesion of the drug-polymer layer on the mesh surface.

The additional topcoat layer of PVB, PVA, PVP or Shellac can be applied which may serve as a release rate limiting membrane which further controls the rate of release of the drug.

According to the invention, the anti-proliferative drug can be released up to 25-30 days from the biodegradable mesh coated with drug polymer layer by layer formulation which prevents restenosis as well target lesion revascularization while anti-platelet & anti-thrombic agent can release at a slow rate to prevent sub-acute thrombosis up to 1-3 months. The degradation of PLA starts after complete endothelialisation of target site. The mesh is completely degraded within 4 to 6 month after implantation.

The current Bioresorbable mesh is composed of either a polymer or bioresorbable metal alloy. Numerous different polymers are available, each with different chemical compositions, mechanical properties, and subsequently bio absorption times (table 1). The most frequently used polymer in the current generation of Bio Resorbable mesh is PLLA. PLLA is already in widespread clinical use with applications such as resorbable sutures, soft-tissue implants, orthopaedic implants, and dialysis media. The key mechanical traits for candidate material in coronary indications include high-elastic module to impart radial stiffness, large-break strains to impart the ability to withstand tensile strength from the crimped to expanded states of metal platform. Bioresorbable Stent developers look to increase stent strut dimensions to compensate for mechanical shortcomings of bioresorbable materials. As bioresorbable mesh is good alternative compare to bioresorbable stent having lower crossing profile and superior radial strength same as metal platform.

In the PLA family of polymers, molecular-weight degradation occurs in vivo predominantly through hydrolysis, which is a bimolecular nucleophilic substitution reaction that can be catalyzed by the presence of either acids or bases. The schematic diagram shown below describes the hydrolysis reaction in which water catalyzes a chain scission event at an ester bond.



The mechanical properties and degradation time for different polymers that can be used in the present invention are provided in table 1.

Table 1

Mechanical Properties and Degradation Time for Different Polymers

Polymer Composition	Tensile Modulus of Elasticity, GPa	Tensile Strength, MPa	Elongation at Break, %	Degradation Time, month
Poly (L-lactide)	3.1–3.7	60–70	2–6	>24
Poly (D,L-lactide)	3.1–3.7	45–55	2–6	12–6
Poly (glycolide)	6.5–7.0	90–110	1–2	6–12
50/50 D,L-lactide/glycolide	3.4–3.8	40–50	1–4	1–2
82/18 L-lactide/glycolide	3.3–3.5	60–70	2–6	12–18
70/30 L-lactide/caprolactone	0.02–0.04	18–22	>100	12–24
Cobalt chromium	210–235	1449	~40	Bio-stable
Stainless steel 316L	193	668	40+	Bio-stable
Nitinol	45	700–1100	10–20	Bio-stable
Mg alloy	40–45	220–330	2–20	1–3

The coated mesh is secured on the outer surface of metal or polymeric stent scaffold which keep lumen open at site of atherosclerosis or blockage artery. The securing of mesh on stent is achieved at proximal and distal end through the separate filament threading with same material as of mesh.

The thickness of drug eluting bioresorbable polymer mesh covered stent including strut with mesh cover ranges from about 75 to 150 μ m.

The drug coated Bioresorbable Polymer mesh covered stent provided according to the invention is indicated for improving luminal diameter in vessels with reference diameter greater than 2.50mm having lesion length greater than 8 mm and for providing embolic protection in the patients such as:

Symptomatic coronary artery disease due to discrete de novo or restenosis lesion in native coronary artery;

Symptomatic coronary artery disease due to culprit lesion in saphenous vein graft;

Treatment of coronary lesion in patients undergoing primary or rescue PCI for acute ST-segment elevation myocardial infarction (STEMI);

Treatment of coronary lesion having atherothrombotic appearance in patients with non ST-elevation acute coronary syndromes (unstable angina) and non ST-segment elevation myocardial infarction;

Symptomatic peripheral artery disease due to discrete de novo or restenosis lesion in native coronary artery; and also indicated for the improvement of the lumen diameter of carotid arteries in patients considered at high risk for adverse events from carotid endarterectomy who require percutaneous carotid angioplasty and stenting for occlusive artery disease.

The following examples, which fully illustrate the practice of the preferred embodiments of the present invention, are intended to be for illustrative purpose only, and should not be considered to be limiting to the scope of the present invention.

