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(54) Title: MEDICAL DEVICES HAVING A MATRIX ADHERED THEREOF

(57) Abstract: Medical devices having a matrix comprising a pharmaceutically active agent, the matrix being adhered to a surface of the medical device via an adherence, are disclosed herein, as well as methods of utilizing the adherence to modulate a release of the pharmaceutically active agent

# MEDICAL DEVICES HAVING A MATRIX ADHERED THEREOF

## FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to a medical device and, more particularly, but not exclusively, to a medical device comprising a matrix bound to the surface thereof.

In the field of medicine, medical devices structures are often implanted in a living body for various purposes. Such devices include, for example, pacemakers, grafts, stents, wires, orthopedic implants, implantable diffusion pumps and heart valves, to list a few.

One problem associated with medical devices implanted in a living body is the biocompatibility thereof, and more particularly, the blood compatibility and the tissue compatibility of the implants. An implant is typically considered blood biocompatible when activation of coagulation factors (e.g., proteins and platelets) is only mildly induced thereby and tissue compatible when cell proliferation and chronic inflammation are not excessively induced thereby.

One strategy for minimizing undesirable biological reactions associated with implants is to coat the surface, which is frequently a metallic surface, with biomolecules that provide a substrate for the growth of a protective cell layer. Biomolecules used include, for example, growth factors, cell attachment proteins, and cell attachment peptides. A related strategy is to attach molecules or active pharmaceutical ingredients that reduce undesired biological reactions such as antithrombogenics, antiplatelet agents, anti-inflammatory agents, antimicrobials, and the like.

A number of approaches have been provided for attaching beneficial substances to surfaces.

One approach involves coating a metal surface with a polymer having a drug therein, e.g., bound thereto.

The drug may be trapped within the polymer, such that following implantation, the drug diffuses out of the polymer coating. In the CYPHER® stent (Cordis) the drug Sirolimus is trapped within a polymer layer coating the stent. Similarly, in the TAXUS® stent (Boston Scientific), the drug paclitaxel is trapped within a polymer layer coating the stent.

U.S. Patent No. 6,468,304 teaches the ionic bonding of a charged biologically active substance to a polymer film formed on a metallic surface by electropolymerization.

The Journal of Biomedical Materials Research, vol. 44, 1999, pp.121-129 teaches the cationic binding of heparin to polypyrrole on a metal surface.

WO 01/39813, EP Patent No. 1233795 and U.S. Patent Application No. 10/148,665 teach the attachment of active pharmaceutical ingredients to a surface using electropolymerizable monomers by covalent bonding of active pharmaceutical ingredients, or entities carrying active pharmaceutical ingredients, to electropolymerizable monomers prior to polymerization and by providing electropolymerizable monomers having functional groups which, subsequent to film production through electropolymerization, are used to covalently attach the active pharmaceutical ingredients or the entities carrying active pharmaceutical ingredients.

U.S. Patent Application No. 11/183,850 teaches the coating of conductive surfaces using electropolymerizable polymers, to which the active agent is attached by covalent and non-covalent bonds.

One drawback of polymer coatings is that defects (e.g. cracking, peeling) commonly appear in the polymer following implantation, which may cause thrombosis, coronary microembolism of polymer pieces and late inflammatory or neointimal reactions (*J. Invasive Cardiol.* 2007, 19:71-76). This problem is particularly acute in the case of stents, due to the stresses associated with stent expansion.

An alternative approach is to deposit a drug directly onto the surface.

WO 02/066092 teaches electrodepositing a hydrophobic molecule containing a diazonium moiety onto the surface of an endovascular device (e.g. a stainless steel surface) to obtain a functionalized surface, followed by passively depositing a lipophilic drug onto the functionalized surface, providing slow elution of the drug into a tissue when the device is brought into contact with the tissue.

WO 2006/008739 teaches conductive surfaces which have been modified by electrochemically attaching thereto functional substances to which an active agent or polymer having an active agent bound thereto can be bound, or by electrochemically attaching thereto the active agent or polymer having an active agent. The modified conductive surfaces disclosed in this patent application are prepared by utilizing

various electroattachable groups, such as, for example, a carboxylate, a sulfonate, a sulfate, a phosphonate and a phosphate.

WO 07/099137 teaches electrografting of a polymer film onto a conductive or semiconductive surface by reduction of a solution comprising a diazonium salt and a chain polymerizable monomer by applying a cathodic potential to the surface, and that such a polymer film may serve as an adhesion primer for a thicker polymer layer. WO 07/099137 further teaches that a macrostructure such as a polymer, protein, nucleic acid, polysaccharide, liposome or cell, which is functionalized by a chain polymerizable group, may also be electrografted according to the abovementioned procedure.

U.S. Patent No. 6,435,240 describes the modification of the surface of a carbon-containing material by using diazonium salts.

U.S. Patent No. 6,217,740 describes the modification of the surface of a carbon-containing material by reacting carboxylates via the Kolbe reaction.

Chemical Society Rev. 2005, 34:429-439 teaches the electrochemical reduction of aryl diazonium salts on carbon silicon or metals, as well as the use of electrodes electrografted with diazonium salts as sensors of biological compounds.

## SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a medical device comprising an object having a surface and a matrix comprising a pharmaceutically active agent, the matrix coating the surface and being adhered thereto via an adherence.

According to some embodiments of the invention, the adherence comprises an adhesive layer selected capable of strengthening adherence between the surface and the matrix such that peeling of the matrix from the surface with the adhesive layer is at least 10 % lower than peeling of the matrix from the surface without the adhesive layer when performing a comparative D-3359-02 ASTM test following incubation of each of the surfaces with the matrix in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C.

According to some embodiments of the invention, the adherence comprises an adhesive layer selected capable of strengthening adherence between the surface and the matrix such that the percentage of defective areas on the matrix coating the surface with the adhesive layer is at least 10 % lower than the percentage of defective areas on the matrix coating the surface without the adhesive layer when examining each of the surfaces by scanning electron microscopy at a magnification of x300 following incubation of the surfaces in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C, the areas being a field of about 0.9 mm by about 0.9 mm, and the defective areas being any of the areas in which a failure in the integrity of the matrix is visible.

According to some embodiments of the invention, the strengthening of the adherence modulates the release of the pharmaceutically active agent from the matrix when the matrix is subjected to physiological conditions.

According to some embodiments of the invention, the strengthening of the adherence reduces the release rate of the pharmaceutically active agent from the matrix when the matrix is subjected to physiological conditions.

According to an aspect of some embodiments of the invention there is provided a method for modulating a release of a pharmaceutically active agent from a matrix coating a surface, the method comprising strengthening an adherence between the matrix and the surface.

According to some embodiments of the invention, the surface is a surface of a medical device.

According to some embodiments of the invention, the strengthening of the adherence between the matrix and the surface is such that peeling of the matrix from the surface in the presence of the strengthening of the adherence is at least 10 % lower than peeling of the matrix from the surface without the strengthening of the adherence when performing a D-3359-02 ASTM test following incubation of each of the surfaces

with the matrix in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C.

According to some embodiments of the invention, the strengthening of the adherence between the matrix and the surface is such that the percentage of defective areas on the matrix coating the surface in the presence of the strengthening is at least 10 % lower than the percentage of defective areas on the matrix coating the surface without the strengthening of the adherence when examining each of the surfaces by scanning electron microscopy at a magnification of x300 following incubation of the surfaces in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C, the areas being a field of about 0.9 mm by about 0.9 mm, and the defective areas being any of the areas in which a failure in the integrity of the matrix is visible.

According to some embodiments of the invention, the strengthening of the adherence is effected by an adhesive layer between the surface and the matrix.

According to some embodiments of the invention, modulating a release comprises reducing the release rate of the pharmaceutically active agent when the matrix is subjected to physiological conditions.

According to some embodiments of the invention, the strengthening of the adherence reduces the release rate of the pharmaceutically active agent from the matrix when the matrix is subjected to physiological conditions.

According to some embodiments of the invention, the matrix remains physically intact for at least 30 days under physiological conditions.

According to some embodiments of the invention, the surface is a conductive surface.

According to some embodiments of the invention, the medical device is an implantable medical device.

According to some embodiments of the invention, the implantable medical device is a stent.

According to some embodiments of the invention, the adhesive layer comprises at least one moiety selected from the group consisting of an aryl moiety, an organosilane, a carboxylate, a sulfonate, a sulfate, a phosphonate and a phosphate.

According to some embodiments of the invention, the method further comprises attaching the at least one moiety to the surface to thereby obtain the adhesive layer.

According to some embodiments of the invention, the adhesive layer comprises at least one aryl moiety being electrochemically attached to the surface.

According to some embodiments of the invention, attaching the at least one aryl moiety comprises electrochemically attaching the at least one aryl moiety to the surface.

According to some embodiments of the invention:

(i) the adhesive layer comprises at least two aryl moieties being electrochemically attached to the surface, the aryl moieties being different from one another;

(ii) the aryl moiety is substituted by at least one functional group at a meta or ortho position of the aryl moiety, with respect to the position of the aryl moiety that is being electrochemically attached to the surface;

(iii) the aryl moiety is electrochemically attached to the surface via at least two positions thereof;

(iv) the aryl moiety comprises at least two aromatic groups fused to one another; and/or

(vi) the aryl moiety comprises at least two aromatic groups covalently linked to one another via a linker.

According to some embodiments of the invention, the aryl moiety comprises at least one functional group selected from the group consisting of alkyl, hydroxyalkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heteroalicyclic, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, halide, amine, amide, carbonyl, carboxy, thiocarboxy, ether, thioether, epoxide (oxirane), sulfonyl, sulfinyl, sulfonamide, nitro, nitrile, isonitrile, thiirane, aziridine, nitroso, hydrazine, carbamyl and thiocarbamyl.

According to some embodiments of the invention, the functional group is selected from the group consisting of alkyl, hydroxyalkyl, haloalkyl, alkoxy, carboxy and nitro.

According to some embodiments of the invention, the adhesive layer further comprises a polymer grafted onto the aryl moiety.

According to some embodiments of the invention, the polymer is selected from the group consisting of polyacrylic acid, polymethacrylic acid, polyacrylate ester, polymethacrylate ester and copolymers thereof.

According to some embodiments of the invention, the polymer is poly(methyl methacrylate).

According to some embodiments of the invention, the aryl moiety is a polymer comprising a plurality of aromatic groups being covalently linked to one another via a linker.

According to some embodiments of the invention, the plurality of aromatic groups comprises phenyl.

According to some embodiments of the invention, the polymer is polystyrene.

According to some embodiments of the invention, the aryl moiety comprises at least two aromatic groups covalently linked to one another via a linker, and the linker

comprises a plurality of alkoxy groups, each of the alkoxy groups being attached to one of the at least two aromatic groups.

According to some embodiments of the invention, the aryl moiety electrochemically attached to the surface comprises a phenyl attached to the surface via at least two positions thereof.

According to some embodiments of the invention, the two positions of the phenyl are at a meta position with respect to one another.

According to some embodiments of the invention, the aryl moiety comprises an anthracene.

According to some embodiments of the invention, the anthracene is attached to the surface via at least two positions thereof.

According to some embodiments of the invention, the conductive surface has at least two aryl moieties being electrochemically attached thereto, at least one of the aryl moieties comprising a hydrophilic functional group and at least one other of the aryl moieties comprising a hydrophobic functional group.

According to some embodiments of the invention, the matrix comprises a polymer.

According to some embodiments of the invention, the polymer of the matrix has a pharmaceutically active agent embedded therein.

According to some embodiments of the invention, the polymer of the matrix is selected from the group consisting of poly(ethylene-vinyl acetate), poly(butyl methacrylate), poly(styrene-isobutylene-styrene), poly-L-lactide and poly-ε-caprolactone, and mixtures and copolymers thereof.

According to some embodiments of the invention, the pharmaceutically active agent is selected from the group consisting of an anti-thrombogenic agent, an anti-platelet agent, an anti-coagulant, a growth factor, a statin, a toxin, an antimicrobial agent, an analgesic, an anti-metabolic agent, a vasoactive agent, a vasodilator agent, a prostaglandin, a hormone, a thrombin inhibitor, an enzyme, an oligonucleotide, a nucleic acid, an antisense, a protein, an antibody, an antigen, a vitamin, an immunoglobulin, a cytokine, a cardiovascular agent, endothelial cells, an anti-inflammatory agent, an antibiotic, a chemotherapeutic agent, an antioxidant, a phospholipid, an anti-proliferative agent, a corticosteroid, a heparin, a heparinoid, albumin, a gamma globulin, paclitaxel, hyaluronic acid and any combination thereof.

According to some embodiments of the invention, the pharmaceutically active agent is paclitaxel.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

## BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIGs. 1a-b are graphs presenting electrical current as a function of voltage during a cyclic voltammetric electrocoating of a stent with polydiazostyrene;

FIG. 2 is a graph presenting electrical current over time during a fixed potential electrocoating of a stent with polydiazostyrene;

FIG. 3 is a graph presenting the imaginary component of the impedance (y-axis) as a function of the real component of the impedance (x-axis) for bare stents and stents electrocoated with polydiazostyrene;

FIG. 4 is a graph presenting electrical current as a function of voltage during cyclic voltammetry with bare stents (blue) and stents electrocoated with polydiazostyrene (red);

FIGs. 5a-b are graphs presenting electrical current as a function of voltage during electrocoating of a stent with tetrakis[(4-diazophenoxy)methyl]methane;

FIGs. 6a-b are graphs presenting the imaginary component of the impedance (y-axis) as a function of the real component of the impedance (x-axis) for bare stents (red) and stents electrocoated with tetrakis[(4-diazophenoxy)methyl]methane (blue);

FIGs. 7a-b are graphs presenting electrical current as a function of voltage during cyclic voltammetry with bare stents (red) and stents electrocoated with tetrakis[(4-diazophenoxy)methyl]methane (blue);

FIGs. 8a-b are graphs presenting electrical current as a function of voltage during a cyclic voltammetric electrocoating of a stent with 1,8-didiazoanthracene;

FIG. 9 is a graph presenting the imaginary component of the impedance (y-axis) as a function of the real component of the impedance (x-axis) for bare stents (red) and stents electrocoated with 1,8-didiazoanthracene (blue);

FIG. 10 is a graph presenting electrical current as a function of voltage during cyclic voltammetry with bare stents (blue) and stents electrocoated with 1,8-didiazoanthracene (red);

FIGs. 11a-b are graphs presenting electrical current as a function of voltage during electrocoating of a stent with 3,5-didiazobenzoic acid;

FIGs. 12a-b are graphs presenting the imaginary component of the impedance (y-axis) as a function of the real component of the impedance (x-axis) for bare stents (red) and stents electrocoated with 3,5-didiazobenzoic acid (blue);

FIGs. 13a-b are graphs presenting electrical current as a function of voltage during cyclic voltammetry with bare stents (red in Figure 13a, blue in Figure 13b) and stents electrocoated with 3,5-didiazobenzoic acid (blue in Figure 13a, red in Figure 13b);

FIG. 14 is a graph presenting the imaginary component of the impedance (y-axis) as a function of the real component of the impedance (x-axis) for a bare metal stent (1), a stent electrocoated with 4-(2-bromoethyl)phenyl diazonium (2), a non-electrocoated stent subjected to PMMA grafting solution (3) and a stent electrocoated with 4-(2-bromoethyl)phenyl diazonium and then subjected to PMMA grafting solution;

FIG. 15 is a graph presenting the integration of electrical current over time for the cyclic voltammetric electrocoating of stents with various proportions of DS04 (4-(2-hydroxyethyl)phenyl diazonium) and DS06 (4-dodecyloxyphenyl diazonium);

FIG. 16 is a graph presenting the imaginary component of the impedance (y-axis) as a function of the real component of the impedance (x-axis) for bare stents and stents electrocoated with various proportions of DS04 (4-(2-hydroxyethyl)phenyl diazonium) and DS06 (4-dodecyloxyphenyl diazonium);

FIG. 17 is a graph presenting electrical current as a function of voltage during cyclic voltammetry with bare stents and stents electrocoated with various proportions of DS04 (4-(2-hydroxyethyl)phenyl diazonium) and DS06 (4-dodecyloxyphenyl diazonium);

FIGs. 18a-b are photographs showing all of a non-electrocoated stent at low magnification (Figure 18a) and a maximum stress area of the same stent at high magnification (Figure 18b), following spray-coating of the stent with PEVA:PBMA:paclitaxel;

FIGs. 19a-c are photographs showing a non-electrocoated stent coated with PEVA:PBMA:paclitaxel, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 20a-c are photographs showing a stent electrocoated with 4-dodecyloxyphenyl diazonium and coated with PEVA:PBMA:paclitaxel, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 21a-d are scanning electron micrographs showing a non-electrocoated stent (Figures 21a-b) and a stent electrocoated with 4-dodecyloxyphenyl diazonium (Figures 21c-d) which have been coated with PEVA:PBMA:paclitaxel, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 22a-b are scanning electron micrographs showing a non-electrocoated stent coated with PEVA:PBMA:paclitaxel, followed by incubation for 12 days in phosphate buffer with 0.3 % SDS, pH 7, at 60 °C;

FIGs. 23a-b are scanning electron micrographs showing a stent electrocoated with 4-(2-bromoethyl)phenyl diazonium, grafted with PMMA and coated with PEVA:PBMA:paclitaxel, followed by incubation for 12 days in phosphate buffer with 0.3 % SDS, pH 7, at 60 °C;

FIGs. 24a-b are scanning electron micrographs showing a non-electrocoated stent coated with 5 μm of SIBS:paclitaxel, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 25a-b are scanning electron micrographs showing a stent electrocoated with 4-dodecyloxyphenyl diazonium and coated with 5 μm of SIBS:paclitaxel, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 26a-b are scanning electron micrographs showing a non-electrocoated stent coated with 0.5 μm of SIBS:paclitaxel, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 27a-b are scanning electron micrographs showing a stent electrocoated with 4-dodecyloxyphenyl diazonium and coated with 0.5 μm of SIBS:paclitaxel, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs 28a-b are scanning electron micrographs showing a stent coated with PEVA:PBMA:paclitaxel and a PBMA top layer prior to incubation;

FIGs. 29a-b are scanning electron micrographs showing a non-electrocoated stent coated with PEVA:PBMA:paclitaxel and a PBMA top layer, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 30a-b are scanning electron micrographs showing a non-electrocoated stent coated with PEVA:PBMA:paclitaxel and a PBMA top layer, followed by incubation for 30 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 31a-b are scanning electron micrographs showing a stent electrocoated with 4-dodecyloxyphenyl diazonium and coated with PEVA:PBMA:paclitaxel and a PBMA top layer, followed by incubation for 3 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 32a-b are scanning electron micrographs showing a stent electrocoated with 4-dodecyloxyphenyl diazonium and coated with PEVA:PBMA:paclitaxel and a PBMA top layer, followed by incubation for 30 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 60 °C;

FIGs. 33a-c are photographs showing a non-electrocoated stent coated with RESOMER® LC 703 S, followed by incubation for 30 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 37 °C;

FIGs. 34a-c are photographs showing a stent electrocoated with 4-dodecyloxyphenyl diazonium and coated with RESOMER® LC 703 S, followed by incubation for 30 days in phosphate buffer with 0.3 % SDS, pH 7.4, at 37 °C;

FIGs. 35a-b are graphs presenting the amount in micrograms (Figure 35a) and percentage (Figure 35b) of paclitaxel released during incubation in phosphate buffer with 0.3 % SDS (pH 7.4, 37 °C) from stents electrocoated with dodecyloxyphenyl diazonium and coated with a thick (10 μm, 25 % paclitaxel) or thin (0.5 μm, 40 % paclitaxel) coating of SIBS:paclitaxel;

FIG. 36 is a graph presenting the percentage of paclitaxel released during incubation in phosphate buffer with 0.3 % SDS (pH 7.4, 37 °C) from stents coated with a 0.5 μm coating of SIBS:paclitaxel, both with and without pretreatment by electrocoating with dodecyloxyphenyl diazonium (each data point represents the average for 5 stents);

FIGs. 37a-b are graphs presenting the percentage of paclitaxel released during incubation in phosphate buffer with 0.3 % SDS (pH 7.4, 37 °C) from non-sterilized (Figure 37a) and sterilized (Figure 37b) stents coated with PEVA:PBMA:paclitaxel, both with and without pretreatment by electrocoating with dodecyloxyphenyl diazonium;

FIG. 38 is a graph presenting the percentage of paclitaxel released during incubation in phosphate buffer with 0.3 % SDS (pH 7.4, 37 °C) from slow release (SR) and fast release (FR) model stents comprising a PEVA:PBMA:paclitaxel coating on bare metal stents, stents electrocoated with 4-(2-bromoethyl)phenyl diazonium and stents electrocoated with 4-(2-bromoethyl)phenyl diazonium with PMMA grafting;

FIGs. 39a-c are photographs showing a non-electrocoated stent (Figure 39a), a stent electrocoated with 90 % 4-(2-hydroxyethyl)phenyl diazonium and 10 % 4-dodecyloxyphenyl diazonium (Figure 39b) and a stent electrocoated with 90 % 4-

dodecyloxyphenyl diazonium and 10 % 4-(2-hydroxyethyl)phenyl diazonium (Figure 39c), which were coated with PEVA:PBMA:paclitaxel and incubated for 3 days in phosphate buffer with 0.3 % SDS at 60 °C;

FIGs. 40a-c are photographs showing a non-electrocoated stent (Figure 40a), a stent electrocoated with 90 % 4-(2-hydroxyethyl)phenyl diazonium and 10 % 4-dodecyloxyphenyl diazonium (Figure 40b) and a stent electrocoated with 90 % 4-dodecyloxyphenyl diazonium and 10 % 4-(2-hydroxyethyl)phenyl diazonium (Figure 40c) which were coated with PEVA:PBMA:paclitaxel and incubated for 30 days in phosphate buffer with 0.3 % SDS at 60 °C;

FIGs. 41a-b are photographs showing stents electrocoated with 4-dodecyloxyphenyl diazonium, incubated for 30 days in phosphate buffer with 0.3 % SDS at 37 °C, coated with PEVA:PBMA:paclitaxel and further incubated for 3 days (Figure 41a) or 30 days (Figure 41b) at 60 °C;

FIGs. 42a-b are photographs showing non-electrocoated stents incubated for 30 days in phosphate buffer with 0.3 % SDS at 37 °C, coated with PEVA:PBMA:paclitaxel and further incubated for 3 days (Figure 42a) or 30 days (Figure 42b) at 60 °C.

## DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to a medical device and, more particularly, but not exclusively, to a medical device comprising a matrix bound to the surface thereof by an adherence, which can be utilized, for example, to modulate a release of a pharmaceutically active agent from the matrix, and can therefore be beneficially used in a variety of medical applications.