Example 1

Reference is now made to the table 2 showing experimental data, which together with the above description; illustrate the invention in a non-limiting fashion.

Optimization of bioresorbable mesh fiber thickness and aperture square area

Advantages of maintaining small total coverage areas provide:

1. Crimping the stent for insertion is relatively simple;

2. Profile of the crimped stent is small;
3. Mesh covered stent substantially has a minimal influence on the mechanical properties of the stent during the delivery and expansion; and
4. Mesh does not require folding during crimping when the coverage area of the stent is about 9%, or about 10%, or about 11%, or about 12% in balloon expanding stent. In general the coverage area is less than 15%.

The table 2 provides support that the above noted parameters of bioresorbable mesh coverage on a stent can be easily attained in the present invention using a fiber diameter of about 20 micrometers.

Table 2

Stent size (mm)	Fiber size (micron)	Head needle No.	Aperture No.	Transverse Aperture size (micron)	Longitudinal size (micron)	Area (%)
2.5	20	22	44	140	245	15
3	20	22	44	175	245	14
3.5	20	22	44	220	240	11
4	20	30	60	150	250	15
4.5	20	30	60	180	245	14
5	20	30	60	212	240	12
5.5	20	30	60	230	240	12

It is understood that the phraseology and terminology employed herein is for descriptive purpose and should not be regarded as limiting.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. In addition, the descriptions, materials, methods, and examples are illustrative only and not intended to be limiting. Methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention.

The present invention provides bioresorbable polymeric mesh covered stent configured to be positioned in a vessel, and a knitted stent mesh including an expansible mesh structure having a coverage area of less than 15%, having approximate aperture diameters greater than 20 micrometers.

In exemplifications, the drug eluting bioresorbable polymer mesh covered stent structure involves a retracted state and an expanded state, and further wherein in the sent expanded state, the expansible cross section "mesh" structure characterizes gaps, having a base focus measurement, which is more prominent than around 150 μm , hence minimizing events of a solitary endothelial cell holding fast to more than one fiber, crosswise over one of the gaps, and diminishing a possibility of endothelial cells breaking free as an after effect of common stent thromb with blood stream.

Example 2

The Treatment concept of Drug-eluting bioresorbable polymeric mesh covered stent

It is typical in stenting procedures to utilize an embolic shower protection gadget which is situated only at during the stenting procedure downstream or upstream from the treatment area, the thought being that the protection gadget will trap debris which tumbles from the blood vessel walls amid the stenting system.

In a praiseworthy encapsulation of the present innovation, the anti-proliferative medication discharges from a bioresorbable cross section which forestalls neo-intimal hyperplasia in light of vessel harm amid a standard implantation system. The coated mesh cover in accordance with the invention reduces platelet aggregation at the site of embolic trap because of the sustained release of the anti-platelet drug.

In vitro analysis of drug eluting bioresorbable polymer mesh covered stent which includes drug release study of antiproliferative drug and antiplatelet drugs along with in-vitro degradation of bioresorbable polymer mesh and radial strength of device (figure 6).

In an exemplary embodiment of the invention, the coating of the therapeutics agents on the abluminus side of the porous structure lead to better bioavailability compared to the full coating of a porous structure. Therefore, the earlier healing response from the luminal side gives boosting endothelization process.

An additional advantage of using implanted bioresorbable mesh structure instead of a conventional embolic shower protection device is that it remains in place for up to 4 months after the implanting procedure. The absorption process of bioresorbable mesh is different from other drug eluting stent; it starts with nourishing the vessels by which it prevents the late thrombosis.

The bioresorbable mesh according to the invention effectively works through unique dual mechanism which comprises a) sustaining the delivery of anti-proliferative drug (Sirolimus), anti-thrombic (Argatroban), anti-platelet drug (sarpogralate) and b) trapping the embolic debris beneath the micro level bioresorbable mesh. The mesh cover further minimizes body response; promotes revascularization and isolates the pro-thrombotic intima or embolic components from the blood stream and thus makes it an attractive device for any intervention where embolic complications can affect procedural and clinical success.

The comparative effectiveness of the marketed device v/s Bioresorbable mesh covered stent in accordance with the invention is provided in the table 3.