The present inventors have now designed a novel methodology for modulating a release of a pharmaceutically active agent from a matrix coating a device, which is particularly beneficial for implantable medical devices. This methodology is based on strengthening an adherence between the matrix and the surface of the medical device, for example, by using an adhesive layer.

As described in detail in the Examples section that follows, the methodology presented herein is optionally effected by attaching an aryl moiety to the surface of a medical device, for example, by reduction of selected diazonium salts on the surface by application of cathodic potential, resulting in a chemical bond between the metal

and the aryl carbon formerly attached to the diazonium moiety. As shown in the Examples section, the bond formed in this reaction is strong enough to withstand ultrasonication in acetonitrile for 15 minutes, and remains intact following incubation for 30 days and more under physiological conditions (e.g., pH 7.4, at 37 °C). The aryl moieties were found to be excellent adhesion primers for coatings applied onto the aryl moiety layer. The inventors have also developed novel aryl diazonium compounds which are particularly useful for attaching a coating thereto.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Referring now to the drawings, Figures 1 to 4 present electrochemical data indicating that poly(p-diazostyrene) was successfully electroattached to stainless steel stents.

As used herein, the term "electroattach", and grammatical derivatives thereof, describes the electrochemical attachment of an aryl moiety (or aryl moieties) to a conductive surface. The electroattached aryl moiety (or aryl moieties) may form a continuous layer on the surface. Formation of such a layer is also referred to herein as "electrocoating".

Similarly, Figures 5-7 present electrochemical data indicating that tetrakis[(4-diazophenoxy)methyl]methane was successfully electroattached to stents, Figures 9-10 demonstrate electrocoating with 1,8-didiazoanthracene, and Figures 11-13 demonstrate electrocoating with 3,5-didiazobenzoic acid.

Figure 14 presents electrochemical data indicating both the successful electroattachment of 4-(2-bromoethyl)phenyl diazonium to a stent, as well as the successful grafting of PMMA onto the electrochemically attached 4-(2-bromoethyl)phenyl moieties.

Figures 15-17 present electrochemical data for stents electroattached to various proportions of 4-dodecyloxyphenyl diazonium and 4-(2-hydroxyethyl)phenyl diazonium. The results presented therein indicate successful electrocoating. The results further indicate that the electrochemical properties of the stent surface depend on the proportion of the two diazonium compounds used, and thus the properties of the

stent may be modulated by changing the proportions of diazonium compounds used for electrocoating.

Figures 18-35 are photographs and scanning electron micrographs which demonstrate that polymer-based coatings on electrocoated stents are far more stable to incubation than are polymer-based coatings on non-electrocoated stents.

Figures 36-38 present data indicating that electrocoating stents alters the kinetics of the release of paclitaxel from polymer-based coatings on the stents.

Figures 39-40 are photographs showing that polymer-based coatings on stents electrocoated with mixtures of 4-dodecyloxyphenyl diazonium and 4-(2-hydroxyethyl)phenyl are more stable to incubation than polymer-based coatings on non-electrocoated stents. The results further indicate that the degree of stabilization depends on the proportion of the two diazonium salts used to electrocoat the stents.

Figures 41-42 are photographs showing that electrocoated stents which have been incubated under physiological conditions for 30 days before being coated with a polymer retain the ability to preserve the integrity of the polymer-based coating. These results indicate that the aryl moiety layer remains intact on the stent surface even after 30 days of incubation at physiological conditions.

It is expected that during the life of a patent maturing from this application many relevant medical devices, coatings and pharmaceutically active agents will be developed and the scope of these terms is intended to include all such new technologies *a priori*.

As used herein the term "about" refers to ± 10 %.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to". These terms encompass the terms "consisting of" and "consisting essentially of".

The phrase "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicated number "to" a second indicated number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

According to one aspect of the embodiments of the present invention there is provided a medical device comprising an object having a surface and a matrix comprising a pharmaceutically active agent, the matrix coating the surface and being adhered to the surface via an adherence.

As used herein, the term "adherence" encompasses any interaction which causes the matrix to adhere to the surface, as well as any material which interacts with the matrix and/or surface so as to cause the matrix to adhere to the surface. The term "adherence" includes combinations of such interactions and/or materials.

The medical device is optionally an implantable medical device, i.e. a medical device suitable for implantation in a subject. Exemplary implantable medical devices include a pacemaker, a graft, a stent, a wire, an orthopedic implant, an implantable diffusion pump, an injection port and a heart valve. In an exemplary embodiment, the device is a stent.

In an exemplary embodiment of the present invention, the surface of the medical device is a conductive surface.

As used herein, the phrase "conductive surface" encompasses the surface of electrically conductive and electrically semiconductive substances. Exemplary conductive surfaces comprise one or more metals or an alloy thereof. The metal may be, for example, iron, stainless steel, titanium, nickel, tantalum, platinum, gold, silver, copper and any combination thereof. In an exemplary embodiment, the conductive surface comprises stainless steel.

As used herein, the term "matrix" describes a solid or semi-solid (e.g., gel-like) substance having an agent (e.g. a pharmaceutically active agent) bound thereto. The agent may be bound by a molecular interaction with the solid or semi-solid substance. Thus, the agent can be bound to the solid or semi-solid substance via a covalent, electrostatic (ionic), hydrophobic, van der Waals and hydrogen bonding chemical interaction. Alternatively, the agent may be physically bound to the matrix by, for example, being embedded in the solid or semi-solid substance of the matrix.

The matrix is optionally from 0.1 μm to 100 μm thick, and optionally from 0.5 μm to 10 μm thick.

The matrix may comprise a plurality of layers comprising different ingredients. Some of the layers may comprise at least one pharmaceutically active agent, as described herein, while some of the layers may lack a pharmaceutically active agent. For example, a matrix may consist of a layer comprising a pharmaceutically active agent beneath a layer (i.e. a "top coat") which does not comprise a pharmaceutically active agent.

Exemplary pharmaceutically active agents for use in the context of any of the embodiments described herein include, without limitation, an anti-thrombogenic agent, an anti-platelet agent, an anti-coagulant, a growth factor, a statin, a toxin, an antimicrobial agent, an analgesic, an anti-metabolic agent, a vasoactive agent, a vasodilator agent, a prostaglandin, a hormone, a thrombin inhibitor, an enzyme, an

oligonucleotide, a nucleic acid, an antisense, a protein, an antibody, an antigen, a vitamin, an immunoglobulin, a cytokine, a cardiovascular agent, endothelial cells, an anti-inflammatory agent, an antibiotic, a chemotherapeutic agent, an antioxidant, a phospholipid, an anti-proliferative agent, a corticosteroid, a heparin, a heparinoid, albumin, a gamma globulin, paclitaxel, hyaluronic acid and any combination thereof.

An anti-proliferative agent is particularly suitable for certain medical devices (e.g. stents). Paclitaxel is an exemplary anti-proliferative agent.

According to an optional embodiment of the present invention, the solid or gel-like substance in the matrix comprises a polymeric material. Exemplary polymers include poly(ethylene-vinyl acetate) (a copolymer of ethylene and vinyl acetate, also referred to herein as PEVA), poly(butyl methacrylate) (PBMA), poly(styrene-isobutylene-styrene) (SIBS), poly-L-lactide and poly-ε-caprolactone, as well as mixtures and copolymers thereof. The polymer may be, for example, a mixture of PEVA and PBMA, or SIBS, or a copolymer of poly-L-lactide and poly-ε-caprolactone.

As used herein, the phrases "polymeric material" and "polymer-based" describe a material that is made essentially from a polymer.

Optionally, the matrix polymer is biodegradable. Exemplary biodegradable polymers include poly-L-lactide and poly-ε-caprolactone, as well as mixtures and copolymers thereof.

According to preferred embodiments of the present invention, the adherence comprises an adhesive layer.

According to an exemplary embodiment of the present invention, the adhesive layer is selected capable of strengthening an adherence between the surface and the matrix such that peeling of the matrix from the surface with the adhesive layer is at least 10 % lower, optionally at least 20 % lower, optionally at least 30 % lower, optionally at least 50 % lower, optionally at least 75 % lower, optionally at least 90 % lower, and optionally at least 95 % lower, than peeling of the matrix from the surface without the adhesive layer when performing a D-3359-02 comparative test following incubation of each of the surfaces with the matrix in an aqueous solution of a phosphate buffer (e.g. about 0.1 M phosphate) comprising 0.3 % (by weight) sodium dodecyl sulfate (SDS), at a pH of 7.4 and a temperature of 37 °C. Optionally, the incubation is for 3 days. Alternatively, the incubation may be for a longer or shorter period, e.g., 1 day, 15 days or 30 days.

If the medical device is not suitable for performing the abovementioned test, the test may be performed on a suitable surface having an identical composition as the surface of the medical device.

According to a further exemplary embodiment of the present invention, the adhesive layer is selected capable of strengthening an adherence between the surface and the matrix such that the percentage of defective areas on the matrix coating the surface with the adhesive layer is at least 10 % lower, optionally at least 20 % lower, optionally at least 30 %, optionally at least 50 % lower, optionally at least 75 %, optionally at least 90 % lower, optionally at least 95 % lower and optionally at least 98 % lower than the percentage of defective areas on the matrix coating the surface without the adhesive layer when examining each of the surfaces by scanning electron microscopy at a magnification of x300 following incubation of the surfaces in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C, each of the areas being a field of about 0.9 mm by about 0.9 mm, and the defective areas being defined as any of the areas in which a failure in the integrity of the matrix is visible, under the above recited magnification.

As used herein, the phrase "failure in the integrity of the matrix" refers to the presence of any gap or tear in the matrix, such as a crack, or partial or complete detachment of a portion of the matrix so as to reveal an underlying portion of the matrix and/or the surface. Optionally, a failure in the integrity of the matrix is defined as any defect from the group consisting of cracking, flaking, delamination and peeling, as these terms are defined in the art.

According to an exemplary embodiment of the present invention, the strengthening of the adherence modulates the release of the pharmaceutically active agent from the matrix when the matrix is subjected to physiological conditions. The physiological conditions may be identical to the conditions described hereinabove for the phosphate buffer at 37 °C. Alternatively, any other conditions used in the art to model physiological conditions may be used.

As used herein, the phrase "modulates the release" refers to causing any change in the release profile, including, without limitation, a change in the kinetics of release, such is a change in the rate of release and/or a change in the time-dependence of the rate of release, a change in the total amount released, and/or a change in the location of release (e.g. causing a more localized or less localized release). The

change in the rate and/or total amount (either a decrease or an increase) may be by at least 10 %, optionally at least 20 %, optionally at least 30 %, optionally at least 50 %, optionally at least 75 % and optionally at least 90 %.

Optionally, the strengthening of the adherence reduces the release rate of the pharmaceutically active agent from the matrix when the matrix is subjected to physiological conditions.

As used herein, the phrase "reduces the rate" refers to both a reduction in the release rate for the duration of the release as well as a reduction in the release rate for a limited period (e.g. 1 day, 2 days, 3 days, 5 days, 10 days or 20 days). For example, the release rate may optionally be reduced only during the period immediately following the initial exposure of the device to physiological conditions, thereby reducing or eliminating the "burst" of release that is characteristic of many release systems, the release rate being unchanged or even increased following the initial period of a reduced release rate.

According to further exemplary embodiments, the matrix remains intact for at least 3, 6, 10, 20 or even 30 days under physiological conditions. Optionally, the abovementioned aqueous solution at 37 °C is used to reproduce physiological conditions. Alternatively, the matrix remains intact for at least 3, 6, 10, 20 or 30 days under any other conditions used in the art to reproduce physiological conditions.

According to an optional embodiment of the present invention, the adhesive layer comprises at least one moiety selected from the group consisting of an aryl moiety, an organosilane, a carboxylate, a sulfonate, a sulfate, a phosphonate and a phosphate.

The attachment to a conductive surface of moieties selected from the group consisting of an organosilane, a carboxylate, a sulfonate, a sulfate, a phosphonate and a phosphate, and exemplary moieties selected from this group, are described in Patent Application No. WO 2006/008739.

As used herein, the phrase "aryl moiety" refers to a chemical moiety comprising at least one aromatic group. Optionally, the aryl moiety further comprises one or more substituents attached to the aromatic group. The substituent may be an end group or a linking group, as defined herein.

As used herein, the phrase "aromatic group" encompasses aryl and heteroaryl, as these terms are defined herein. In exemplary embodiments, the aromatic group is phenyl.

Herein throughout, the phrase "end group" describes a group (a substituent) that is attached to a single moiety in the compound via one atom thereof.

The phrase "linking group" describes a group (a substituent) that is attached to two or more moieties in the compound.

For example, a linking group in an aryl moiety may be attached to two or more moieties comprised by the aryl moiety (e.g. two or more aromatic groups and/or two or more atoms of a single aromatic group). A linking group may also link the aryl moiety to one or more other moieties.

A substituent attached to an aromatic group may comprise at least one functional group which is an end group or a linking group. Optionally, the substituent consists of the functional group.

As used herein, the phrase "functional group" describes a chemical group which confers a functionality (e.g. a chemical and/or physical property) upon a compound comprising that group. Exemplary functional groups include alkyl, hydroxyalkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heteroalicyclic, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, halide, amine, amide, carbonyl, carboxy, thiocarboxy, ether, thioether, epoxide (oxirane), sulfonyl, sulfinyl, sulfonamide, nitro, nitrile, isonitrile, thiirane, aziridine, nitroso, hydrazine, carbamyl and thiocarbamyl. In an exemplary embodiment, the functional group is selected from the group consisting of alkyl, hydroxyalkyl, haloalkyl, alkoxy, carboxy and nitro.

According to an optional embodiment of the present invention, the surface has at least two aryl moieties being electrochemically attached thereto, at least one of the aryl moieties comprising a hydrophilic functional group and at least one other of the aryl moieties comprising a hydrophobic functional group. Dodecyloxy is an exemplary hydrophobic functional group. 2-hydroxyethyl is an exemplary hydrophilic functional group. 4-dodecyloxyphenyl is an exemplary aryl moiety comprising a hydrophobic functional group. 4-(2-hydroxyethyl)phenyl is an exemplary aryl moiety comprising a hydrophilic functional group.

As used herein, the phrases "electrochemically attached" and "electrochemically attaching" describe a moiety attached to a substance (e.g. a conductive surface) by a chemical reaction that is induced by an application of an electric potential and/or current. Preferably, the chemical reaction is a redox reaction. Optionally, the application of the electric potential and/or current is by connecting the conductive surface to a voltage source and/or current source. The moiety may be attached by one or more of any type of molecular interaction (e.g. a covalent bond, a hydrogen bond, a hydrophobic interaction, an ionic bond, a van der Waals interaction).

The term "alkyl" describes a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms. Whenever a numerical range; *e.g.*, "1-20", is stated herein, it implies that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms. More preferably, the alkyl is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, unless otherwise indicated, the alkyl is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. Substituted alkyl may have one or more substituents, whereby each substituent group can independently be, for example, hydroxyalkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, amine, halide, sulfonate, sulfoxide, phosphonate, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, azo, sulfonamide, carboxy, thiocarbamate, urea, thiourea, carbamate, amide, guanyl, guanidine and hydrazine.

The alkyl group can be an end group, as this phrase is defined hereinabove, wherein it is attached to a single adjacent atom, or a linking group, as this phrase is defined hereinabove, which connects two or more moieties.

The term "cycloalkyl" describes an all-carbon monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of carbon atoms) group where one or more of the rings does not have a completely conjugated pi-electron system. The cycloalkyl group may be substituted or unsubstituted. Substituted cycloalkyl may have one or more substituents, whereby each substituent group can independently be, for example, hydroxyalkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, amine, halide, sulfonate, sulfoxide, phosphonate, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, azo, sulfonamide, carboxy,

thiocarbamate, urea, thiourea, carbamate, amide, guanyl, guanidine and hydrazine. The cycloalkyl group can be an end group, as this phrase is defined hereinabove, wherein it is attached to a single adjacent atom, or a linking group, as this phrase is defined hereinabove, connecting two or more moieties.

The term "aryl" describes an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. The aryl group may be substituted or unsubstituted. Substituted aryl may have one or more substituents, whereby each substituent group can independently be, for example, hydroxyalkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, amine, halide, sulfonate, sulfoxide, phosphonate, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, azo, sulfonamide, carboxy, thiocarbamate, urea, thiourea, carbamate, amide, guanyl, guanidine and hydrazine. The aryl group can be an end group, as this term is defined hereinabove, wherein it is attached to a single adjacent atom, or a linking group, as this term is defined hereinabove, connecting two or more moieties.

The term "heteroaryl" describes a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms, such as, for example, nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups include pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline and purine. The heteroaryl group may be substituted or unsubstituted. Substituted heteroaryl may have one or more substituents, whereby each substituent group can independently be, for example, hydroxyalkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, amine, halide, sulfonate, sulfoxide, phosphonate, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, azo, sulfonamide, C-carboxy, O-carboxyl, N-thiocarbamate, O-thiocarbamate, urea, thiourea, O-carbamate, N-carbamate, C-amide, N-amide, guanyl, guanidine and hydrazine. The heteroaryl group can be an end group, as this phrase is defined hereinabove, where it is attached to a single adjacent atom, or a linking group, as this phrase is defined hereinabove, connecting two or more moieties. Representative examples are pyridine, pyrrole, oxazole, indole, purine and the like.

As used herein, the term "amine" describes both a –NRxRy group and a –NRx- group, wherein Rx and Ry are each independently hydrogen, alkyl, cycloalkyl, or aryl, as these terms are defined herein.

The amine group can therefore be a primary amine, where both Rx and Ry are hydrogen, a secondary amine, where Rx is hydrogen and Ry is alkyl, cycloalkyl or aryl, or a tertiary amine, where each of Rx and Ry is independently alkyl, cycloalkyl or aryl.

The term "organosilane" as used herein describes an organic compound that has at least one silicon atom and at least one carbon atom. Preferably, the organosilane is of a general formula:

$$X_mSiR_{(4-m)}$$

wherein: m is an integer from 1 to 3; X is selected from the group consisting of halide, alkoxy and thioalkoxy; and R is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl or aryl.

The term "carboxylate" refers to a substance having or terminating with a –C(=O)Y group, where Y can be hydrogen, alkyl, cycloalkyl, aryl, hydroxyl, thiohydroxyl, halide, azide, alkoxide, thioalkoxide. This term therefore encompasses aldehydes, ketones, esters, acyl halides, amides, carboxylic acids and thio derivatives thereof.

The term "phosphonate" refers to a substance having or terminating with an -O-P(=O)$(ORx)_2$ group, with Rx as defined hereinabove, or to an -O-P(=O)(ORx)- group per se.

The term "phosphate" refers to a substance having or terminating with a P(=O)$(ORx)_2$ group, with Rx as defined hereinabove, or to a - P(=O)$(ORx)_2$ group per-se.

The term "halide" and "halo" describes fluorine, chlorine, bromine or iodine.

The term "haloalkyl" describes an alkyl group as defined above, further substituted by one or more halide(s).

The term "hydroxyalkyl" describes an alkyl group as defined above, further substituted by one or more hydroxy groups.

The term "aminoalkyl" describes an alkyl group as defined above, further substituted by one or more amines.

The term "sulfate" describes a substance having or terminating with a -$OS(=O)_2ORx$ group or to a $-O-S(=O)_2-ORx$ end group or $-O-S(=O)_2-O-$ linking group, as these phrases are defined hereinabove, where $R_X$ is as defined hereinabove.

The term "thiosulfate" describes a –O–S(=S)(=O)–ORx end group or a –O–S(=S)(=O)–O– linking group, as these phrases are defined hereinabove, where Rx is as defined hereinabove.

The term "sulfite" describes an –O–S(=O)–O–Rx end group or a -O-S(=O)-O– group linking group, as these phrases are defined hereinabove, where $R_X$ is as defined hereinabove.

The term "thiosulfite" describes a –O–S(=S)–O–Rx end group or an –O–S(=S)–O– group linking group, as these phrases are defined hereinabove, where $R_X$ is as defined hereinabove.

The term "sulfinate" describes a –S(=O)-ORx end group or an –S(=O)–O– group linking group, as these phrases are defined hereinabove, where $R_X$ is as defined hereinabove.

The term "sulfoxide" or "sulfinyl" describes a –S(=O) Rx end group or an –S(=O)– linking group, as these phrases are defined hereinabove, where Rx is as defined hereinabove.

The term "sulfonyl" describes a $-S(=O)_2$-Rx end group or an $-S(=O)_2-$ linking group, as these phrases are defined hereinabove, where Rx is as defined herein.

The term "sulfonate" refers to a substance having or terminating with a sulfonyl group, as this term is defined hereinabove, or to a sulfonyl group per se.

The term "sulfonamide", as used herein, encompasses both S-sulfonamides and N-sulfonamides.

The term "S-sulfonamide" describes a $-S(=O)_2-NRxR_Y$ end group or a $-S(=O)_2-NRx-$ linking group, as these phrases are defined hereinabove, with Rx and $R_Y$ as defined herein.

The term "N-sulfonamide" describes an $RxS(=O)_2-NR_Y-$ end group or a $-S(=O)_2-NRx-$ linking group, as these phrases are defined hereinabove, where Rx and $R_Y$ are as defined herein.

The term "disulfide" refers to a –S–SRx end group or a –S-S- linking group, as these phrases are defined hereinabove, where Rx is as defined herein.

The term "carbonyl" or "carbonate" as used herein, describes a -C(=O)-Rx end group or a -C(=O)- linking group, as these phrases are defined hereinabove, with Rx as defined herein.

The term "aldehyde" as used herein, describes a carbonyl end group wherein Rx is hydrogen.

The term "thiocarbonyl" as used herein, describes a -C(=S)- Rx end group or a -C(=S)- linking group, as these phrases are defined hereinabove, with Rx as defined herein.

The term "oxo", as used herein, describes an =O end group.

The term "oxime" describes a =N–OH end group or a =N-O- linking group, as these phrases are defined hereinabove.

The terms "hydroxy" and "hydroxyl" describe a –OH group.

The term "alkoxy" describes both an -O-alkyl and an -O-cycloalkyl group, as defined herein.

The term "aryloxy" describes both an -O-aryl and an -O-heteroaryl group, as defined herein.

The term "thiohydroxy" describes a -SH group.

The term "thioalkoxy" describes both a -S-alkyl group, and a -S-cycloalkyl group, as defined herein.

The term "thioaryloxy" describes both a -S-aryl and a -S-heteroaryl group, as defined herein.

The term "ether" describes groups in which a carbon atom in an alkyl, cycloalkyl, aryl or heteroaryl is attached to an alkoxy or aryloxy group.