Table 3

Marketed Medical Device	Balloon Angioplasty	Bare Metal Stents	Drug Eluting Stent	Drug eluting Bioresorbable stent	Drug eluting Bioresorbable mesh covered stent
Limitation	Restenosis, Recoil	Restenosis, neo-intimal hyperplasia	Thrombosis, Incomplete healing of endothelium	Radial strength, strut thickness (150µm), In stent thrombosis	Resolve all impediment, for example, Radial strength like Metal Stent, Strut thickness (70-90µm), finish and quick endothelization

Acute occlusion	-	+++	+++	++	+++
Acute scaffold thrombosis	NA	-	+/-	+	+++
Sub-acute scaffold thrombosis	NA	-	-	+	+++
Acute recoil	-	+	+	-	+++
Constructive remodeling	-	+	+	+	+
Neointimal hyperplasia	-	-	+	+	+++
Expansive remodeling	+	-	-	+	+
Late luminal enlargement	+	-	-	+	+
Late scaffold thrombosis	NA	-	-	+	+++
Radial strength	NA	+++	+++	+	+++

“+” Implies prevented or not restricted;

“-“Not prevented or restricted;

“NA” Not Applicable because of absence of stent.

We claim,

1. A drug eluting bioresorbable protective polymer mesh covered embolic protection device characterised in that comprising;
 - a) A hybrid metallic stent to be positioned in body lumen; and
 - b) Bioresorbable & biocompatible protective polymer mesh cover, to be placed over the stent co-axially, fabricated from an oriented bioresorbable polymeric monofilament of diameter in the range of 15 to 50 μ m, knitted into expandable mesh structure having longitudinal aperture from 100 to 300 μ m with transverse aperture from 100 to 250 μ m; Wherein, the polymeric mesh cover is coated abuminmusly with at least one drug selected from anti-proliferative drug; anti-thrombic and anti-platelet dispersed in polymeric matrix to provide sustained release to prevent restenosis, late thrombosis and to prevent plaque dislodgement and blocks debris (Emboli shower) from entering the bloodstream during and post stenting procedure.
2. The drug eluting bioresorbable polymer mesh covered embolic protection device according to claim 1, wherein, the bioresorbable & biocompatible polymers may be one or more polymers selected from the group consisting of PLA or any other degradable co-polymeric combination, such as poly lactic-co-polyglycolic ("PLGA"), polycaprolactone ("PCL"), polygluconate, polylactic acid-polyethylene oxide copolymers, poly(hydroxybutyrate), polyanhydride, poly-phosphoester, poly(amino acids), poly-L-lactide, poly-D-lactide, polyglycolide, poly(alpha-hydroxy acid) and combinations thereof.
3. The bioresorbable embolic Protective mesh according to claim 1, wherein, the mesh is fabricated from an oriented PLA monofilament using circular weft knitting technology.
4. The bioresorbable embolic Protective mesh according to claim 3, wherein, the oriented PLA monofilament has diameter in the range from 15 to 50 μ m with tolerance diameter of +/- 2 μ m (0.002 mm).

5. The bioresorbable embolic Protective mesh according to claim 1, wherein, the mesh is fabricated from an oriented monofilament of the bioresorbable polymeric component comprise one or more such as polycaprolactone ("PCL"), poly(hydroxybutyrate), poly L-lactide, poly D-lactide, polyglycolide, or any combination thereof.
6. The bioresorbable embolic Protective mesh according to claim 1, wherein, the mesh is fabricated from an oriented monofilament fabricated from the combination of PLA and PCL.
7. The bioresorbable embolic Protective mesh according to claim 1, wherein, the anti-proliferative drugs used for coating the mesh are selected from Sirolimus, Everolimus, Paclitaxel, Actinomycin D (ActD), Taxol, 5-FU, Daunomycin, Mitomycin and Dexamethasone.,
8. The bioresorbable embolic Protective mesh according to claim 1, wherein, the anti-thrombic and anti-platelet drugs are selected from the group consisting of sodium heparin, low molecular weight heparin, hirudin, Argatroban, sarpogralate, recombinant hirudin, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-argchloromethylketone, dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist and thrombin inhibitor.
9. The bioresorbable embolic Protective mesh according to claim 1, wherein, the anti-thrombic drug is Argatroban.
10. The bioresorbable embolic Protective mesh according to claim 1, wherein, the anti-platelet drug is sarpogralate.
11. The bioresorbable embolic Protective mesh according to claim 1, wherein, the coating of the mesh with therapeutic agents by micro spray coating comprises base layer and top layer.
12. The bioresorbable embolic Protective mesh according to claim 11, wherein, the base layer comprises anti-platelet & anti-thrombic drug in a dose ranging from 0.4 to 0.7 $\mu\text{g}/\text{mm}^2$, to prevent platelet deposition and promote healing of vessel endothelial cell.

13. The bioresorbable embolic Protective mesh according to claim 11, wherein, the top layer comprises combination of anti-proliferative, anti-thrombic as well as anti-platelet category of drugs in a dose ranging from 0.5 to 0.8 $\mu\text{g}/\text{mm}^2$, to prevent vascular intimal hyperplasia, platelet deposition & aggregation.
14. The bioresorbable embolic Protective mesh according to claim 3, wherein, the PLA monofilament is fabricated from medical grade PLA polymer granule through micro extrusion system and orientation is performed by heating under oven, stretching & heating process.
15. The bioresorbable embolic Protective mesh according to claim 3, wherein, the weft knitting of micro-porous mesh structure is performed by circular knitting machine head having 15 to 40 needles by varying the configuration of knitting head speed (RPM), mesh traction speed (frequency) & fiber initial tension, to obtain desired aperture size of mesh.
16. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the oriented monofilament is subjected to Plasma modification to increase in surface wettability and better response to revascularisation.
17. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the plasma modification is plasma amination to improve cell behaviour on contact with bioresorbable fiber for vessel implant.
18. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the thickness of the drug loaded bioresorbable polymer mesh ranges from about 15 to 50 μm .
19. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the polymers used in the drug matrix is selected from the group consisting of PVB [poly (vinyl acetyl-co-vinyl alcohol-co vinyl acetate)] alone or with PLLA, PLGA, PCL, PDLLA polymer matrix.

20. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, an optional primer layer of PVB can be applied on the mesh surface to improve the adhesion of the drug-polymer layer on the mesh surface.
21. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, additional topcoat layer of PVB, PVA, or Shellac can be applied which may serve as a release rate limiting membrane to further control the rate of release of the drug.
22. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the coating of mesh is designed such that the anti-proliferative drug will be released up to 25-30 days while anti-platelet & anti-thrombic agent can release at a slow rate from the biodegradable mesh to prevent sub-acute thrombosis up to 1-3 months with the complete degradation of the mesh within 4 to 6 month after implantation.
23. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the coated mesh is secured on the outer surface of metal or polymeric stent scaffold at proximal and distal end through the separate filament threading with same material as of mesh to keep lumen open at site of atherosclerosis or blockage artery.
24. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the thickness of drug eluting bioresorbable polymer mesh covered stent including strut with mesh cover ranges from about 75 to 150 μ m.
25. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the mesh structure being formed from a solitary fiber having a coverage about under 15% in respect to fiber diameter 20 micrometers to achieve minimum center dimension of 150 micrometers.
26. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the active pharmaceutical agent is eluted Abluminously from the bioresorbable polymer mesh.

27. The bioresorbable embolic Protective mesh according to any of the preceding claims, wherein, the hybrid stent consisting of partially closed at the top and bottom cells.