The term "thioether" describes groups in which a carbon atom in an alkyl, cycloalkyl, aryl or heteroaryl is attached to a thioalkoxy or thioaryloxy group.

The terms "cyano" and "nitrile" describe a -C≡N group.

The term "isonitrile" describes a -N≡C group.

The term "isocyanate" describes an –N=C=O group.

The term "nitro" describes an $-NO_2$ group.

The term "acyl halide" describes a –(C=O) Rz group wherein Rz is halide, as defined hereinabove.

The term "azo" or "diazo" describes an -N=NR' end group or an -N=N- linking group, as these phrases are defined hereinabove, with R' as defined hereinabove.

The term "peroxo" describes an –O–ORx end group or an –O–O- linking group, as these phrases are defined hereinabove, with Rx as defined hereinabove.

The terms "carboxy" and "carboxyl", as used herein, encompasses both C-carboxy and O-carboxy groups.

The term "C-carboxy" describes a -C(=O)-ORx end group or a -C(=O)-O- linking group, as these phrases are defined hereinabove, where Rx is as defined herein.

The term "O-carboxy" describes a -OC(=O)-Rx end group or a -OC(=O)- linking group, as these phrases are defined hereinabove, where R' is as defined herein.

The term "thiocarboxy", as used herein, encompasses both C-thiocarboxy and O-thiocarboxy groups.

The term "C-thiocarboxy" describes a -C(=S)-ORx end group or a -C(=S)-O- linking group, as these phrases are defined hereinabove, where Rx is as defined herein.

The term "O-thiocarboxy" describes a -OC(=S) Rx end group or a -OC(=S)- linking group, as these phrases are defined hereinabove, where Rx is as defined herein.

The term "urea" describes a -NRxC(=O)-NRyRw end group or a -$NR_XC(=O)$-$NR_Y$- linking group, as these phrases are defined hereinabove, where Rx and Ry are as defined herein and Rw is as defined herein for Rx and Ry.

The term "thiourea" describes a -NRx-C(=S)-NRyRw end group or a -NRx-C(=S)-NRy- linking group, with Rx, Ry and Ry as defined herein.

The term "amide", as used herein, encompasses both C-amides and N-amides.

The term "C-amide" describes a -C(=O)-NRxRy end group or a -C(=O)-NRx- linking group, as these phrases are defined hereinabove, where Rx and Ry are as defined herein.

The term "N-amide" describes a RxC(=O)-NRy- end group or a RxC(=O)-N- linking group, as these phrases are defined hereinabove, where Rx and Ry are as defined herein.

The term "carbamyl" or "carbamate", as used herein, encompasses both N-carbamates and O-carbamates.

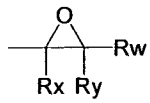
The term "N-carbamate" describes an RyOC(=O)-NRx- end group or a -OC(=O)-NRx- linking group, as these phrases are defined hereinabove, with Rx and Ry as defined herein.

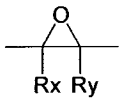
The term "O-carbamate" describes an -OC(=O)-NRxRy end group or an -OC(=O)-NRx- linking group, as these phrases are defined hereinabove, with Rx and Ry as defined herein.

The term "thiocarbamyl" or "thiocarbamate", as used herein, encompasses both O-thiocarbamates and N-thiocarbamates.

The term "O-thiocarbamate" describes a -OC(=S)-NRxRy end group or a -OC(=S)-NRx- linking group, as these phrases are defined hereinabove, with Rx and Ry as defined herein.

The term "N-thiocarbamate" describes an RyOC(=S)NRx- end group or a -OC(=S)NRx- linking group, as these phrases are defined hereinabove, with Rx and Ry as defined herein.

As used herein, the term "epoxide" describes a 

end group or a 

linking group, as these phrases are defined hereinabove, where Rx, Ry and Rw are as defined herein.

As used herein, the term "thiirane" describes a group that is equivalent to an epoxide, wherein the oxygen atom of the epoxide is replaced with a sulfur atom.

As used herein, the term "aziridine" describes a group that is equivalent to an epoxide, wherein the oxygen atom of the epoxide is replaced with a nitrogen atom, and the nitrogen atom binds, in addition to two adjacent carbon atoms, Rq, wherein Rq is defined according to the same definition as Rx.

The term "guanyl" describes a RxRyNC(=N)- end group or a –RxNC(=N)- linking group, as these phrases are defined hereinabove, where Rx and $R_y$ are as defined herein.

The term "nitroso" describes a –O-N=O group.

The term "guanidine" describes a –RxNC(=N)-NRyRw end group or a –RxNC(=N)-NRy- linking group, as these phrases are defined hereinabove, where Rx, Ry and Rw are as defined herein.

The term "hydrazine", as used herein, describes a -NRx-NRyRw end group or a -$NR_x$-NRy- linking group, as these phrases are defined hereinabove, with Rx, Ry, and Rw as defined herein.

As used herein, the term "disulfide" describes an end group –S-S-Rx, or a linking group –S-S-, wherein Rx is as defined hereinabove.

As used herein, the term "ester" describes an end group –C(=O)O-Rx, wherein Rx is as defined hereinabove with the proviso that Rx is not hydrogen, or a linking group –C(=O)O-.

As used herein, the term "imine" describes an end group –C(Rx)=N-Ry, wherein Rx and Ry are as defined hereinabove, or a linking group –C(Rx)=N-.

The term "heteroalicyclic" describes a monocyclic or fused ring group having in the ring(s) one or more atoms such as nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. The heteroalicyclic may be substituted or unsubstituted. Substituted heteroalicyclic may have one or more substituents, whereby each substituent group can independently be, for example, hydroxyalkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, amine, halide, sulfonate, sulfoxide, phosphonate, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, cyano, nitro, azo, sulfonamide, C-carboxy, O-carboxy, N-thiocarbamate, O-thiocarbamate, urea, thiourea, O-carbamate, N-carbamate, C-amide, N-amide, guanyl, guanidine and hydrazine. The heteroalicyclic group can be an end group, as this phrase is defined hereinabove, where it is attached to a single adjacent atom, or a linking group, as this phrase is defined hereinabove, connecting two or more moieties. Representative examples are piperidine, piperazine, tetrahydrofuran, tetrahydropyran, morpholino and the like.

As used herein, the phrases "electrochemically attached" and "electrochemically attaching" describe a moiety attached to a substance (e.g. a conductive surface) by a chemical reaction that is induced by an application of an electric potential and/or current. Preferably, the chemical reaction is a redox reaction. Optionally, the application of the electric potential and/or current is by connecting the conductive surface to a voltage source and/or current source. The moiety may be attached by one or more of any type of molecular interaction (e.g. a covalent bond, a hydrogen bond, a hydrophobic interaction, an ionic bond, a van der Waals interaction).

Optionally, the aryl moiety is non-covalently attached to the surface. In an exemplary embodiment, the aryl moiety is covalently attached to the surface. Herein,

an aryl moiety is considered covalently attached to a surface when a bond between the aryl moiety and the surface represents at last one of the valence bonds of the aryl moiety.

The present inventors have devised a methodology that utilizes various aryl moieties, designed suitable to achieve the desired properties of the resulting medical device.

According to one embodiment of the present invention, the layer of at least one aryl moiety being electrochemically attached to the surface comprises at least two aryl moieties being electrochemically attached to the surface, the aryl moieties being different from one another. As exemplified in the Examples section herein, the properties of the surface with the attached aryl moiety layer may be modulated by selecting appropriate proportions of the different aryl moieties.

According to another embodiment of the present invention, the aryl moiety is substituted by at least one functional group at a meta or ortho position of the aryl moiety, with respect to the position of the aryl moiety that is being electrochemically attached to the surface.

According to another embodiment of the present invention, the aryl moiety is electrochemically attached to the surface via at least two positions of the aryl moiety. Such an aryl moiety provides a particularly strong attachment of the aryl moiety layer to the surface thereby increasing the durability of the layer.

According to another embodiment of the present invention, the aryl moiety comprises at least two aromatic groups covalently linked to one another via a linker. As aromatic groups are particularly suitable for attachment to a surface, such an aryl moiety allows attachment to the surface at a plurality of positions, while minimizing the steric hindrance typically involved in attaching an aryl moiety to a surface via more than one position.

In one embodiment, the aryl moiety comprises one or more functional groups which are alkyl and/or alkoxy. Exemplary alkyl and alkoxy groups suitable for use in the context of the present embodiments include alkyl and alkoxy groups comprising from 4 to 20 carbon atoms (e.g. hexyloxy, dodecyloxy and octadecyloxy groups). In one embodiment, the alkyl and/or alkoxy groups are unsubstituted. In an exemplary embodiment, the alkoxy group is dodecyloxy (e.g. $-O-C_{12}H_{25}$).

Optionally, the aryl moiety comprises a hydroxyalkyl functional group. 2-hydroxyethyl is an exemplary hydroxyalkyl group.

Optionally, the aryl moiety comprises a haloalkyl functional group. 2-haloethyl (e.g. 2-bromoethyl) is an exemplary haloalkyl group.

Optionally, the aryl moiety comprises a nitro group as a functional group.

Optionally, the aryl moiety comprises a phenyl group electrochemically attached to the surface.

As used herein, the term "phenyl" describes an aromatic group consisting of a 6-carbon aryl ring, the ring being either substituted or non-substituted. The phenyl may be an end group (e.g. $-C_6H_5$) or a linking group (e.g. $-C_6H_4-$), as these terms are defined hereinabove.

The phenyl can be substituted by any of the abovementioned alkyl, hydroxyalkyl, haloalkyl, alkoxy, carboxy and/or nitro functional groups. Optionally, such a functional group is attached to the phenyl at a para position with respect to a position of the phenyl that is electrochemically attached to the surface. Optionally, the phenyl is substituted by a single functional group, such that the aryl moiety consists of alkylphenyl, hydroxyalkylphenyl, haloalkylphenyl, alkoxyphenyl, carboxyphenyl or nitrophenyl. Optionally, the carboxy is $-C(=O)OH$. Optionally, the phenyl is attached to the surface at a single position of the phenyl.

According to an embodiment of the present invention, the aryl moiety is a polymer comprising a plurality of aromatic groups being covalently linked to one another via a linker. Optionally, the plurality of aromatic groups comprises a plurality of phenyl groups. Polystyrene, wherein one or more of the phenyl groups thereof is attached to the surface, is an exemplary polymer comprising a plurality of phenyl groups. Preferably, a plurality of phenyl groups of the polystyrene are attached to the surface (e.g. at the para position with respect to the linker). Optionally, all of the phenyl groups are attached to the surface. Optionally, the polystyrene is further substituted by a substituent (e.g. a substituent attached to a phenyl).

As used herein, the term "polymer" describes a molecule comprising 3 or more repeating, covalently bound, structural units. In the context of these embodiments, the structural units are a substituted aromatic group (e.g. styrene).

Optionally, the polymer (e.g., the polystyrene described herein) comprises 10 or more repeating structural units (e.g., aromatic groups). In one embodiment, the

polymer comprises from about 10 to about 40 aromatic groups. The polystyrene preferably comprises from about 15 to about 30 aromatic groups (i.e. phenyl), more preferably from about 20 to about 25 aromatic groups.

As used herein, the number of aromatic groups in a polymer refers to the mean number of aromatic groups in the polymer, which may be calculated for example, from the number average molecular weight of the polymer, as determined by any suitable method (e.g. gel permeation chromotography). Optionally, the polydispersity of the polymer size is less than 1.3. Optionally, the polydispersity is less than 1.2.

According to another optional embodiment of the present invention, the aryl moiety comprises at least two aromatic groups covalently linked to one another via a linker.

The aryl moiety may comprise more than one linker linking at least two aromatic groups. Each linker may link two or more aromatic groups.

The linker may be any linking group, as this term is defined herein. Alternatively, the linker is a bond linking two aromatic groups, such that the aryl moiety comprises at least two aromatic groups linked by one or more bonds (e.g. biphenyl, terphenyl, polyphenylene, fluorene and the like).

In one embodiment, the linker comprises a plurality of alkoxy groups, wherein each of the alkoxy groups is attached to one of the at least two aromatic groups of the aryl moiety. Optionally, each aromatic group is attached to a single alkoxy group on the linker. Optionally, the aryl moiety is a polymer, as described hereinabove. Alternatively, the aryl moiety is not a polymer, as defined hereinabove. A linking group derived from pentaerythritol (e.g. $C(CH_2O\text{-})_4$) is an exemplary linker.

According to another optional embodiment of the present invention, the aryl moiety comprises a phenyl attached to the surface via at least two positions of the phenyl. Optionally, the two attached positions of the phenyl are at a meta position with respect to one another. Optionally the phenyl is further substituted by a carboxy group. The carboxy group may be, for example, -C(=O)OH. Exemplary aryl moieties include benzoic acid attached to the surface at the 3- and 5- positions thereof.

According to another optional embodiment of the present invention, the aryl moiety comprises at least two aromatic groups fused to one another. In exemplary embodiments the aryl moiety comprises anthracene. Optionally, the anthracene is

attached to the surface via at least two positions thereof. Exemplary aryl moieties include anthracene attached to the surface via the 1- and 8- positions thereof.

According to an optional embodiment of the present invention, the adhesive layer further comprises a polymer grafted onto the aryl moiety. Exemplary polymers include polyacrylic acid, polymethacrylic acid, polymers of esters of acrylic acid and polymers of esters of methacrylic acid as well as copolymers thereof.. Optionally, the polymer is poly(methyl methacrylate).

Optionally, the polymer is grafted onto the aryl moiety after the aryl moiety has been attached to the surface. The grafting may comprise either reacting a polymer with the aryl moiety or reacting a monomer with the aryl moiety such that the monomer undergoes polymerization to form a polymer grafted to the aryl moiety.

The abovementioned adhesive layer optionally comprises the aryl moiety electrochemically attached to the surface by electrochemically reacting a diazo-substituted derivative of the aryl moiety with the surface.

As used herein, the terms "diazo" and "diazonium moiety" refer to a $-N^{+}\equiv N$ end group.

The diazo-substituted derivative of the aryl moiety will in many cases be electrically charged, and thus will be in the form of a salt comprising the substituted aryl moiety and at least one counter-ion. Tetrafluoroborate (i.e. $BF_4^-$) is an exemplary counter-ion for inclusion in salts of diazo-substituted aryl moieties.

Preferably, the diazonium moiety is a substituent(s) of an aromatic group of the aryl moiety.

Preferably, the diazo-substituted aryl moiety is substituted by a diazonium moiety at each position of the aryl moiety that is electrochemically attached to the surface. Optionally, the diazo-substituted aryl moiety is electrochemically attached to the surface at only part of the positions substituted by a diazonium moiety. Exemplary diazo-substituted aryl moieties, as developed by the inventors, are designed to be capable of reacting with a so as to provide a high yield of bonds between the aryl moiety and the surface. However, as will be apparent to one skilled in the art, due to steric hindrance and other factors, it is not always possible to ensure that 100 % of the positions substituted by a diazonium moiety will become attached to the surface, and such positions may react such that the diazonium moiety is replaced by another substituent (e.g. hydroxy).

As exemplified in detail in the Examples section hereinbelow, the medical device described hereinabove was found to exhibit a different release profile for the release of the pharmaceutically active agent from the matrix thereof than that exhibited by control stents.

Hence, in another aspect of the present invention there is provided a method for modulating a release of a pharmaceutically active agent from a matrix coating a surface, the method comprising strengthening an adherence between the matrix and the surface. In exemplary embodiments the surface is a surface of a medical device.

The phrase "modulating a release" is defined as hereinabove. Optionally, the modulating comprises reducing a release rate of a pharmaceutically active agent when the matrix is subjected to physiological conditions, as described hereinabove.

Optionally, the strengthening of adherence is effected by an adhesive layer between the surface and the matrix. Alternatively, the adherence is strengthened, for example, by generating a reaction of the matrix and/or surface which strengthens an adherence between the matrix and the surface. For example, the reaction may generate an attractive molecular interaction between the surface and the matrix, such as a covalent bond, an ionic bond, a hydrogen bond, a hydrophobic interaction and/or a van der Waals interaction.

According to an exemplary embodiment of the present invention, the method comprises strengthening the adherence such that peeling of the matrix from the surface in the presence of the strengthening of the adherence is at least 10 % lower, optionally at least 20 % lower, optionally at least 30 % lower, optionally at least 50 % lower, optionally at least 75 % lower, optionally at least 90 % lower, and optionally at least 95 % lower, than peeling of the matrix from the surface in the absence of the strengthening of the adherence when performing the comparative D-3359-02 ASTM test according to the procedure described hereinabove.

According to further exemplary embodiments, the method comprises strengthening the adherence such that the percentage of defective areas on the matrix coating the surface in the presence of the strengthening of the adherence is at least 10 % lower, optionally at least 20 % lower, optionally at least 30 %, optionally at least 50 % lower, optionally at least 75 %, optionally at least 90 % lower, optionally at least 95 % lower and optionally at least 98 % lower than the percentage of defective areas on the matrix coating the surface without the strengthening of the adherence when

examining each of said surfaces by scanning electron microscopy at a magnification of x300 according to the procedure described hereinabove.

According to an exemplary embodiment of the present invention, the adhesive layer comprises at least one moiety selected from the group consisting of an aryl moiety, an organosilane, a carboxylate, a sulfonate, a sulfate, a phosphonate and a phosphate, the method further comprising attaching the at least one moiety to the surface. An aryl moiety is an exemplary moiety. Exemplary adhesive layers and exemplary aryl moieties are described hereinabove.

An exemplary method for attaching an aryl moiety to a surface comprises providing a diazo-substituted derivative of the aryl moiety and electrochemically attaching the diazo-substituted derivative of the aryl moiety to the surface as described hereinabove.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

# EXAMPLES

Reference is now made to the following examples, which together with the above descriptions, illustrate some embodiments of the invention in a non-limiting fashion.

## *MATERIALS AND METHODS*

***Materials:***

Stainless steel stents (STI 316L, 0.9 cm) were obtained from STI Laser Industries Ltd. (Israel);

Acetonitrile was obtained from Biolab;

Acetonitrile (extra-dry, <10 ppm water) was obtained from Sigma-Aldrich;

4-aminophenol was obtained from Sigma-Aldrich;

2-(4-aminophenyl)ethanol was obtained from Fluka;

Chloroform was obtained from Biolab;

CuCl and $CuCl_2$ were obtained from Sigma-Aldrich;

Dichloromethane was obtained from Biolab;

3,5-diaminobenzoic acid was obtained from Sigma-Aldrich;

1,8-dinitroanthroquinone was obtained from Sigma-Aldrich;

Ethanol (HPLC-grade) was obtained from Biolab;

Methyl methacrylate was obtained from Fluka;

Nitrophenolate was obtained from Sigma-Aldrich;

Paclitaxel was obtained from BioxelPharma;

Palladium on carbon was obtained from Sigma-Aldrich;

Pentaerythritol was obtained from Sigma-Aldrich;

*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDETA) was obtained from Sigma-Aldrich;

1-phenyl ethyl bromide (1-PEBr) was obtained from Sigma-Aldrich;

Poly(butyl methacrylate) (molecular weight 340,000 Da) was obtained from Sigma-Aldrich;

Poly(ethylene-vinyl acetate) was obtained from Dupont;

Pyridine (dry) was obtained from Baker Analyzed;

Sodium borohydride was obtained from Sigma-Aldrich;

Sodium nitrite was obtained from Merck;

Sodium sulfide nonahydrate was obtained from Sigma-Aldrich;

Tetrabutyl ammonium tetrafluoroborate (TBATFB, or $Bu_4N^+$ $BF_4^-$) was obtained from Sigma-Aldrich;

Tetrafluoroboric acid was obtained from Sigma-Aldrich;

Tosyl chloride was obtained from Sigma-Aldrich.

All other materials were purchased from known vendors unless otherwise indicated.

***Chemical Syntheses:***

***Synthesis of 4-(2-bromoethyl)phenyl diazonium tetrafluoroborate:***

2.00 grams of 2-(4-aminophenyl)ethanol and 50 ml of 48 % HBr were placed in a 100 ml flask equipped with a magnetic stirrer and an efficient condenser cooled with tap water. The mixture was heated to 150 °C for 4 hours, followed by cooling to 0 °C. A white precipitate appeared immediately and was allowed to stand for 20 minutes before being filtrated. The solid was then neutralized with 25 % ammonium hydroxide, extracted with dichloromethane and dried over $MgSO_4$. The product was evaporated and vacuum dried with an oil pump. The yield was 2.44 grams of unpurified 2-(4-aminophenyl)ethyl bromide.

The 2.44 grams of 2(4-aminophenyl)ethyl bromide was then mixed with 1.8 ml of 48 % $HBF_4$ and 6 ml DDW in a 100 ml flask equipped with a magnetic stirrer. The mixture was heated gently until a transparent solution appeared, and the solution was then cooled to 0 °C with a water-ice bath. A cooled solution of 0.925 grams of sodium nitrite in 20 ml DDW was added at 0 °C in 3 portions over the course of 2 minutes. The yellow transparent solution was then stirred for 15 minutes, filtrated, washed with 6 ml of 5 % $NaBF_4$ solution, followed by 6 ml methanol, frozen with dry nitrogen and lyophilized for 24 hours. The product, a dark yellow powder, was stored at -4 °C.

**NMR:** $^1$H-NMR (DDW) δ: 8.30 (d, J=9.0 Hz, 2H, CH-β), 7.66 (d, J=8.7, 2H, CH-α), 3.59 (t, J=6.6 Hz, 2H, $CH_2Br$), 3.28 (t, J=6.6, Hz 2H, $ArCH_2$).

**FTIR:** 3005-3097 $CH_2$, C-H stretching; 2254 diazonium; 1211-1399 C-H aromatic stretching; 633 C-Br; 1081 $BF_4^-$

***Synthesis of poly(p-diazostyrene tetrafluoroborate):***

36.1 grams of styrene and 200 ml of toluene were introduced into a 1,000 ml flask equipped with a magnetic stirrer and a Dean-Stark apparatus and a $CaCl_2$ tube, and refluxed for 60 minutes at a bath temperature of 150 °C. The temperature was reduced to 135 °C, and 2.09 grams of benzoyl peroxide was added. The reaction was stirred under these conditions for 20 hours, and the toluene was then removed by evaporation. The remaining solid was dissolved in 50 ml of chloroform and 200 ml of isopropanol, 100 ml of hexane was added while the mixture was being constantly stirred, and a suspension was formed. The stirring was then stopped and the solid was allowed to sink for 10 minutes, after which it was filtrated. The wet solid was vacuum dried using an oil pump. The yield was 23.57 grams of polystyrene.

**Gel-permeation chromatography:** (polystyrene was used as a calibration standard): Mn=2414, Mw=2866.

**$^1$H-NMR:** (500 MHz, $CD_3COCD_3$): 1.20-1.80 (m, 2H), 1.80-2.05, (m, 1H), 6.35-6.85 (m, 2H), 6.85-7.18 (m, 3H).

**FTIR:** 3058, 3024 (aryl C-H stretching theoretic value 3010-3080); 1600 (aryl C-H stretching theoretic value 1600); 697, (mono-substituted benzene theoretic value 690-710).

15.5 grams of polystyrene was dissolved in a mixture of 100 ml dichloromethane, 60 ml acetic anhydride, 100 ml acetic acid and concentrated sulfuric acid at 0 °C. A cold mixture of 22 ml of 70 % nitric acid and 27 ml of concentrated sulfuric acid was added dropwise while stirring and maintaining a temperature of less then 2 °C. 100 ml dichloromethane was added to dilute the solution and dissolve the yellow product. 52 ml of the cold solution of nitric acid and sulfuric acid was added dropwise, followed by 100 ml of acetic acid. The result is a clear yellow solution that was stirred for 24 hours at 0 °C to room temperature. The organic solvents were then removed by evaporation with an oil pump, and 200 ml double-distilled water (DDW) was added. The solid was filtered out and the liquid was then neutralized with sodium hydroxide solution and filtered again. The solids were combined, stirred in DDW and filtrated, and then washed with a solution of 1:1 isopropanol and diethyl ether, filtrated again and vacuum dried. The yield was 29 grams of poly(p-nitrostyrene) as a yellow powder.

**FTIR:** 2931 (aliphatic C-H stretching theoretic value 2980-2900); 1517 and 1350 (nitro theoretic value 1517 and 1347).

2.51 grams of polynitrostyrene and 9.9 grams tin were placed in a 250 ml round flask equipped with a magnetic stirrer, a condenser, and a dropping funnel on the condenser. 120 ml of 37 % HCl was added dropwise over 2 minutes at room temperature, and the mixture was heated to reflux. After 20 minutes, the product appeared as a yellow ball in a transparent solution. 20 ml acetic acid was added and the heat was increased until a yellow transparent solution was obtained. The reaction mixture was then stirred for 4 days, followed by cooling to room temperature. The product was then precipitated with a solution of 1:1 isopropanol and diethyl ether, filtrated, washed with the solution and vacuum dried to yield 2.135 grams of poly(p-aminostyrene) as a yellow powder.

**FTIR:** 2921-3421 (primary amine theoretic value ~3300, conjugated with ~1600 area); 1508-1617 ($NH_2$ bending, conjugated with the ~3300 area, theoretic value 1600); 1122-1200, (aromatic amine C-N band, theoretic value 1180-1280).

0.50 gram of polyaminostyrene, 4 ml of 48 % tetrafluoroboric acid, and 20 ml DDW were placed in a 250 ml round flask equipped with a magnetic stirrer and a condenser, and heated to form a clear yellow solution. The mixture was cooled to 0 °C to form a suspension. 0.28 gram sodium nitrite in 20 ml DDW was added over the course of 5 minutes and the mixture was then stirred for 30 minutes, filtrated, washed with DDW and dried. The yield was 0.232 gram of poly(p-diazostyrene tetrafluoroborate) as a yellow powder.

**FTIR:** 2929 (aliphatic C-H stretching theoretic value 2980-2900); 2263 (diazonium group theoretic value 2260-2280); 1123-1032 ($BF_4^-$ theoretic value 1060).

In an alternative method, 0.50 gram of polyaminostyrene and 10 ml of 48 % tetrafluoroboric acid were placed in a 250 ml round flask equipped with a magnetic stirrer and condenser and heated to form a clear solution. Tetrahydrofuran (THF) was added to improve solubility and the heating was continued for another 5 minutes. The mixture was then evaporated to remove the THF, followed by cooling to 0 °C. 0.23 gram sodium nitrite was added as a solid in 3 portions over the course of 5 minutes while stirring and shaking. 20 ml DDW and 50 ml dichloromethane were then added and the reaction mixture was transferred to a separator funnel, and the organic layer

was evaporated to form a solid. 20 ml acetonitrile was then added and evaporated to concentrate the solution. Isopropanol was added to precipitate the solid, which was then filtrated and washed with DDW to remove residual acid. The product was vacuum dried to yield 0.446 gram of poly(p-diazostyrene tetrafluoroborate) as an orange-colored product.

**FTIR:** 2930 (aliphatic C-H stretching theoretic value 2980-2900); 2263 (diazonium group theoretic value 2260-2280); 1124-1036 ($BF_4^-$ theoretic value 1060).

***Synthesis of tetrakis[(4-diazophenoxy)methyl]methane tetrafluoroborate:***

13.6 grams of pentaerythritol and 85.5 grams of tosyl chloride were placed in a 1 liter round flask equipped with a magnetic stirrer, a condenser and a calcium chloride tube, the flask being placed in an ice bath. 150 ml of dry pyridine (dried over KOH) were added and the reaction was stirred for 1 hour at 0 °C. The ice bath was removed and the reaction mixture was then stirred at room temperature for 48 hours. The reaction mixture was then transferred to a beaker with 200 ml of a cold solution of 50 % HCl. The product was filtrated, washed with DDW, and lyophilized. The yield was 107.5 grams of tetrakis(tosylmethyl)methane as white crystals.

**$^1$H-NMR:** (500 MHz, DMSO): 2.525 (s, 12H, Me); 3.896 (s, 8H, $CCH_2O$); 7.560 (d, J = 9.5 Hz, 8H); 7.745, (d, J = 8.5 Hz, 8H).

**FTIR:** 3067 ($MeC_6H_4$- theoretic value 3000-3150), 1467 ($CH_2$ theoretic value 1440-1480), 1179 ($SO_3R$ theoretic value 1280-1150 and 1,4 substituted benzene ring theoretic value 1225-1175).

**Mass spectrometry:** m/z (%) 753 (55.4)$[MH]^+$ ; 581 (100)$[M\text{-tosyl}]^+$ ; 427 (12)[M-2 tosyl units)]$^+$ ; 832.0(15) $[(M+adduct)H]^+$

2.405 grams of tetrakis(tosylmethyl)methane, 2.57 grams of nitrophenolate (dried by lyophilization) and 25 ml ethanol (dried over BaO and distilled) were placed in a stainless steel bomb with an internal glass tube and a Teflon coated seal, with a magnetic stirrer. The bomb was then closed and heated to 170 °C for 24 hours. The bomb was then cooled and opened, and the reaction mixture was washed with DDW until the water was clear. The remaining white solid was washed with methanol and vacuum dried. The yield was 1.38 grams of tetrakis[(4-nitrophenoxy)methyl]methane as a white solid.

**Mass spectrometry:** m/z (%) 661(2) $[M+CI\ adduct]^+$, 621(12)$[MH]^+$ ; 591 (5)$[M-NO]^+$ ; 140 (100) $[NO_2C_6H_4OH]^+$ 140 ; 110(52) $[NO_2C_6H_4OH - NO]^+$.

**FTIR**: 1460 ($CH_2$ theoretic value 1440-1480), 1251 ($CH_2$-O-$C_6H_4$ theoretic value 1230-1270), 1514-(aromatic nitro theoretic value 1510-1550) ; 1342 (aromatic nitro theoretic value 1365-1335); 851 (aromatic nitro theoretic value 840-860).

0.96 gram of tetrakis[(4-nitrophenoxy)methyl]methane, 0.5 gram palladium on carbon (Pd/C) 10 % and 50 ml tetrahydrofuran (THF) were placed in a hydrogenation bottle and hydrogenated using a Parr instrument at 65 pounds per square inch for 72 hours. The THF solution was filtrated twice, and the solvent was then evaporated. The yield was 0.74 gram of tetrakis[(4-aminophenoxy)methyl]methane as a brown oil.

0.5 gram of tetrakis[(4-aminophenoxy)methyl]methane, 0.6 ml of 48 % tetrafluoroboric acid in water and 4 ml DDW were mixed by vigorous stirring. A further 0.4 ml of 48 % (by weight) tetrafluoroboric acid in water, 10 ml acetonitrile and 10 ml DDW were added and the solution was then cooled to -10 °C (using ice, isopropanol and liquid nitrogen). 0.29 gram sodium nitrite was added and the reaction mixture was then stirred for 20 minutes, filtrated, evaporated to remove the organic solvent, frozen with liquid nitrogen and lyophilized in the dark. The product is a gray-brown solid strongly attached to the flask. The yield was 0.465 gram of tetrakis[(4-diazophenoxy)methyl]methane tetrafluoroborate.

**FTIR:** ~2250 (diazonium theoretic value 2200-2300), 1038 ($BF_4^-$ theoretic value 1030-1060); 1384 ($OC_6H_4$ - theoretic value 1310-1410).

***Synthesis of 1,8-didiazoanthracene tetrafluoroborate:***

6.00 grams of 1,8-dinitroanthraquinone was refluxed in a 60 ml 3:1 solution of ethanol:$H_2O$. 18 grams of sodium sulfide nonahydrate was added in portions over the

course of 10 minutes and the color changed from yellow to red and then to black. After 16 hours, the reaction was cooled to room temperature, and 30 % sulfuric acid was added until the pH was about 5. 300 ml DDW was added, and the mixture was extracted with about 300 ml dichloromethane and filtrated to remove the insoluble material, dried over magnesium sulfate, and the solvent was then evaporated to yield about 2.1 grams of 1,8-diaminoanthraquinone as a red product.

**Mass spectrometry:** 239(100)$[MH]^+$, 238(64)$[M]^+$

1.8 grams of 1,8-diaminoanthraquinone and 100 ml dry isopropanol (freshly distilled over barium oxide) were placed into a 250 ml round flask with a magnetic stirrer and a condenser with a calcium chloride tube. 4.00 grams sodium borohydride was added in portions over the course of 2 minutes and the condenser was then put in place. The reaction mixture was heated to reflux for 48 hours, cooled to room temperature and poured into 200 ml ice and water. The mixture was extracted with dichloromethane, filtrated to remove salts, and dried over magnesium sulfate.

The product was purified using chromatography with silica gel 60 and chloroform to elute the first fraction of red material, followed by chloroform with 5 % methanol to elute a yellow-green solution which was evaporated to obtain 350 mg of 1,8-diaminoanthracene as a green powder.

**Mass spectrometry:** 209(41)$[MH]^+$ ,208(100)$[M]^+$

0.25 gram of 1,8-diaminoanthracene, 10 ml of DDW, 2 ml of 48 %$HBF_4$, and 10 ml acetonitrile (spectro pure grade) were placed in a 100 ml flask equipped with a magnetic stirrer. The mixture was heated gently for 10 minutes and then filtrated to obtain a dark solution. The acetonitrile was evaporated and 30 ml DDW was then added. The solution was cooled to -5°C with ice and salt. A cold solution of 0.18 gram sodium nitrite in 20 ml DDW was then added while the suspension was being vigorously stirred until the temperature was 0 °C. The reaction mixture was filtrated, frozen by dry nitrogen and lyophilized for 24 hours. The yield was 0.835 gram of a brown powder, which was kept at -4 °C.

**FTIR:** 3200- 3400 (aryl C-H stretching theoretic value 3010-3080); 2366 and 2260 (diazonium group theoretical value 2200-2500); 1010-1100 ($BF_4^-$ theoretic value ~1060)

***Synthesis of 3,5-didiazobenzoate tetrafluoroborate:***

1.02 gram of 3,5-diaminobenzoic acid, 20 ml of DDW and 2 ml of 48 % $HBF_4$ were placed in a 100 ml flask equipped with a magnetic stirrer. The mixture was heated gently for 10 minutes and then filtrated to obtain a dark solution. 20 ml DDW was added and the solution was cooled with a -30 °C bath of isopropanol cooled with liquid nitrogen. A cold solution of 0.923 gram sodium nitrite in 20 ml DDW was added while the suspension was vigorously stirred until the temperature was 0 °C. The reaction mixture was then filtrated, frozen by dry nitrogen and lyophilized for 24 hours. The yield was 0.26 gram of a brown powder, which was kept at -4 °C.

**FTIR:** 3415-3547 (OH in carboxylic acid, theoretic value 3300-3500); 2362 and 2339 (diazonium group theoretical value 2200-2500); 1716 (C=O theoretic value 1650-1725); 1033-1085 ($BF_4^-$ theoretic value ~1060).

***Synthesis of 4-alkoxyphenyl diazonium tetrafluoroborate:***

4-aminophenol (7.5 grams, 69 mmol) and 50 ml dimethylformamide (DMF) were introduced into a 250 ml 3-neck flask equipped with a condenser, dropping funnel and efficient magnetic stirrer. The reaction mixture was stirred until the solid was completely dissolved. KOH (4.0 grams, 71 mmol) was added in portions and the mixture was stirred until almost all the KOH disappeared and the color changed to black. Another 50 ml of DMF were then added and the mixture was heated to 80 °C for an hour, and cooled to room temperature. Bromooctane (51 mmol, 9.9 grams) was added to the reaction mixture and the reaction mixture was stirred for additional 30 minutes. The condenser was thereafter replaced with a vacuum distillation apparatus and the DMF was distilled out under reduced pressure at 45 °C. The reaction mixture was cooled to room temperature and extracted with 200 ml of dichloromethane, washed with 10 % solution of ammonium chloride, dried over $MgSO_4$, mixed with carbon powder, filtered and evaporated to yield a black oil, which was purified by distillation at 180-190 °C under reduced pressure to give 4-octyloxyaniline.

Using the same procedure, 4-butoxyaniline was prepared using n-butyl bromide and 4-dodecyloxyaniline was prepared using n-dodecyl bromide.

4-dodecyloxyaniline (0.502 gram, 1.81 mmol) was dissolved in a mixture of 4 ml DDW, 3 ml $HBF_4$ 48 % and 5 ml methyl cyanide, and the solution was cooled to 0

°C. A solution of sodium nitrite (0.125 gram, 1.80 mmol) in 1 ml DDW was added at once. The mixture was diluted to 20 ml stirred for 5 minutes and kept at -4 °C.

***Electrocoating:***

Stents were first cleaned in an ultrasonic cleaner in order to remove impurities from the surface of the metal. The stents were then immersed in an etching solution consisting of 10 % (v/v) of nitric acid (70 %), 2 % (v/v) of hydrofluoric acid (50 %) and 88 % (v/v) double-distilled water (DDW), followed by rinsing with distilled water. The etched stents were subjected to an electrical discharge of 0.35 Amperes for approximately 40 seconds in a solution consisting of 50 % (v/v) glycerol, 35 % of phosphoric acid (85 %) and 15 % DDW, then rinsed with distilled water and immersed again in the etching solution, and then rinsed with distilled water, dried with acetone and kept in a desiccator.

Stents were electrocoated with a solution of either 1, 4 or 8 mM of a diazonium salt in acetonitrile with 0.1 M tetrabutyl ammonium tetrafluoroborate (TBATFB), using either cyclic voltammetry (application of 10 or more repetitive potential cycles between OCP (open circuit potential) and 300 mV negative to the reduction peak of the diazonuim salt and reverse) or potentiostatic electrocoating (setting the potential at a value that was 300 mV negative to the voltammetric peak for 400 seconds). After electrolysis, the stents were thoroughly rinsed with acetonitrile in an ultrasonic cleaner for 15 minutes.

The whole electrocoating process was carried out in a glove box under dry and inert conditions to avoid inhibition by impurities such as $H_2O$ or $O_2$, which were kept at concentrations lower than 5-10 ppm in the electrochemical solution.

Electrochemical curves were obtained with a Potentiostat/Galvanostat (CH630 B, CH Instruments, U.S.A.) in a cylindrical three electrode cell. The counter-electrode was a circular platinum foil, the reference electrode was a platinum rod and the working electrode was a 316L stainless steel stent wrapped with a stainless steel wire and placed in the center of the cell.

***PMMA grafting:***

Stainless steel stents and plates were electrocoated with 4-(2-bromoethyl)phenyl diazonium, according to the procedure described hereinabove.

Bare metal stents and plates (which were sonicated in acetonitrile) were used as a control. Electrocoated and bare metal were both subjected to the grafting procedure. All stents were spray-coated following the grafting procedure, as described hereinabove.

Methyl methacrylate (MMA), the monomer for the polymerization reaction, was passed through an alumina column to remove deactivators. *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDETA), CuCl, and $CuCl_2$ were used as catalysts. 1-PEBr (1-phenyl ethyl bromide) was used as a sacrificial initiator.

Two 50 ml bottlenecked flasks, equipped with a magnetic stir bar and sealed with a rubber septum, were deoxygenated by vacuum and back-filled with argon three times. Plates/stents were introduced into the flask under nitrogen flow. 15 mg of CuCl and 10 mg of $CuCl_2$ powders were weighed in the flasks followed by the injection of MMA (10 ml), PMDETA (50 µl) and 1-PEBr (65 µl). The flasks were placed in an oil bath at 100 °C for 4 hours. The polymerization was stopped by cooling and opening the flasks. The polymer was then diluted in chloroform and was passed through a column filled with neutral alumina to remove the copper complex. The polymer was dissolved in excess chloroform, and taken to molar mass analysis by gel permeation chromatography.

Plates/stents were removed from the flasks and rinsed in chloroform (twice), dichloromethane, and acetonitrile, under sonication, in 4 periods of 15 minutes each, in order to remove any physisorbed polymer chains that have been synthesized in solution without any anchoring site on the metal surface.

***Spray-coating of stents:***

The following spray-coating solutions were used:

(a) 2 % PEVA:PBMA [poly(ethylene-vinyl acetate):poly(butyl methacrylate)] at a 3:7 weight:weight ratio and 1.33 % paclitaxel in ethyl acetate;

(b) 2 % PBMA in ethyl acetate;

(c) 2 % SIBS [poly(styrene-isobutylene-styrene) and 0.67 % paclitaxel in toluene:tetrahydrofuran (THF) at a 3:1 volume:volume ratio;

(d) 1 % poly(L-lactide-co-ε-caprolactone) in toluene:THF at a 3:1 volume:volume ratio.

The polymer was weighed in a new vial and the solution was then shaken until all polymer dissolved. The solution was then filtered through a syringe filter with 0.2 μm pores. Solutions with drug were vortexed until homogeneous. Solutions were stored in a refrigerator for up to one week.

The spray-coating was performed using a stent spray-coating device (Sono-Tek). Each stent was placed on a new Petri dish in a glove box. The stent was placed gently on the stent holder. Each half of the stent was then sprayed separately. Following spray-coating, the entire stent was examined in the X and Y axes. All movement of the stent was performed carefully with clean tweezers in order to avoid mechanical deformations. All procedures were performed while avoiding exposure to oxygen.

***Electrochemical impedance spectroscopy (EIS):***

EIS was performed in an electrochemical cell having a calomel electrode as a reference electrode, which was installed using a salt bridge with a Lugin capillary in the center of the stent. A platinum wire with a 25 $mm^2$ surface area was used as a counter-electrode, and the immersed half of the stent in the electrolyte was used as the working electrode. The solution was phosphate buffer adjusted to a pH of 7, with 5 mM $Fe(CN)_6^{3-}$, 5 mM $Fe(CN)_6^{4-}$ and 0.1 M KCl.

After setting up the electrochemical cell, it was necessary to wait until the open circuit potential (OCP) stabilized. The initial potential was then set to the OCP value in the impedance technique, and scanning from 100 KHz to 1 mHz was performed with 3 measurements for each frequency, with the amplitude set to 5 mV (Faradic current).

***Out of process cyclic voltammetry:***

Cyclic voltammetry was performed using the electrochemical cell described above for EIS. After setting up the electrochemical cell, scanning was performed from the OCP to -0.7 V vs. OCP and back to 0.7 V vs. OCP.

***Nuclear magnetic resonance (NMR) spectroscopy:***

NMR spectra were recorded using a Varian 300 MHz spectrometer.

***Fourier transform infrared (FTIR) spectroscopy:***

Spectra were recorded on a FTIR spectrometer (Nicolet Instrument Corp.) at a 4 $cm^{-1}$ spectral resolution, in a KBr pellet, and using a standard DTGS detector. 16 scans were performed for each measurement.

***X-ray photoelectron spectroscopy (XPS):***

XPS measurements were performed on a Kratos Axis Ultra X-ray photoelectron spectrometer. Spectra were acquired with a monochromated Al K 1486.7 eV) X-ray source with a 0° takeoff angle. The pressure in the chamber was maintained at 1.5 x $10^{-9}$ torr during acquisition. The survey spectra were collected from 1200 to -5 eV (binding energy) with pass energy 80 eV. High resolution XPS scans were collected for C 1s, O 1s, Fe 2p, Cr 2p and Br 3d peaks with pass energy 20 eV. Step size was 1 eV for survey scans and 0.1 eV for high-resolution spectra. XPS binding energy was calibrated with respect to the peak position of $Fe^0$ $2p_{3/2}$ as 707.0 eV. Data analysis and processing were performed with Vision processing data reduction software (Kratos Analytical Ltd.) and CasaXPS (Casa Software Ltd.).

***Incubation conditions:***

Metal surfaces were incubated in 0.1 M phosphate buffer with 0.3 % SDS (sodium dodecyl sulfate) at a pH of 7.4, in order to assess the effect of incubation on the surfaces. Incubation at 37 °C was considered exposure to physiological conditions. Incubation at 60 °C was considered as "accelerated conditions".

***High pressure liquid chromatography (HPLC) analysis of drug elution:***

Stents were kept in 5 ml glass vials. Each vial was filled with 1 ml of phosphate buffer, contained one expanded stent, and was sealed tightly with a cork. Vials were then placed in a shaking incubator (100 rpm) either at 37 °C (physiological conditions) or 60 °C (accelerated conditions).

Solution samples were taken at intervals of 0, 3, 7, 12, 21 and 30 days. Samples were drawn from the vials with a sterile 1 ml pipette and put into HPLC detection vials. All samples were vortexed before running.

In every set of HPLC measurements, calibration curve samples were obtained first by using ascending concentrations of known amounts of drug from 1 to 100 μg

per sample, followed by measurement of the drug elution samples and a blank measurement. Known amounts of paclitaxel and polymer formulation were weighted into glass vials and completed to 740 mg in each vial with chloroform. Each vial was vortexed and its content added to a pre-prepared centrifuge probe containing 10 ml of acetonitrile:double-distilled water (60:40). The probes were shaken and left to rest for an hour, thus resulting in phase separation (hydrophobic phase at the top, aqueous phase at the bottom, with the polymer at the interphase) and the volume of each phase was measured. The hydrophobic phase was left overnight (or incubated at 37 °C for 1 hour) to evaporate the chloroform. The hydrophobic phase was then brought to the initial volume by addition of acetonitrile, and filtered through a polytetrafluoroethylene filter with 0.2 μm pores. 20 μl of each phase was injected into the HPLC system (Hewlett Packard) with a diode array to obtain the paclitaxel spectrum.