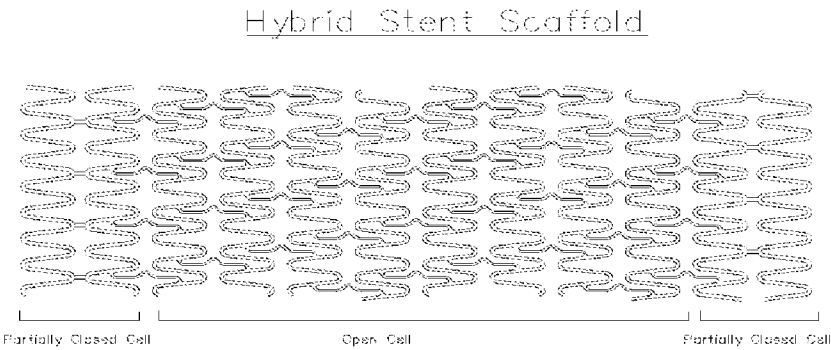


Figure 1

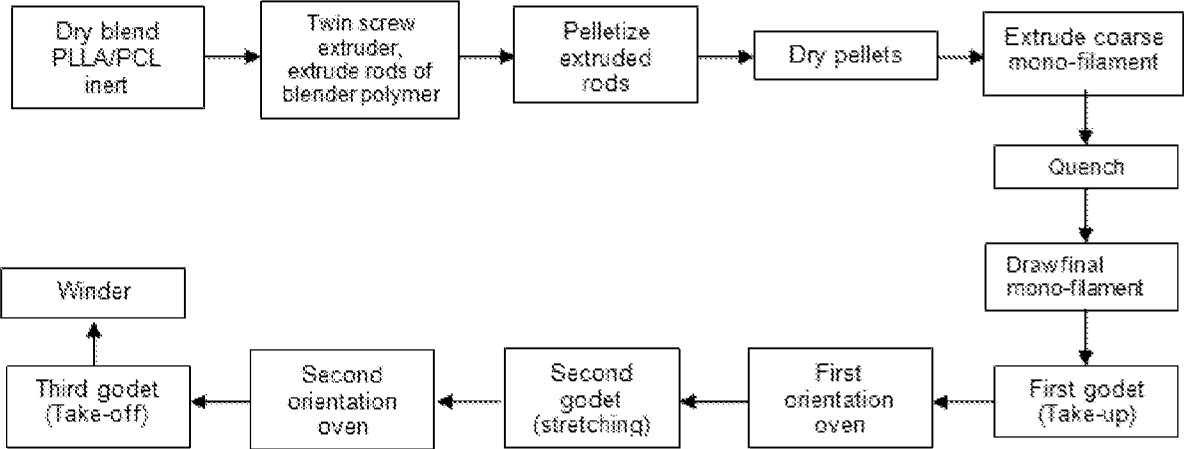


Figure 2

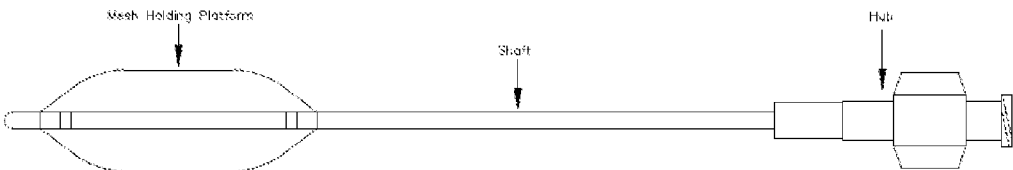


Figure 3