Paclitaxel was measured at a rate of 15 minutes per sample, a flow rate of 1 ml per minute and a wavelength of 220 nm.

***Defect analysis by light microscopy:***

Each stent was removed from solution and placed gently (without using tweezers) to dry on a KIMWIPES® paper. The dry stent was placed gently on a plastic tissue culture plate by putting the plate on the stent and turning the plate and stent upside-down. The plate was covered with its cover and sealed with a paraffin strip at the edges.

Each stent was then placed on a clean and transparent surface (or on a white paper), and fixed in a special holding device. The light intensity was then adjusted, and the entire stent was examined in the X and Y axes. The light intensity was fixed for all images taken, in order to enable a more reliable comparison of the stents. Two images were taken for every frame. When one side of the stent was imaged, the other side was also imaged. Pictures of the whole stent were taken first. If the stent exhibited a defect, such as visible detachment of a portion of the coating and/or changes in color, two representative areas of that defect were framed and images were taken of the area.

***Defect analysis by scanning electron microscopy (SEM):***

Each stent was removed from solution, placed gently (without using tweezers) to dry on a KIMWIPES® paper, and placed gently in a plastic tissue culture plate, as described hereinabove.

After drying further in the plastic plate for 24 hours, the stent was weighed, and then gently placed (without using tweezers) on conductive carbon paper in designated holders of the scanning electron microscope. The stents were then coated with gold at a thickness of 10 nm using a spray deposition machine.

5 treated stents and 5 control stents were placed in the microscope and examined during the same run, with no more than 2 stents per holder. Holders with control stents and holders with treated stents were separated from each other.

The microscope parameters were then set as following: acceleration voltage, 30 V; and working distance, 10mm.

The stents were then scanned in order to assess damage. Scanning was conducted only on the three internal stent struts, and not on the two side struts, in order to avoid the possible damage which may have been caused to the side struts during handling. Five of each of the two types of areas of interest (AOIs), the maximum stress areas and the flexible curves, were selected randomly on each stent and pictured, and the AOIs having visible defects (i.e. cracking, flaking, delamination and/or peeling) were quantified.

***Ethylene oxide sterilization:***

Sterilization of coated stents in ethylene oxide was conducted by Mediplast Israel Ltd., under an ISO 9001:2000 approval of it quality assurance system, and sterilization was conducted according to international standards (e.g., EN ISO 13485 (EN 550), ISO-11135).

Sterilization parameters were as follows: exposure time, 360 minutes; number of cycles, 1; ventilation time, 24 hours.

# RESULTS

## *EXAMPLE 1*

### *Electrocoating of stents with poly(p-diazostyrene)*

Stents were electrocoated with a solution comprising 20 mg/ml polydiazostyrene tetrafluoroborate, according to the procedure described hereinabove.

As shown in Figures 1a-b, the reduction peak of the polydiazostyrene, as measured by in-process cyclic voltammetry, decreased as the electrocoating process progressed. These results indicate that the surface of the stents became progressively more insulated by the formation of an electrocoated layer.

The insulation of the stent surface was confirmed by electrocoating a stent using a chronoamperometric method. A potential of -1.5 V vs. Ag/AgBr was applied for 500 seconds.

As shown in Figure 2, the current decreased considerably over time, indicating the electrocoating of the stent surface by the polydiazostyrene.

The electrocoating was further characterized by impedance spectroscopy.

As shown in Figure 3, stents electrocoated with polydiazostyrene have a different capacitance from that of non-treated stents.

The insulation resulting from the electrocoating was also observed by out-of-process cyclic voltammetry in a redox couple solution.

As shown in Figure 4, electrocoating stents with polydiazostyrene blocks the current through the stent surface.

## *EXAMPLE 2*

### *Electrocoating of stents with tetrakis[(4-diazophenoxy)methyl]methane*

Stents were electrocoated with a solution comprising 8 mM tetrakis[(4-diazophenoxy)methyl]methane tetrafluoroborate, according to the procedure described hereinabove.

As shown in Figures 5a-b, the reduction peak of the diazonium compound, as measured by in-process cyclic voltammetry, decreased as the electrocoating process

progressed. These results indicate that the surface of the stents became progressively more insulated by the formation of an electrocoated layer.

The electrocoating was further characterized by impedance spectroscopy. As shown in Figures 6a-b, stents electrocoated with the diazonium compound have a higher polarization resistance and capacitance than that of bare stents.

The insulation resulting from the electrocoating was also observed by out-of-process cyclic voltammetry in a redox couple solution.

As shown in Figures 7a-b, electrocoating stents with the diazonium compound blocked the current through the stent surface.

## *EXAMPLE 3*

### *Electrocoating of stents with 1,8-didiazoanthracene*

Stents were electrocoated with a solution comprising 8 mM 1,8-didiazoanthracene tetrafluoroborate, according to the procedure described hereinabove.

As shown in Figures 8a-b, the reduction peak of the didiazoanthracene, as measured by in-process cyclic voltammetry, decreased as the electrocoating process progressed. These results indicate that the surface of the stents became progressively more insulated by the formation of an electrocoated layer.

The electrocoating was further characterized by impedance spectroscopy. As shown in Figure 9, stents electrocoated with the didiazoanthracene have a higher polarization resistance and capacitance than that of bare stents.

The insulation resulting from the electrocoating was also observed by out-of-process cyclic voltammetry in a redox couple solution.

As shown in Figure 10, electrocoating stents with didiazoanthracene blocks the current through the stent surface.

## *EXAMPLE 4*

### *Electrocoating of stents with 3,5-didiazobenzoate*

Stents were electrocoated with a solution comprising 8 mM 1,8-didiazoanthracene tetrafluoroborate, according to the procedure described hereinabove.

As shown in Figures 11a-b, the reduction peak of the didiazobenzoate, as measured by in-process cyclic voltammetry, decreased as the electrocoating process progressed. These results indicate that the surface of the stents became progressively more insulated by the formation of an electrocoated layer.

The electrocoating was further characterized by impedance spectroscopy. As shown in Figures 12a-b, stents electrocoated with the didiazobenzoate have a higher polarization resistance and capacitance than that of bare stents.

The insulation resulting from the electrocoating was also observed by out-of-process cyclic voltammetry in a redox couple solution.

As shown in Figures 13a-b, electrocoating stents with didiazobenzoate blocks the current through the stent surface.

## *EXAMPLE 5*

### *Electrocoating of stents with 4-(2-bromoethyl)phenyl diazonium and PMMA grafting*

Stents were electrocoated using 8 mM 4-(2-bromoethyl)phenyl diazonium, as described hereinabove. PMMA was grafted onto some of the electrocoated stents as described hereinabove. Control stents were prepared by omitting the electrocoating procedure and/or the grafting procedure.

The coating on the stent was analyzed by cyclic voltammetry, X-ray photoelectron spectroscopy (XPS) elemental analysis as well as impedance measurements.

As shown in Table 1 below, the metal (iron and chromium) content of the surface of the stent was decreased and the carbon content was increased by electrocoating, and even more so by electrocoating followed by PMMA grafting.

However, PMMA grafting without prior electrocoating did not have this effect. As further shown in Table 1, the electrocoating led to the presence of bromine on the stent surface.

These results confirm that the electrocoating procedure results in a coating of the stent by an organic coating comprising bromine, which in turn serves as a substrate for a second organic coating formed by the PMMA grafting procedure.

**Table 1: XPS elemental analysis of stent surfaces following electrocoating with 4-(2-bromoethyl)phenyl diazonium and PMMA-grafting**

| **Pretreatment of the stent** | %Fe 2p 710 eV | %Cr 2p 577 eV | %O 1s 532ev | %C 1s 285ev | %Br 3d 70 eV |
|---|---|---|---|---|---|
| Bare stent | 8.50 | 8.60 | 62.81 | 19.92 | --- |
| Bare stent with PMMA grafting | 16.50 | 10.80 | 45.31 | 26.68 | --- |
| Electrocoated stent | 7.02 | 7.08 | 45.78 | 38.18 | 1.21 |
| Electrocoated stent with PMMA grafting | 5.80 | 6.40 | 40.78 | 46.74 | 0.37 |

Further evidence for the successful grafting of PMMA onto the stent surface was obtained by high-resolution XPS, which allowed the quantification of different components of the abovementioned peaks.

As shown in Table 2, the oxygen composition is highest for bare stents due to the thick (~50 μm) oxide layer on stainless steel. As further shown therein, the combination of electrocoating and PMMA grafting shifted the oxygen 1s peak to a higher energy (component III), suggesting the presence of an organic compound comprising oxygen (e.g. the carboxyl group of PMMA) as the main component instead of the inorganic oxides typical of stainless steel (e.g. component II).

**Table 2: high-resolution XPS analysis of oxygen on stent surfaces following electrocoating with 4-(2-bromoethyl)phenyl diazonium and PMMA-grafting**

| O 1s | Position (eV) | Bare stent (%) | Bare stent with PMMA grafting (%) | Electrocoated stent (%) | Electrocoated stent with PMMA grafting (%) |
|---|---|---|---|---|---|
| O 1s (I) | 529.98 | --- | 15.06 | 2.5 | 7.69 |
| O 1s (II) | 532.66 | 100.0 | 84.93 | 97.42 | 20.92 |
| O1s (III): O=C-O | 533.36 | --- | --- | ---- | 70.60 |
| (%) Total oxygen | | 62.8 | 45.3 | 45.78 | 40.7 |

As shown in Table 3, not only is the carbon content on the stent surface increased by electrocoating and PMMA grafting, but PMMA grafting increases the percentage of the carbon from carboxyl groups (component III), particularly on electrocoated stents, indicating the presence of PMMA, which comprises carboxyl groups.

**Table 3: high-resolution XPS analysis of carbon on stent surfaces following electrocoating with 4-(2-bromoethyl)phenyl diazonium and PMMA-grafting**

| C 1s | position (eV) | Bare stent (%) | Bare stent with PMMA grafting (%) | Electrocoated stent (%) | Electrocoated stent with PMMA grafting (%) |
|---|---|---|---|---|---|
| C 1s(I) | 285 | 44.56 | 44.40 | 35.72 | 39.42 |
| C 1s(II) | 286.5 | 46.07 | 41.00 | 50.85 | 37.89 |
| C 1s(III) O=C-O- | 289.3 | 9.3 | 14.58 | 13.4 | 22.88 |
| (%)Total carbon | | 19.9 | 26.6 | 38.2 | 46.5 |

As shown in Figure 14, the polarization resistance and impedance are increased by either electrocoating with 4-(2-bromoethyl)phenyl diazonium or exposure to the PMMA grafting solution, and increased the most by electrocoating with 4-(2-bromoethyl)phenyl diazonium followed by PMMA grafting.

## *EXAMPLE 6*

### *Electrocoating of stents with two diazonium compounds*

Stainless steel stents were electrocoated as described hereinabove with 4-dodecyloxyphenyl diazonium tetrafluoroborate (DS06) and 4-(2-hydroxyethyl)phenyl diazonium tetrafluoroborate (DS04) in ratios of 0:100, 10:90, 50:50, 90:10 and 100:0 (weight percentage ratios), at a combined concentration of 8 mM. The electrocoated stents were characterized by XPS, cyclic voltammetry and electrochemical impedance spectroscopy. Non-electrocoated bare metal stents (BMS) were used as a control.

The integral of current over time during the electrocoating process, as determined by in-process cyclic voltammetry, indicates the amount of material reduced during the process. As shown in Figure 15, the amount of reduction depended on the proportion of 4-dodecyloxyphenyl diazonium and 4-(2-hydroxyethyl)phenyl diazonium used to electrocoat the stents.

As shown in Figure 16, the polarization resistance and capacitance of electrocoated stents were significantly higher than those of control stents, indicating that the stents were successfully electrocoated. Furthermore, the polarization resistance and capacitance were dependent on the proportion of 4-dodecyloxyphenyl diazonium and 4-(2-hydroxyethyl)phenyl diazonium used to electrocoat the stents.

As shown in Figure 17, electrocoating of stents blocked the current through the stent surface, as observed by out-of-process cyclic voltammetry, further indicating successful electrocoating of the stents. Furthermore, the degree to which current was blocked depended on the proportion of 4-dodecyloxyphenyl diazonium and 4-(2-hydroxyethyl)phenyl diazonium used to electrocoat the stents.

As shown in Table 4 below, the electrocoating of stents in each of various proportions of the two diazonium compounds resulted in a considerable increase in

carbon, as well as a considerable decrease in metal (e.g. iron and chromium), on the stent surface.

**Table 4: XPS elemental analysis of stents surfaces following electrocoating with DS06 and DS04**

| Diazonium compound ratio | % C | % N | % O | % Cr | % Fe |
|---|---|---|---|---|---|
| 90% DS06<br>10% DS04 | 72.23 | 2.18 | 24.60 | 1.00 | - |
| 50% DS06<br>50% DS04 | 79.81 | 4.23 | 15.54 | 0.42 | - |
| 10% DS06<br>90% DS04 | 78.95 | 3.94 | 16.69 | 0.43 | - |
| 100% DS04 | 72.47 | 2.68 | 23.15 | 0.99 | 0.70 |
| Control | 39.66 | 3.44 | 43.44 | 9.24 | 3.44 |

As shown in Table 5, the C-H component of the carbon peak is increased, and the C-O component is decreased, by electrocoating with the diazonium compounds, which comprise more C-H than C-O.

**Table 5: high-resolution XPS analysis of carbon on stent surfaces following electrocoating with DS06 and DS04**

| Diazonium compound ratio | (C-H) % | (C-O) % | C (other) % |
|---|---|---|---|
| 90% DS06 10% DS04 | 62.33 | 23.40 | 14.27 |
| 50% DS06 50% DS04 | 63.92 | 30.57 | 5.50 |
| 10% DS06 90% DS04 | 58.92 | 29.28 | 11.81 |
| 100% DS04 | 67.79 | 29.38 | 2.83 |
| Control | 38.66 | 53.57 | 7.77 |

As shown by Table 6, the metal oxide component of the oxygen peak is decreased, and the organic component is increased, by electrocoating with the organic diazonium compounds.

**Table 6: high-resolution XPS analysis of oxygen on stent surfaces following electrocoating with DS06 and DS04**

| Diazonium compound ratio | (C-O-H) % | $Cr_2O_3$ | $Fe_2O_3$ |
|---|---|---|---|
| 90% DS06 10% DS04 | 49.67 | 4.62 | 45.71 |
| 50% DS06 50% DS04 | 78.43 | 1.62 | 19.94 |
| 10% DS06 90% DS04 | 77.93 | 2.10 | 19.97 |
| 100% DS04 | 52.50 | 34.04 | 13.46 |
| Control | 18.61 | 66.18 | 15.21 |

## *EXAMPLE 7*

### *Stents electrocoated with aliphatic aryl group and coated with PEVA:PBMA*

Stainless steel stents were electrocoated as described hereinabove, using 8 mM of 4-dodecyloxyphenyl diazonium tetrafluoroborate as the diazonium salt.

Electrocoated stents were then spray-coated with spray-coating solution (a) (PEVA:PBMA:paclitaxel in ethyl acetate), as described hereinabove. Non-electrocoated stents were spray-coated as a control.

As shown in Figures 18a-b, no damage is visible under the light microscope following spray-coating of stents (a non-electrocoated stent is shown).

However, as shown in Figures 19a-c, the surface of non-treated stents, after incubation for 3 days at accelerated conditions, became whiter and more reflective with wavy characteristics, due to changes in the stent surface properties.

In contrast, as shown in Figures 20a-c, the surface of treated stents remained smooth and had no visible damage following incubation for 3 days at accelerated conditions.

All 5 non-treated stents had observable defects when examined by light microscopy following incubation for 3 days at accelerated conditions. In contrast, none of the 5 treated stents examined by light microscopy had observable defects following incubation for 3 days.

Similar results were obtained by scanning electron microscopy (SEM).

As shown in Figures 21a-b, the surface of non-treated stents was covered with bumps following incubation for 3 days at accelerated conditions, indicating swelling and detachment of the coating from the metal surface.

In contrast, as shown in Figures 21c-d, the surface of treated stents after 3 days of incubation remained smooth and defect-free.

Non-treated stents were observed to have defects in 47 ± 14.8 % of all AOIs examined by SEM following incubation for 3 days at accelerated conditions. In contrast, no defects were observed in any AOIs of treated stents SEM following incubation for 3 days at accelerated conditions.

## *EXAMPLE 8*

### *Stents with polymethylmethacrylate (PMMA) grafted onto a functionalized aryl group and coated with PEVA:PBMA*

Stents were electrocoated with 4-(2-bromoethyl)phenyl diazonium tetrafluoroborate and grafted with PMMA as described hereinabove, and then spray-coated with spray-coating solution (a) (PEVA:PBMA:paclitaxel in ethyl acetate), as described hereinabove. Non-treated (bare metal) stents were spray-coated as a control.

The stents were then incubated for 12 days at accelerated conditions.

As shown in Figure 22, the surfaces of non-treated stents exhibited considerable peeling of the polymer-based coating from the stainless steel of the stent.

In contrast, as shown in Figure 23, the surfaces of treated stents exhibited full adhesion of the coating to the stent surface, with no peeling.

## *EXAMPLE 9*

### *Stents electrocoated with aliphatic aryl group and coated with SIBS*

Stents were prepared as described in Example 7, except that solution (c) was used instead of solution (a) for spray-coating. Coatings with a thickness of either 5 μm or 0.5 μm were applied by spray-coating.

As shown in Figures 24a-b, considerable delamination was observable in non-treated stents with 5 μm thick coatings incubated for 3 days under accelerated conditions.

In contrast, as shown in Figures 25a-b, the surface of treated stents with 5 μm thick coatings incubated under the above conditions remained smooth, and no significant defects were visible.

The SIBS polymer is more cohesive than the PBMA:PEVA polymer. Hence, only drug near the surface is released. Thin SIBS coatings may thus be desirable. However, relatively thick SIBS coatings (e.g. 12 μm in the TAXUS® stent) are typically used in order to improve the adhesion of the SIBS coating to the metal surface of the stent.

As shown in Figures 26a-b, severe delamination and peeling of a 0.5 μm thick SIBS + paclitaxel coating was observable in non-treated stents.

In contrast, as shown in Figures 27a-b, no peeling or delamination of the 0.5 μm thick SIBS + paclitaxel coating was observable in treated stents.

Thus, the electrocoated diazonium compound is capable of causing even a 0.5 μm thick SIBS + paclitaxel coating to remain adhered to the surface of the stent.

## *EXAMPLE 10*

### *Stents electrocoated with aliphatic aryl group and coated with PEVA:PBMA and PBMA top coat*

Stents were treated as described in Example 7, except that a 0.5 μm thick top coat of PBMA (solution (b)) was added in order to slow the release of paclitaxel from the polymer + paclitaxel coating.

Treated and non-treated stents were incubated under accelerated conditions. Damage was assessed on days 0, 3 and 30 of the incubation by measuring weight loss and quantifying defects using scanning electron microscopy.

As shown in Table 7 below, treated stents exhibited considerable less damage than non-treated stents.

**Table 7: weight loss and defects in electrocoated and control stents incubated under accelerated conditions**

| Incubation Time | Weight loss | | PV | SEM-quantified defects | | PV |
|---|---|---|---|---|---|---|
| days | micrograms | | % | % | | % |
| | electrocoated | control | | electrocoated | control | |
| 0 | 0 | 0 | - | 2.5 ± 5 | 2.5 ± 5 | |
| 3 | 7.5 ± 2.1 | 8.7 ± 0.9 | 26.9750 | 10 ± 12 | 57.5 ± 18 | 0.6955 |
| 30 | 31.6 ± 5.7 | 58.8 ± 5.6 | 0.0063 | 7.5 ± 10 | 95 ± 5 | 0.0004 |

Figure 28 shows stents prepared as described above before incubation.

As shown in Figure 29, some damage to the surface of non-treated stents was observable after 3 days of incubation under accelerated conditions. For example, some of the pores in the coating appear enlarged.

As shown in Figure 30, severe delamination of the polymer-based coating was observed on the surface of non-coated stents following 30 days of incubation at 60 °C. Large patches on the surface were completely delaminated.

In contrast , as shown in Figures 31 and 32, no damage to the stent surfaces was observable in treated stents following 3 days (Figure 16) or 30 days (Figure 17) incubation at 60 °C.

## *EXAMPLE 11*

### *Stents electrocoated with aliphatic aryl group and coated with biodegradable coating*

Stents were electrocoated with 4-dodecyloxyphenyl diazonium as described hereinabove, and then coated with a 5 μm thick coating of RESOMER® LC 703 S (spray-coating solution (d)), a biodegradable copolymer of L-lactide and ε-

caprolactone, which is absorbed completely in the human body within approximately 6 months, and metabolized to generate carbon dioxide and water.

As shown in Figure 33, the surface of non-treated stents was severely damaged following incubation of the stents for 30 days at physiological conditions, as seen by light microscopy. The coating of the stents disintegrated completely.

In contrast, as shown in Figure 34, no damage to the surface of treated stents was visible following incubation for 30 days at physiological conditions.

## *EXAMPLE 12*

### *Pharmacokinetics of stents treated with aliphatic aryl group and coated with SIBS*

Stents were prepared as described in Example 8, and the controlled release of paclitaxel from stents incubated in physiological conditions was monitored over a period of 30 days.

Stents were prepared with either a thick or thin SIBS coating. Thick coatings were approximately 10 μm thick, weighed approximately 200 μg and comprised approximately 50 μg of paclitaxel. Thin coatings were approximately 0.5 μm thick, weighed approximately 10 μg and comprised approximately 4 μg of paclitaxel.

As shown in Figure 35, the release pattern of paclitaxel from the treated stents was significantly related to the coating thickness. The thin coating had released 98 % of the drug following 30 days of incubation, with an initial burst release of 55 %, while the thick coating released less than 10 % of the drug following 30 days of incubation, with only a small burst. The absolute amount of drug that had been released was fairly similar in both systems (1.4 μg, and 1.6 μg respectively).

These results suggest that the rate of drug release is controlled mainly by the surface and not by the total volume. As the treated stents adhere more strongly to the polymer-based coating and exhibit considerably less delamination and cracking of the coating, as demonstrated hereinabove, it is thus possible for treated stents to have a stable thin coat, with a similar release profile (in absolute quantities of drug released) to that of thicker coats, which may be beneficial due to the reduction of materials applied to the stent.

The pattern of release also differed between treated and untreated stents.

As shown in Figure 36, initial burst of drug release from thin coatings was significantly lower in treated stents than in non-treated stents. The results shown were obtained from 5 samples for each group.

## *EXAMPLE 13*

### *Pharmacokinetics of sterilized and unsterilized stents treated with aliphatic aryl group and coated with PEVA:PBMA*

Stents were electrocoated and coated with PEVA:PBMA:paclitaxel as described in Example 7.

The polymer-based coatings were 5 μm thick and comprised approximately 90 μg paclitaxel. Some of the stents were sterilized with ethylene oxide after being spray-coated, as described hereinabove.

As shown in Figure 37, drug release was significantly slower in treated stents than in non-treated stents, in both sterilized and unsterilized stents.

## *EXAMPLE 14*

### *Pharmacokinetics of stents treated with polymethylmethacrylate (PMMA) grafted onto a functionalized aryl group*

Stents electrocoated with 4-(2-bromoethyl)phenyl diazonium were prepared as described hereinabove. Some of the electrocoated stents were PMMA-grafted as described hereinabove.

Slow release (SR) and fast release (FR) model stents were prepared. The slow release model comprised a 250 μg PBMA:PEVA:paclitaxel coating, whereas the fast release model further comprised a 50 μg PBMA top coat above the PBMA:PEVA:paclitaxel coating.

As shown in Figure 38, electrocoating with 4-(2-bromoethyl)phenyl diazonium resulted in a slower rate of drug release, and a smaller initial burst of drug release, in both slow release and fast release models. As further shown in Figure 23, PMMA grafting further delayed drug release in comparison to electrocoated stents without PMMA grafting.

## *EXAMPLE 15*

### *Adhesion tests on stainless steel plates*

316 L stainless steel plates were polished and sonicated in acetonitrile for 15 minutes. The plates were then electrocoated with 8 mM 4-dodecyloxyphenyl diazonium or tetrakis[(4-diazophenoxy)methyl]methane in extra dry acetonitrile and 0.1 M TBATFB, using 30 cycles from between 0.1 V negative to the OCP and 1.3 V negative to the OCP vs. a Pt electrode.

The electrocoated plates were dip-coated in ethyl acetate with 1 % (w/v) PEVA:PBMA at a 3:7 weight ratio and 0.67 % (w/v) paclitaxel to form a 2 μm thick coating, and dried for 48 hours before testing adhesion. Non-electrocoated plates were dip-coated as controls.

The coated plates were incubated in phosphate buffer with 0.3 % SDS at 37 °C. The adhesion test was then performed by applying and removing 3M 250 adhesion tape, according to the D-3359-02 ASTM standard test. All plates were photographed with a microscope camera following the adhesion test, and the percentage of the surface which peeled off was calculated.

As shown in Table 8, almost all of the PEVA:PBMA coating peeled off during adhesion tests performed on non-treated plates following incubation for 3 or 15 days. In contrast, only a relatively fraction of the PEVA:PBMA coating peeled off of the surface of plates electrocoated with 4-dodecyloxyphenyl diazonium even after 15 days of incubation.

**Table 8: Adhesion of PEVA:PBMA coating to stainless steel plates electrocoated with 4-dodecyloxyphenyl diazonium**

| **Incubation** | **Peeling of coating non-electrocoated plates** | | **Peeling of coating electrocoated plates** | |
|---|---|---|---|---|
| Days | Value (%) | STDEV (%) | Value (%) | STDEV (%) |
| 0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 3 | 86.6 | ±13.0 | 24.2 | ±11.2 |
| 15 | 90.6 | ±4.2 | 30.4 | ±22.1 |

In another test, the effectiveness of 4-dodecyloxyphenyl diazonium and tetrakis[(4-diazophenoxy)methyl]methane in promoting adhesion were compared.

As shown in Table 9, tetrakis[(4-diazophenoxy)methyl]methane, which has 4 diazonium groups, was considerably more effective than 4-dodecyloxyphenyl diazonium in preventing a PEVA:PBMA coating from peeling off, following incubation for 3 days at 37 °C.

**Table 9: Effects of 4-dodecyloxyphenyl diazonium and tetrakis[(4-diazophenoxy)methyl]methane on adhesion**

| Electrocoating compound | Peeling (%) | STDEV (%) |
|---|---|---|
| tetrakis[(4-diazophenoxy)methyl]methane | 6.9 | 4.12 |
| 4-dodecyloxyphenyl diazonium | 60.8 | 7.18 |
| none | 96.2 | 0.88 |

*EXAMPLE 16*

***Electrocoating with two functionalized aryl groups and coated with PEVA:PBMA***

Stainless steel stents were electrocoated with various proportions of 4-dodecyloxyphenyl diazonium tetrafluoroborate (DS06) and 4-(2-hydroxyethyl)phenyl diazonium tetrafluoroborate (DS04), as described in Example 6.

The stents were then spray-coated with PEVA:PBMA with paclitaxel, as described in Example 7. The integrity of the polymer-based coating was then determined following incubation of the stents in phosphate buffer with 0.3 % SDS, using light microscopy.

As shown in Figure 39, following incubation for 3 days, significant delamination of the polymer-based coating was observed on the surface of non-electrocoated stents (Figure 40a), whereas slight delamination was observed in stents electrocoated with a mixture of 90 % 4-(2-hydroxyethyl)phenyl diazonium and 10 % 4-dodecyloxyphenyl diazonium (Figure 40b), and no delamination was observed in stents electrocoated with 90 % 4-dodecyloxyphenyl diazonium and 10 % 4-(2-hydroxyethyl)phenyl diazonium (Figure 40c).

As shown in Figure 40, similar results were obtained following incubation for 30 days. Severe delamination was observed on the surface of non-electrocoated stents (Figure 40a), whereas less delamination was observed in stents electrocoated with a mixture of 90 % 4-(2-hydroxyethyl)phenyl diazonium and 10 % 4-dodecyloxyphenyl diazonium (Figure 40b), and no delamination was observed in stents electrocoated with 90 % 4-dodecyloxyphenyl diazonium and 10 % 4-(2-hydroxyethyl)phenyl diazonium (Figure 40c).

## *EXAMPLE 17*

### *Durability of electrocoated layer in physiological conditions*

Stainless steel stents were electrocoated with 4-dodecyloxyphenyl diazonium tetrafluoroborate as described hereinabove, and incubated at 37 °C in phosphate buffer with 0.3 % SDS for 3 days. Stents were analyzed by out-of-process cyclic voltammetry before and after incubation. Before incubation, the peak current through the surface of electrocoated stents was 0.04 ± 0.02 mA, whereas the peak current for non-treated control stents was 0.1836 ± 0.071 mA. Following incubation for 3 days, the peak current for electrocoated stents was 0.081 ± 0.044 mA, whereas the peak current for non-treated stents was 0.146 ± 0.012 mA. Thus, the surface of electrocoated stents remained blocked relative to controls after incubation for 3 days.

Electrocoated stents were also incubated for 30 days at 37 °C in phosphate buffer with 0.3 % SDS and then spray-coated with PEVA:PBMA with paclitaxel. The polymer-coated stents were then incubated at 60 °C, and the ability of the electrocoated layer to preserve the integrity of a coating of PEVA:PBMA with paclitaxel was observed following 3 and 30 days incubation at 60 °C.

As shown in Figures 41 and 42, no delamination was observed in the electrocoated stents after incubation for 3 days (Figure 41a) or even 30 days (Figure 41b), whereas severe delamination was observed in the non-treated control stents following incubation for 3 days (Figure 42a), and especially after incubation for 30 days (Figure 42b). Thus, electrocoated stents incubated for 30 days at 37 °C retained

the ability to preserve the integrity of the polymer-based coating following incubation for an additional 3 or 30 days at 60 °C.

These results indicate that the electrocoated layer withstands incubation for at least 30 days.

## *EXAMPLE 18*

### *Binding nanoparticles to functionalized aryl group*

A conductive surface is electrocoated with a functionalized aryl moiety as described hereinabove in the Methods section.

Nanoparticles are prepared by adding about 200 mg of a polymer (e.g. polylactic acid) dissolved in about 18 ml of a volatile hydrophobic solvent (e.g. dichloromethane or acetone) to a solution comprising about 200 ml DDW and about 20 mg of a surfactant such as tocopherol and stirring with a homogenizer for at least 1 hour. The mixture is then frozen and lyophilized, yielding nanoparticles.

In order to introduce a functional group not present in the polymer to the nanoparticles, 5 % (by weight) of a compound (preferably hydrophobic) having the desired functional group (e.g. a long-chain alkyl thiol in order to introduce a thiohydroxy group) is dissolved in the hydrophobic solvent.

When the aryl moiety and the nanoparticle both comprise thiohydroxy groups, a covalent disulfide bond is formed by electrolyzing a solution of an alcohol (e.g. methanol) comprising about 0.5 M of a sodium alkoxide (e.g. $NaOCH_3$) and he nanoparticles, using a platinum foil as anode and the electrocoated conductive surface as a cathode. A current in the range of 250 to 700 mA is used.

Alternatively, a solution of hydrogen peroxide is used to oxidize the thiohydroxy groups to a disulfide group.

When the aryl moiety comprises an amine group and the nanoparticle comprises a –C(=O)OH group (or vice versa), a covalent amide bond is formed by placing the electrocoated conductive surface and the nanoparticles in a solvent such as dichloromethane and adding about 150 mM of hydroxybenzotriazole and about 150 mM of N,N'-diisopropylcarbodiimide, followed by stirring for about 2 hours.

When the aryl moiety comprises a –C(=O)OH group and the nanoparticle comprises a hydroxy group (or vice versa), a covalent ester bond is formed by placing the electrocoated conductive surface and the nanoparticles in an alcohol (e.g. methanol) and adding boric acid and stirring overnight.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

Citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A medical device comprising an object having a surface and a matrix comprising a pharmaceutically active agent, said matrix coating said surface and being adhered thereto via an adherence.

2. The medical device of claim 1, wherein said surface is a conductive surface.

3. The medical device of any of claims 1 to 2, wherein said adherence comprises an adhesive layer selected capable of strengthening adherence between said surface and said matrix such that peeling of said matrix from said surface with said adhesive layer is at least 10 % lower than peeling of said matrix from said surface without said adhesive layer when performing a comparative D-3359-02 ASTM test following incubation of each of said surfaces with said matrix in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C.

4. The medical device of any of claims 1 to 3, wherein said adherence comprises an adhesive layer selected capable of strengthening adherence between said surface and said matrix such that the percentage of defective areas on said matrix coating said surface with said adhesive layer is at least 10 % lower than the percentage of defective areas on said matrix coating said surface without said adhesive layer when examining each of said surfaces by scanning electron microscopy at a magnification of x300 following incubation of said surfaces in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C, said areas being a field of about 0.9 mm by about 0.9 mm, and said defective areas being any of said areas in which a failure in the integrity of the matrix is visible.

5. The medical device of any of claims 3 and 4, wherein said strengthening of said adherence modulates the release of said pharmaceutically active agent from said matrix when said matrix is subjected to physiological conditions.

6. The medical device of any of claims 3 and 4, wherein said strengthening of said adherence reduces the release rate of said pharmaceutically active agent from said matrix when said matrix is subjected to physiological conditions.

7. The medical device of any of claims 3 to 6, wherein said matrix remains physically intact for at least 30 days under physiological conditions.

8. The medical device of any of claims 3 to 7, wherein said adhesive layer comprises at least one moiety selected from the group consisting of an aryl moiety, an organosilane, a carboxylate, a sulfonate, a sulfate, a phosphonate and a phosphate.

9. The medical device of claim 8, wherein said adhesive layer comprises at least one aryl moiety being electrochemically attached to said surface.

10. The medical device of claim 9, wherein:

(i) said adhesive layer comprises at least two aryl moieties being electrochemically attached to said surface, said aryl moieties being different from one another;

(ii) said aryl moiety is substituted by at least one functional group at a meta or ortho position of said aryl moiety, with respect to the position of the aryl moiety that is being electrochemically attached to said surface;

(iii) said aryl moiety is electrochemically attached to said surface via at least two positions thereof;

(iv) said aryl moiety comprises at least two aromatic groups fused to one another; and/or

(vi) said aryl moiety comprises at least two aromatic groups covalently linked to one another via a linker.

11. The medical device of any of claims 9 to 10, wherein said aryl moiety comprises at least one functional group selected from the group consisting of alkyl, hydroxyalkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heteroalicyclic, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, halide,

amine, amide, carbonyl, carboxy, thiocarboxy, ether, thioether, epoxide (oxirane), sulfonyl, sulfinyl, sulfonamide, nitro, nitrile, isonitrile, thiirane, aziridine, nitroso, hydrazine, carbamyl and thiocarbamyl.

12. The medical device of claim 11, wherein said functional group is selected from the group consisting of alkyl, hydroxyalkyl, haloalkyl, alkoxy, carboxy and nitro.

13. The medical device of any of claims 9 to 12, wherein said adhesive layer further comprises a polymer grafted onto said aryl moiety.

14. The medical device of claim 13, wherein said polymer is selected from the group consisting of polyacrylic acid, polymethacrylic acid, polyacrylate ester, polymethacrylate ester and copolymers thereof.

15. The medical device of claim 14, wherein said polymer is poly(methyl methacrylate).

16. The medical device of any of claims 9 to 10, wherein said aryl moiety is a polymer comprising a plurality of aromatic groups being covalently linked to one another via a linker.

17. The medical device of claim 16, wherein said plurality of aromatic groups comprises phenyl.

18. The medical device of claim 17, wherein said polymer is polystyrene.

19. The medical device of any of claims 9 to 10, wherein said aryl moiety comprises at least two aromatic groups covalently linked to one another via a linker, and said linker comprises a plurality of alkoxy groups, each of said alkoxy groups being attached to one of said at least two aromatic groups.

20. The medical device of any of claims 9 to 12, wherein said aryl moiety electrochemically attached to said surface comprises a phenyl attached to said surface via at least two positions thereof.

21. The medical device of claim 20, wherein said two positions of said phenyl are at a meta position with respect to one another.

22. The medical device of any of claims 9 to 10, wherein said aryl moiety comprises an anthracene.

23. The medical device of claim 22, wherein said anthracene is attached to said surface via at least two positions thereof.

24. The medical device of any of claims 9 to 12, wherein said conductive surface has at least two aryl moieties being electrochemically attached thereto, at least one of said aryl moieties comprising a hydrophilic functional group and at least one other of said aryl moieties comprising a hydrophobic functional group.

25. The medical device of any of claims 1 to 24, being an implantable medical device.

26. The implantable medical device of claim 25, being a stent.

27. A method for modulating a release of a pharmaceutically active agent from a matrix coating a surface, the method comprising strengthening an adherence between said matrix and said surface.

28. The method of claim 27, wherein said surface is a conductive surface.

29. The method of any of claims 27 to 28, wherein said surface is a surface of a medical device.

30. The method of any of claims 27 to 29, wherein said strengthening of said adherence between said matrix and said surface is such that peeling of said matrix from said surface in the presence of said strengthening of said adherence is at least 10 % lower than peeling of said matrix from said surface without said strengthening of said adherence when performing a D-3359-02 ASTM test following incubation of each of said surfaces with said matrix in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C.

31. The method of any of claims 27 to 30, wherein said strengthening of said adherence between said matrix and said surface is such that the percentage of defective areas on said matrix coating said surface in the presence of said strengthening is at least 10 % lower than the percentage of defective areas on said matrix coating said surface without said strengthening of said adherence when examining each of said surfaces by scanning electron microscopy at a magnification of x300 following incubation of said surfaces in an aqueous solution of a phosphate buffer comprising 0.3 % sodium dodecyl sulfate, at a pH of 7.4 and a temperature of 37 °C, said areas being a field of about 0.9 mm by about 0.9 mm, and said defective areas being any of said areas in which a failure in the integrity of the matrix is visible.

32. The method of any of claims 27 to 31, wherein said strengthening of said adherence is effected by an adhesive layer between said surface and said matrix.

33. The method of any of claims 27 to 32, being for reducing the release rate of said pharmaceutically active agent when said matrix is subjected to physiological conditions.

34. The method of any of claims 32 to 33, wherein said adhesive layer comprises at least one moiety selected from the group consisting of an aryl moiety, an organosilane, a carboxylate, a sulfonate, a sulfate, a phosphonate and a phosphate, the method further comprising attaching said at least one moiety to said surface to thereby obtain said adhesive layer.

35. The method of claim 34, wherein said adhesive layer comprises at least one aryl moiety, wherein said attaching comprises electrochemically attaching said at least one aryl moiety to said surface.

36. The method of any of claims 34 and 35, said adhesive layer strengthening an adherence between the surface and the matrix of the medical device of any of claims 9 to 24.

37. The medical device or method of any of claims 1 to 36, wherein said matrix comprises a polymer.

38. The medical device or method of claim 37, wherein said polymer of said matrix has a pharmaceutically active agent embedded therein.

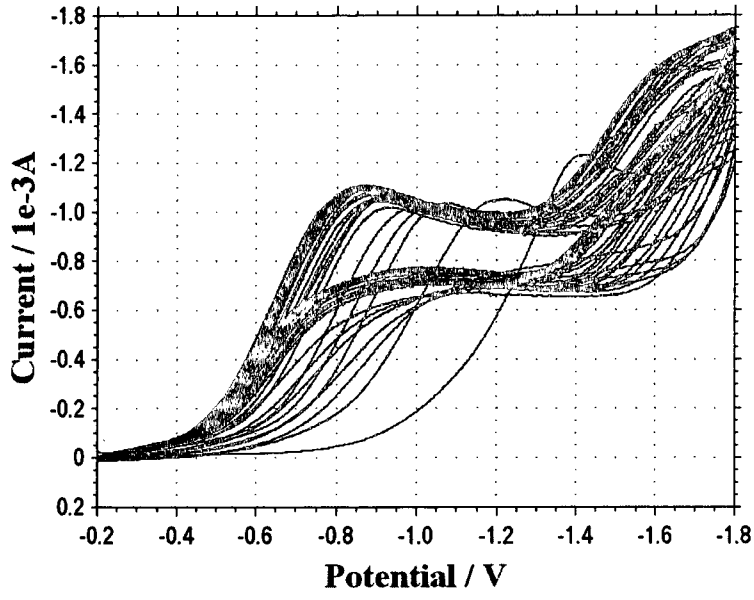
39. The medical device or method of any of claims 37 and 38, wherein said polymer of said matrix is selected from the group consisting of poly(ethylene-vinyl acetate), poly(butyl methacrylate), poly(styrene-isobutylene-styrene), poly-L-lactide and poly-ε-caprolactone, and mixtures and copolymers thereof.

40. The medical device or method of any of claims 1 to 39, wherein said pharmaceutically active agent is selected from the group consisting of an anti-thrombogenic agent, an anti-platelet agent, an anti-coagulant, a growth factor, a statin, a toxin, an antimicrobial agent, an analgesic, an anti-metabolic agent, a vasoactive agent, a vasodilator agent, a prostaglandin, a hormone, a thrombin inhibitor, an enzyme, an oligonucleotide, a nucleic acid, an antisense, a protein, an antibody, an antigen, a vitamin, an immunoglobulin, a cytokine, a cardiovascular agent, endothelial cells, an anti-inflammatory agent, an antibiotic, a chemotherapeutic agent, an antioxidant, a phospholipid, an anti-proliferative agent, a corticosteroid, a heparin, a heparinoid, albumin, a gamma globulin, paclitaxel, hyaluronic acid and any combination thereof.