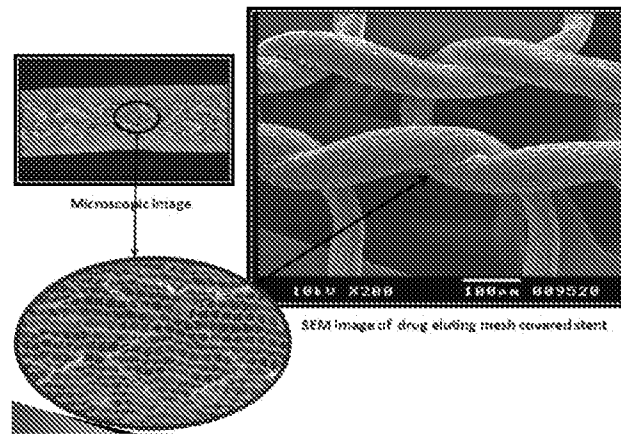


Figure 4

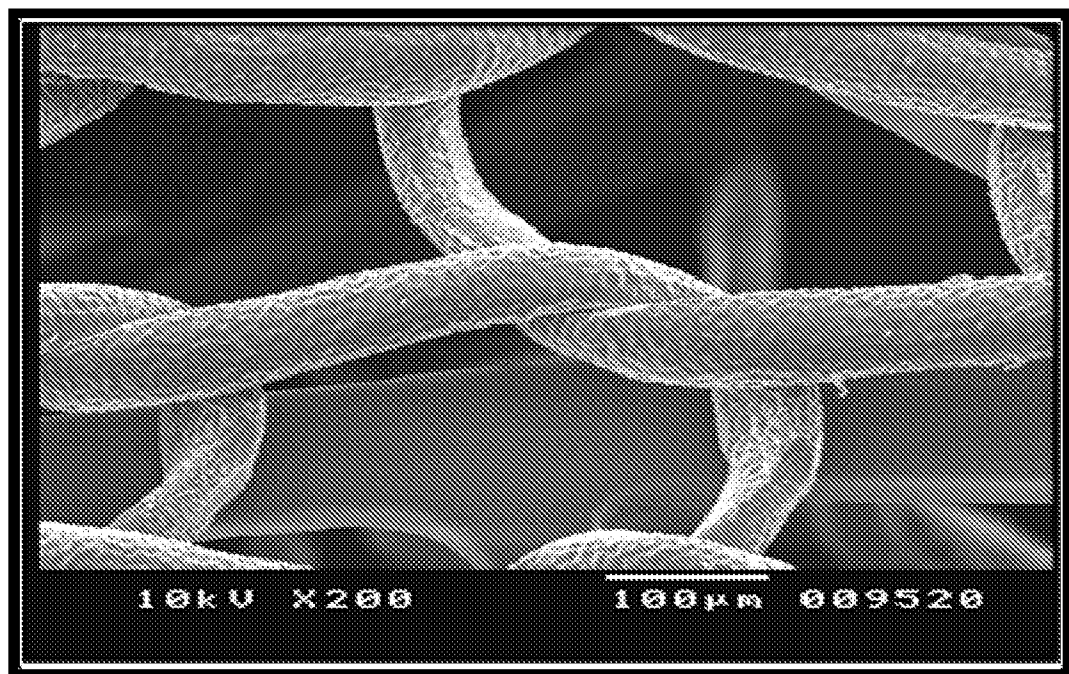


Figure 5

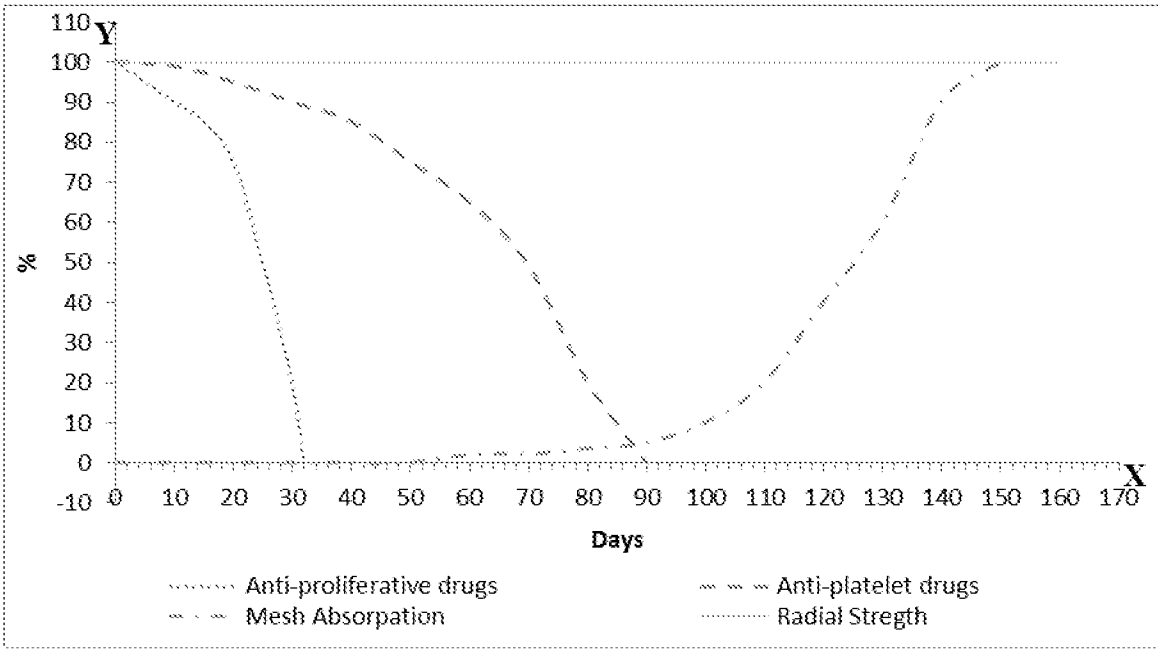


Figure 6