41. The medical device or method of claim 40, wherein said pharmaceutically active agent is paclitaxel.

Figure 1:

a)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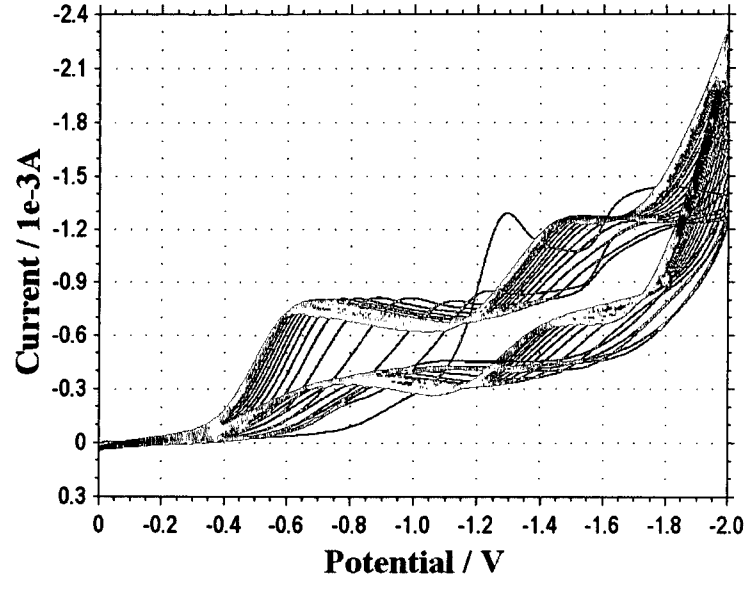
Potential / V

b)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0
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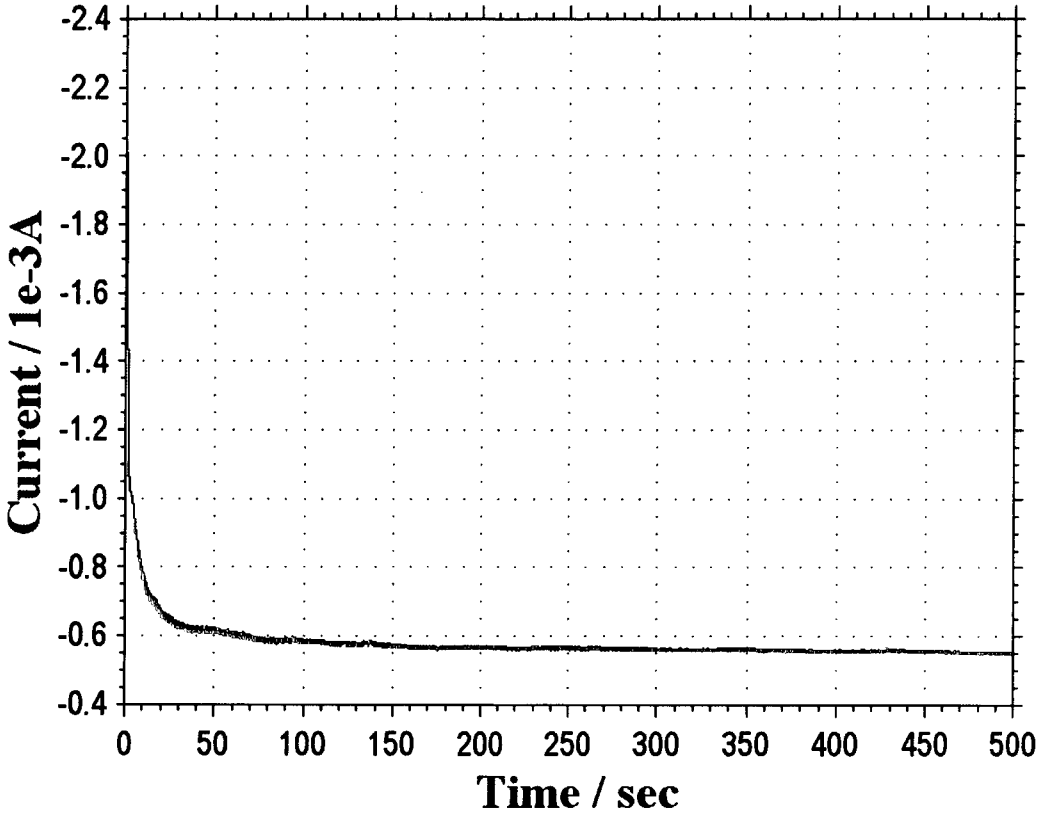
Potential / V

Figure 2: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0
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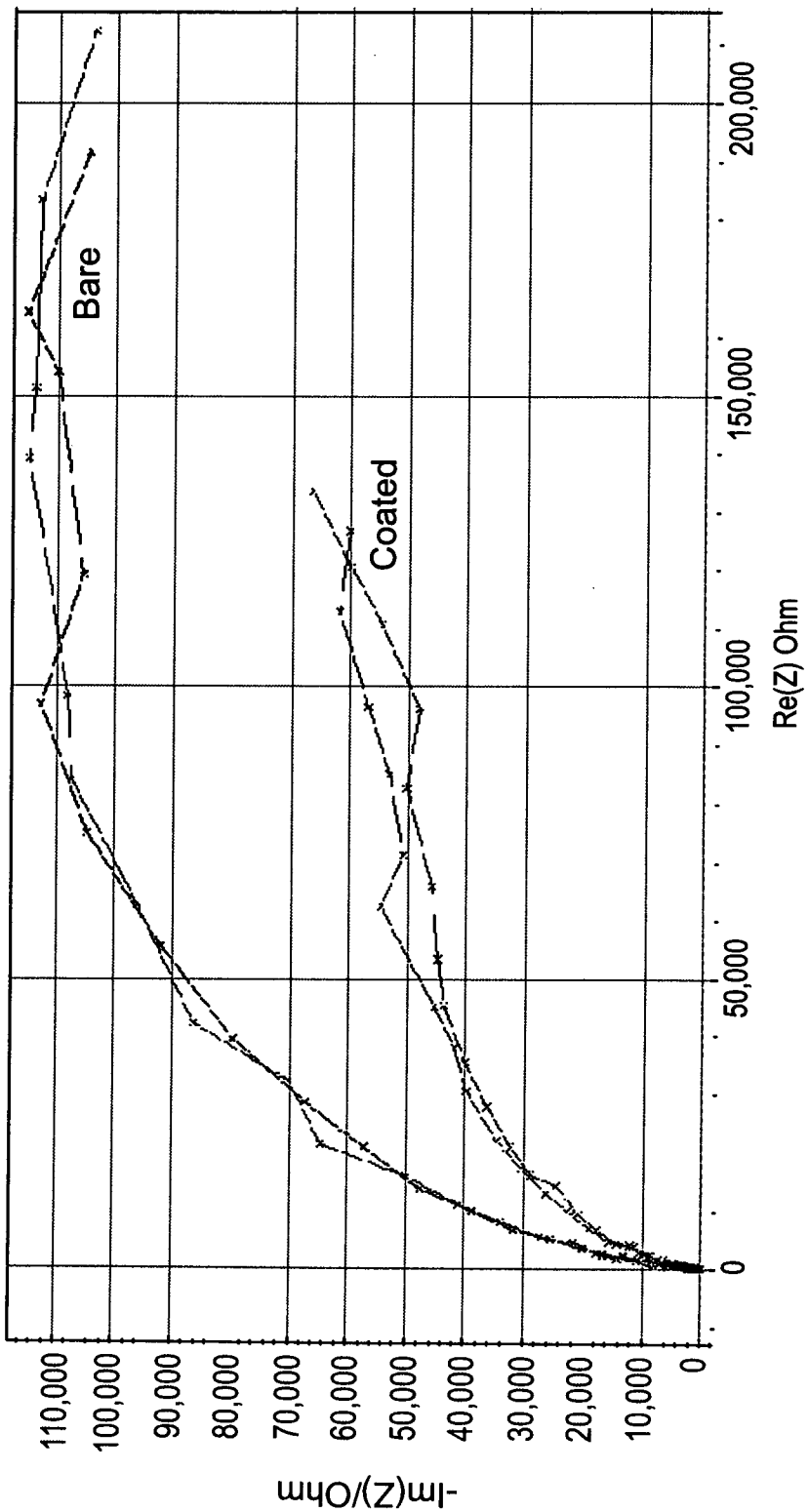
250
300
350
400
450
500
Time / sec


Bare
Coated
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Re(Z) Ohm
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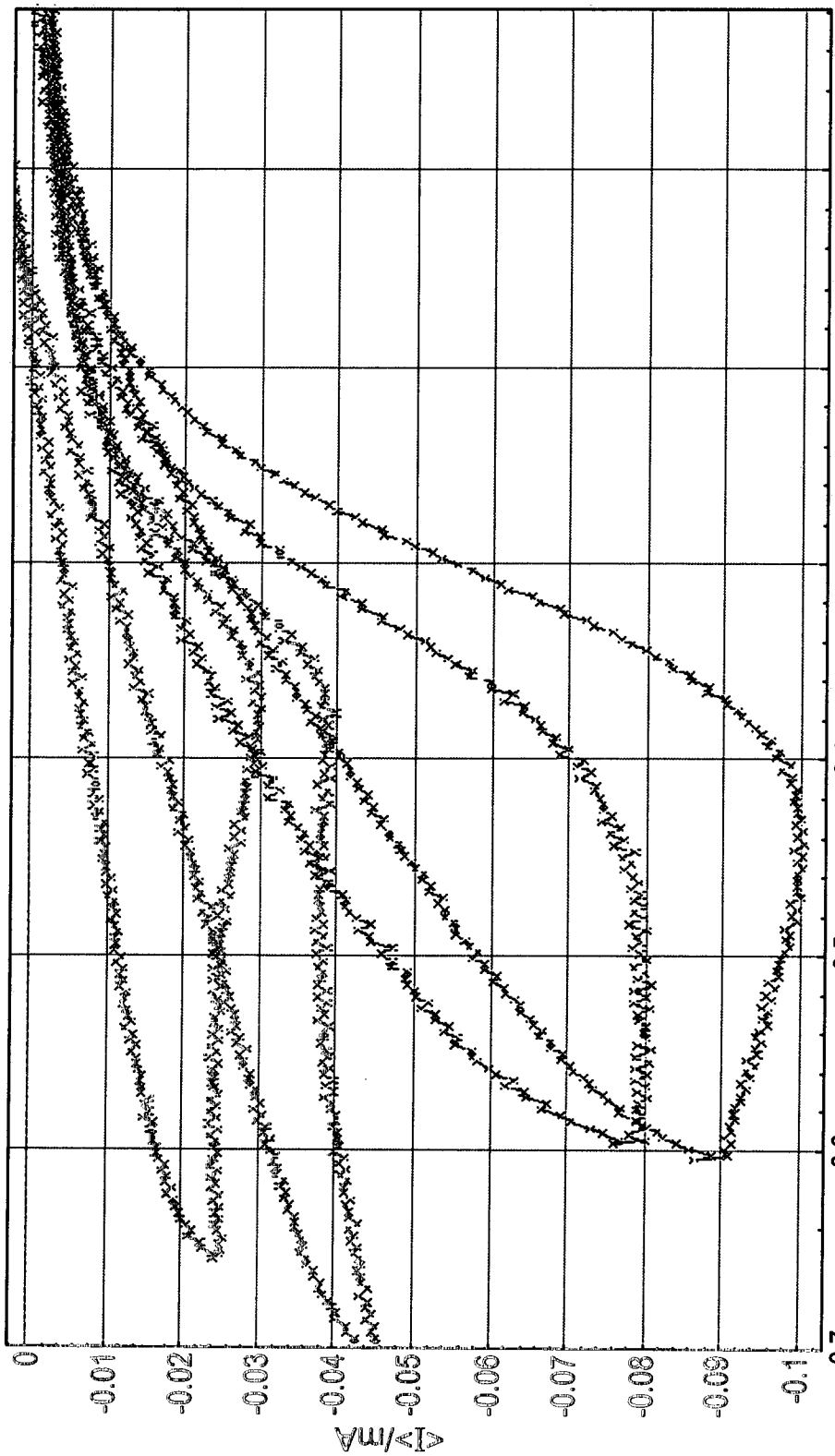
Fig. 3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<I>/mA
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-0.4
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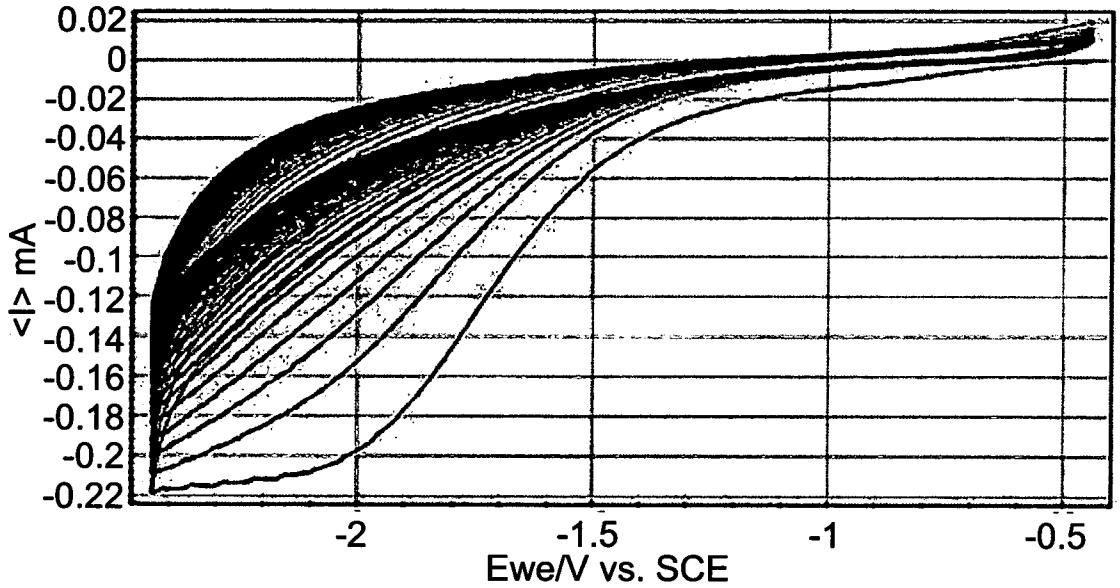
-0.7
Ewe/V vs.SCE

Fig. 4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-0.04
-0.06
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-0.14
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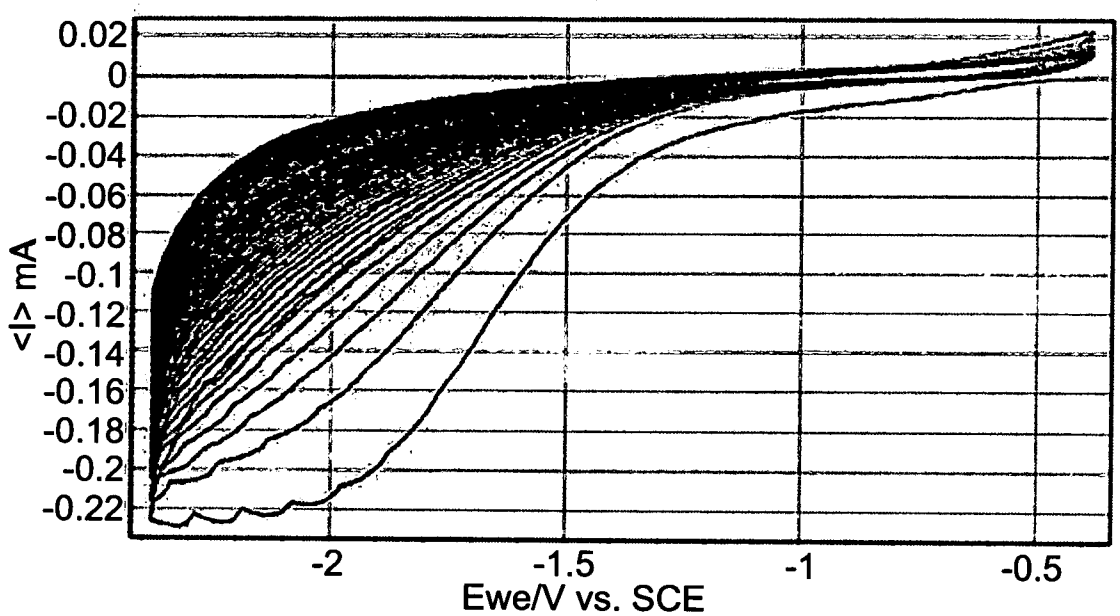
-1
-0.5
Ewe/V vs. SCE

Fig. 5a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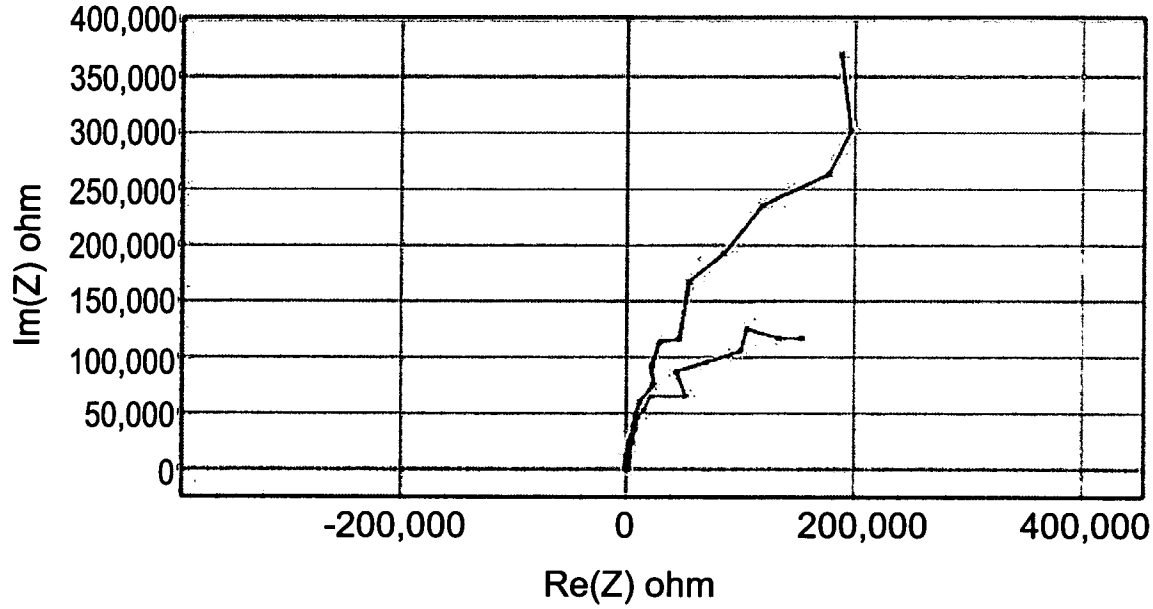
-0.5
Ewe/V vs. SCE

Fig. 5b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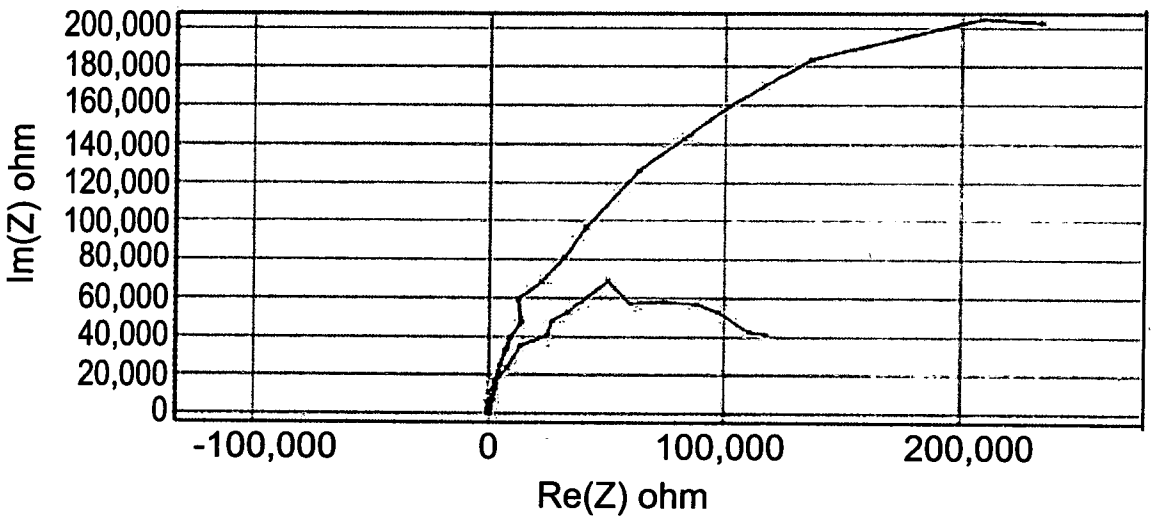
250,000
200,000
150,000
100,000
50,000
0
Im(Z) ohm
-200,000
0
200,000
400,000
Re(Z) ohm

Fig. 6a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100,000
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60,000
40,000
20,000
0
Im(Z) ohm
-100,000
0
100,000
200,000
Re(Z) ohm

Fig. 6b

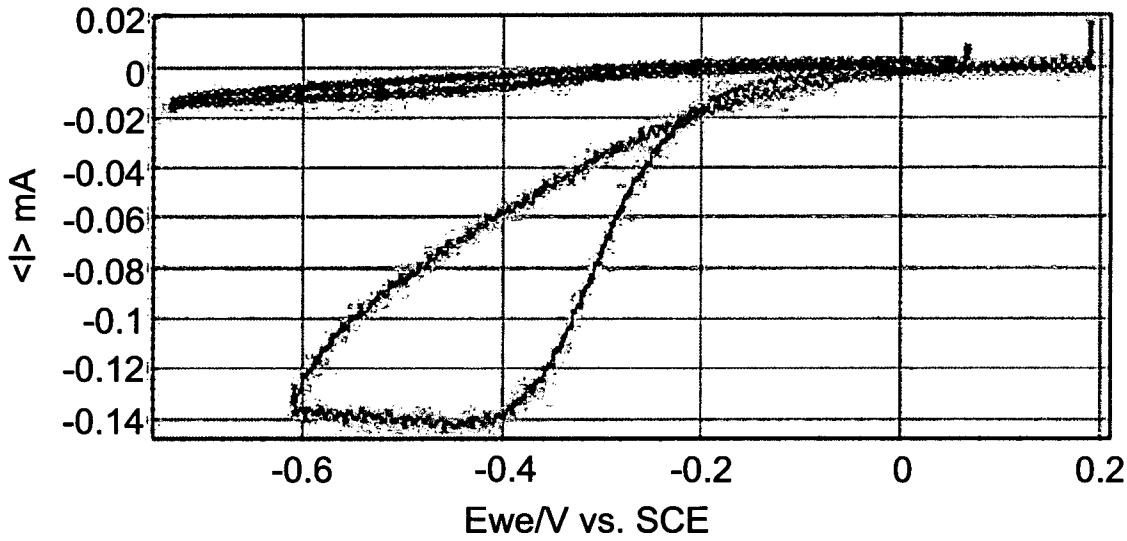

0.02
0
-0.02
-0.04
-0.06
-0.08
-0.1
-0.12
-0.14
<I> mA
-0.6
-0.4
-0.2
0
0.2
Ewe/V vs. SCE

Fig. 7a

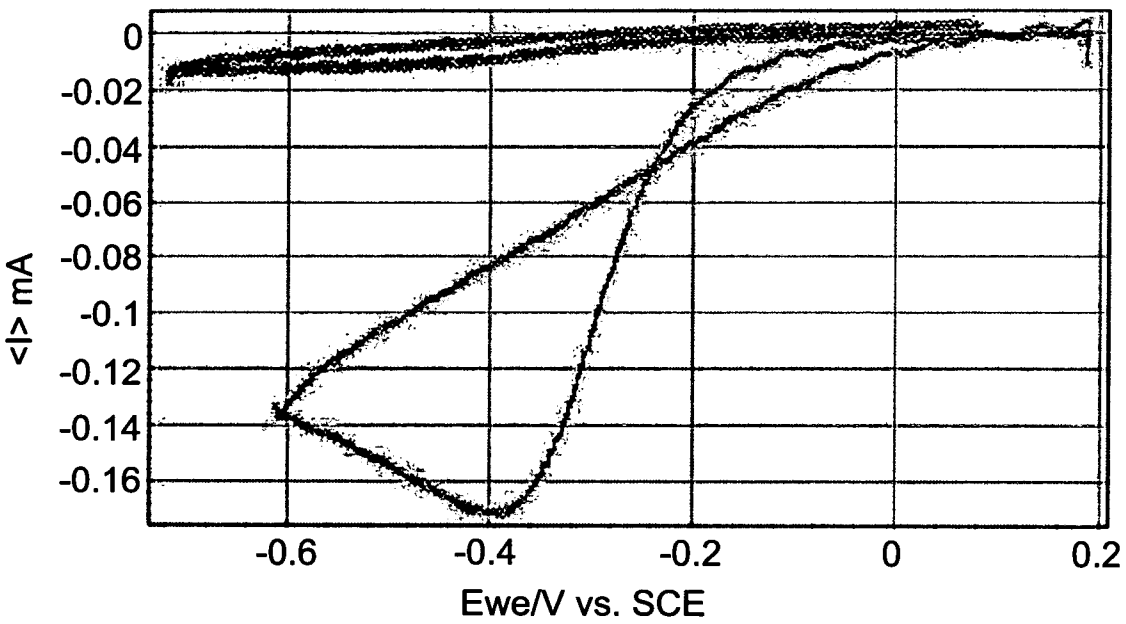

0
-0.02
-0.04
-0.06
-0.08
-0.1
-0.12
-0.14
-0.16
<I> mA
-0.6
-0.4
-0.2
0
0.2
Ewe/V vs. SCE

Fig. 7b

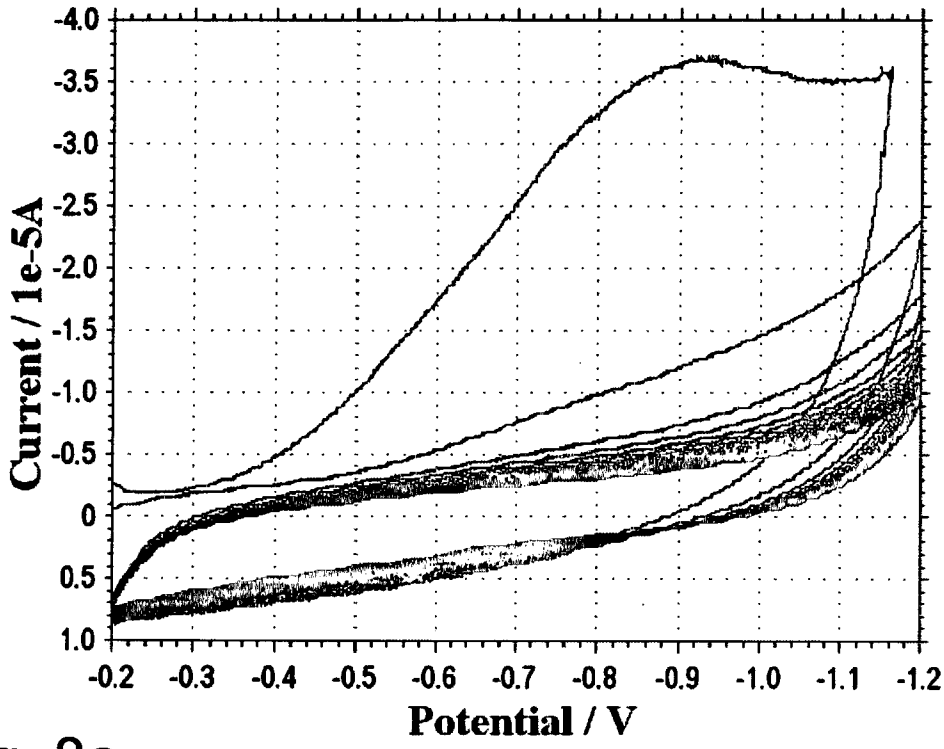

Current / 1e-5A
-4.0
-3.5
-3.0
-2.5
-2.0
-1.5
-1.0
-0.5
0
0.5
1.0
-0.2 -0.3 -0.4 -0.5 -0.6 -0.7 -0.8 -0.9 -1.0 -1.1 -1.2
Potential / V

Fig. 8a

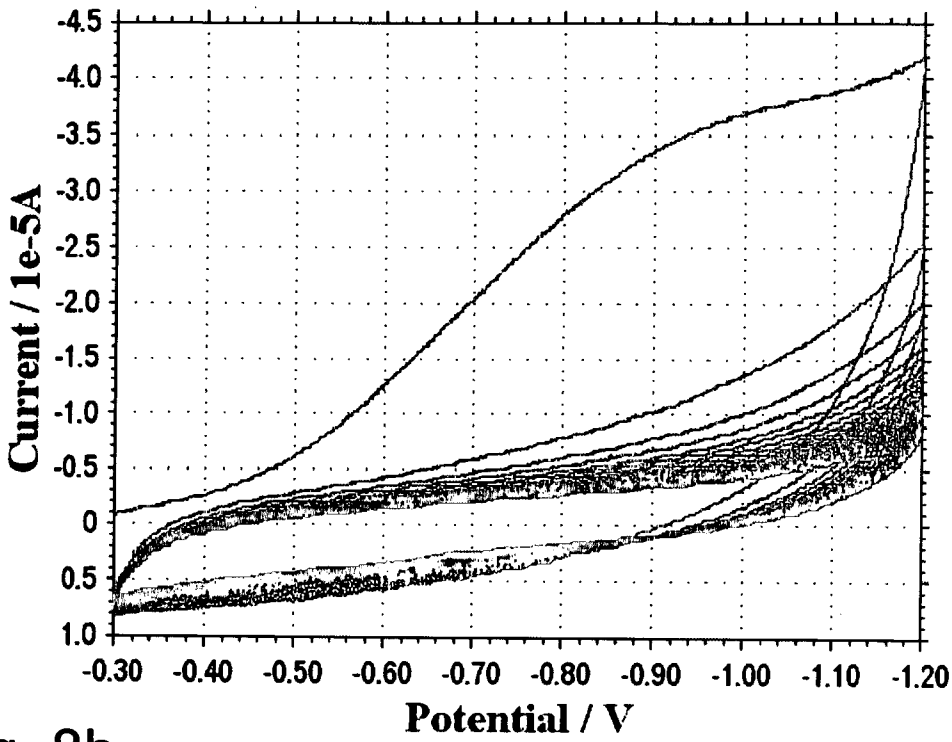

Current / 1e-5A
-4.5
-4.0
-3.5
-3.0
-2.5
-2.0
-1.5
-1.0
-0.5
0
0.5
1.0
-0.30 -0.40 -0.50 -0.60 -0.70 -0.80 -0.90 -1.00 -1.10 -1.20
Potential / V

Fig. 8b

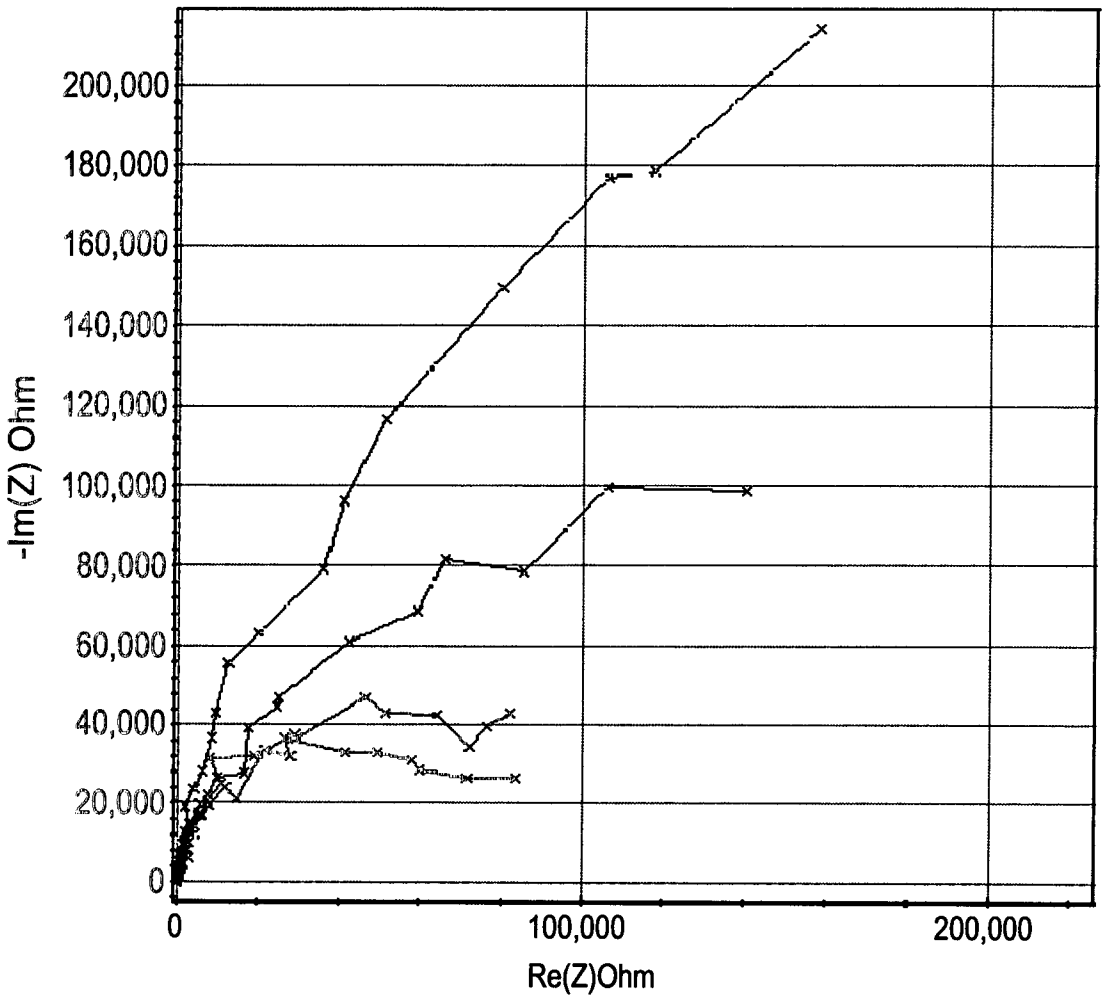

200,000
180,000
160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
-Im(Z) Ohm
0
100,000
200,000
Re(Z)Ohm

Fig. 9

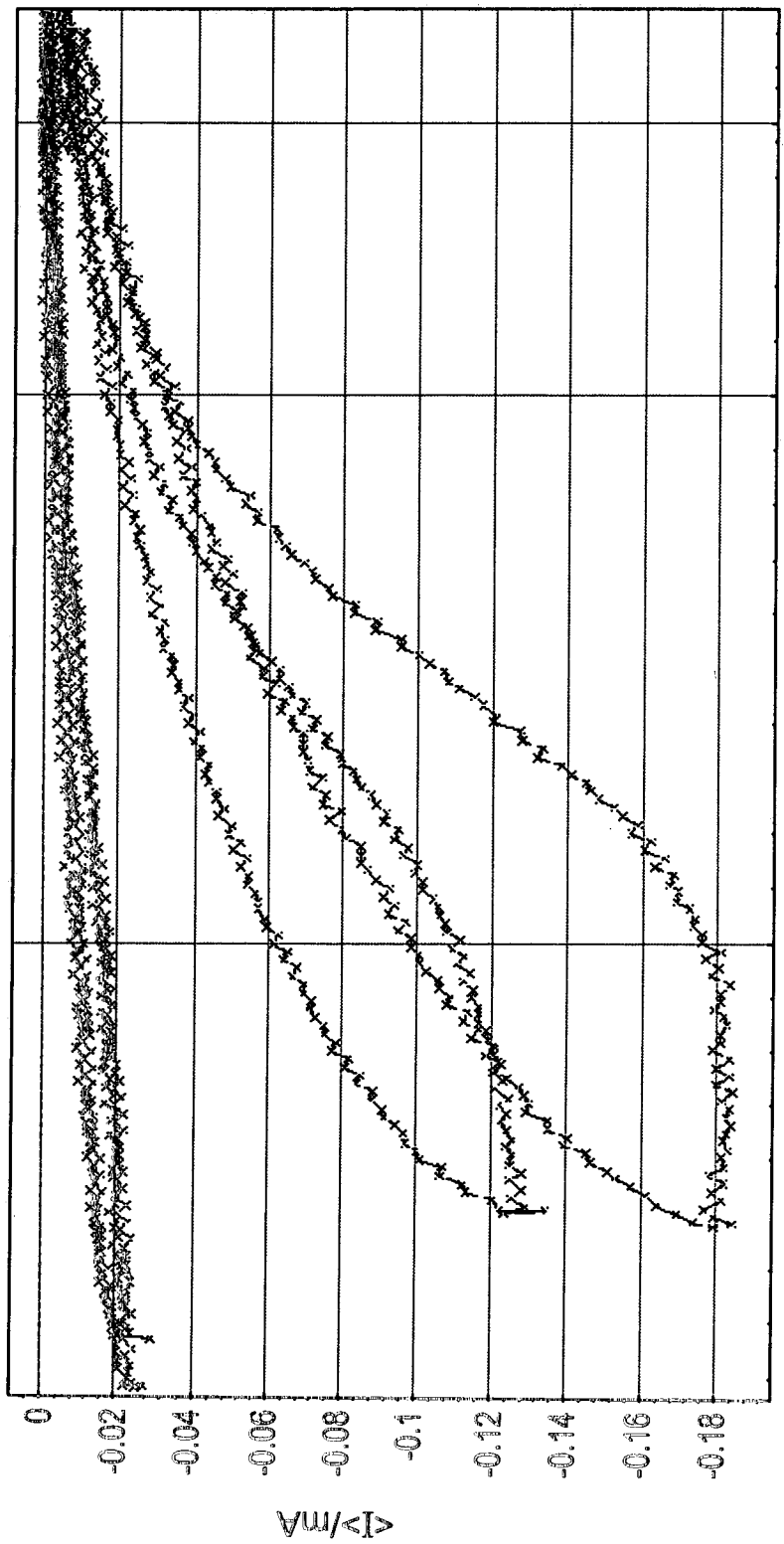



Fig. 10

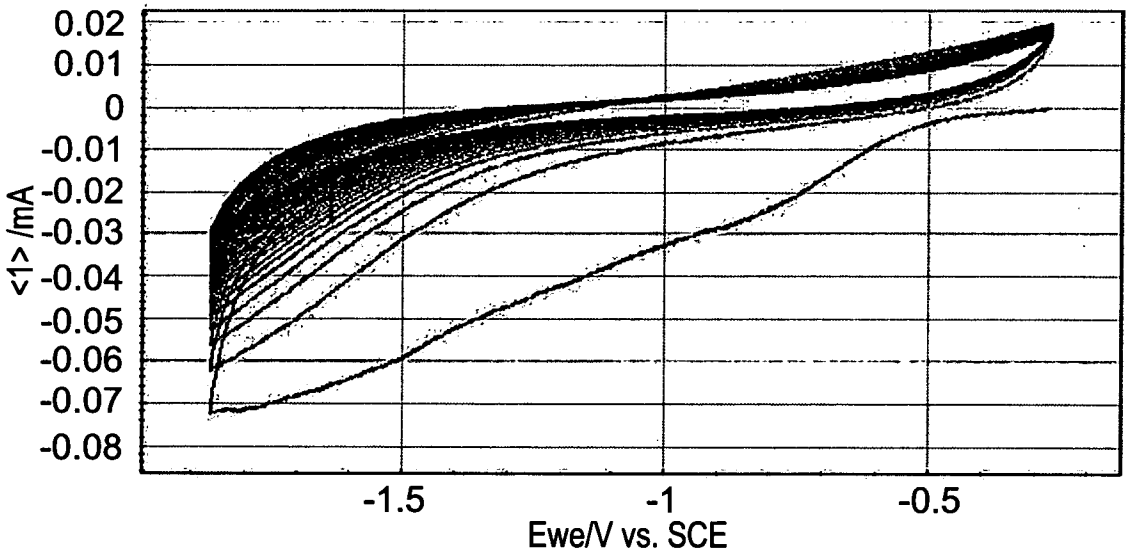



Fig. 11a

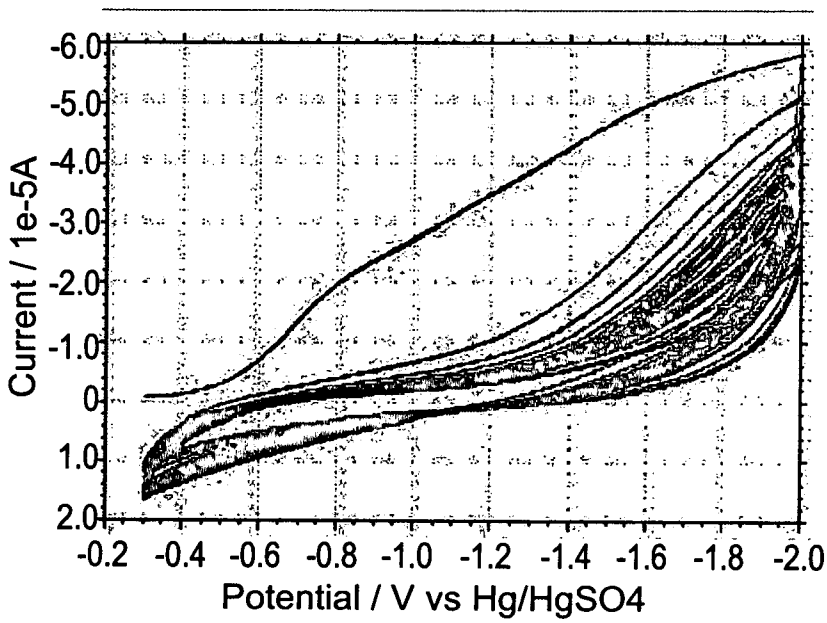



Fig. 11b

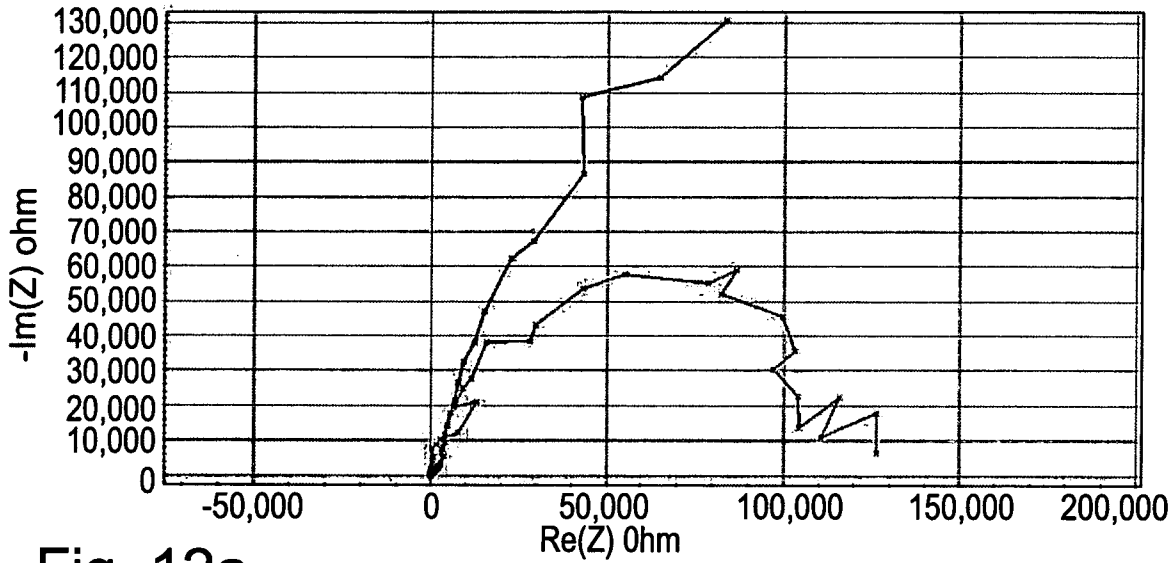



Fig. 12a

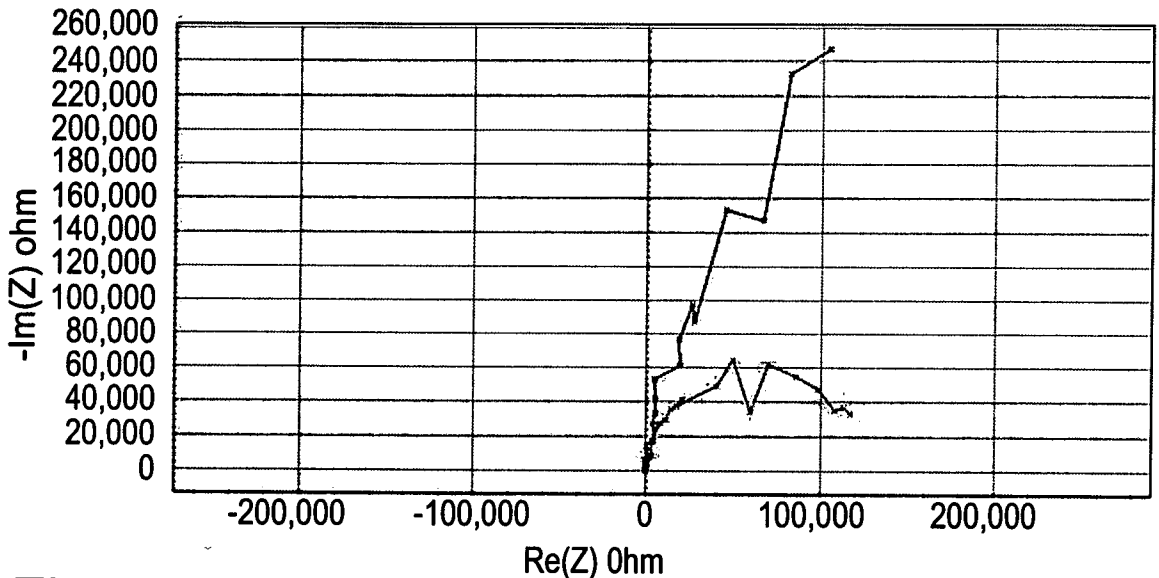



Fig. 12b

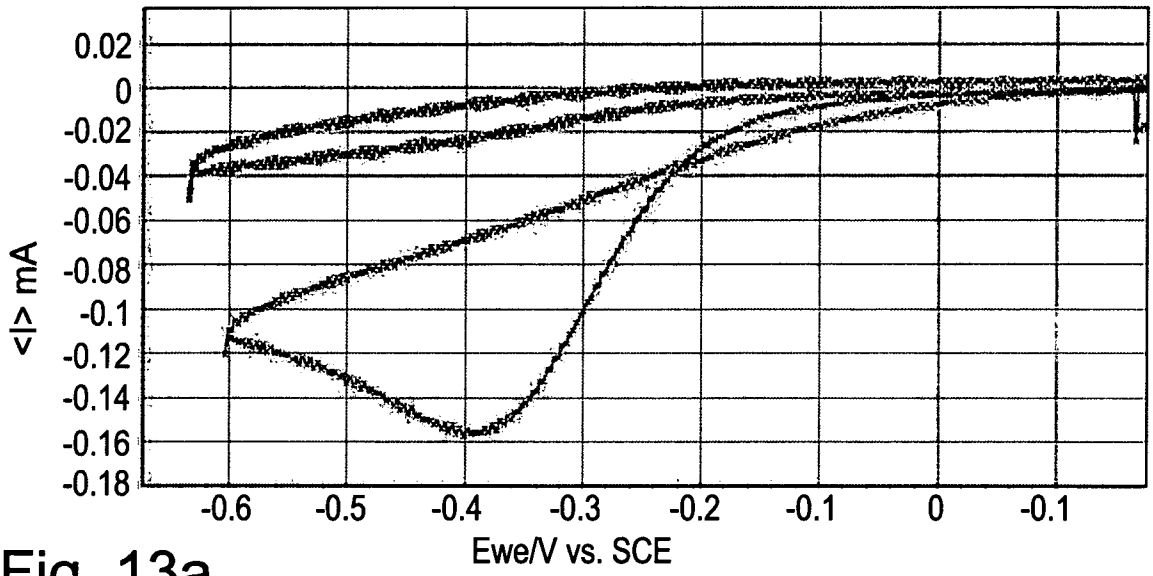



Fig. 13a

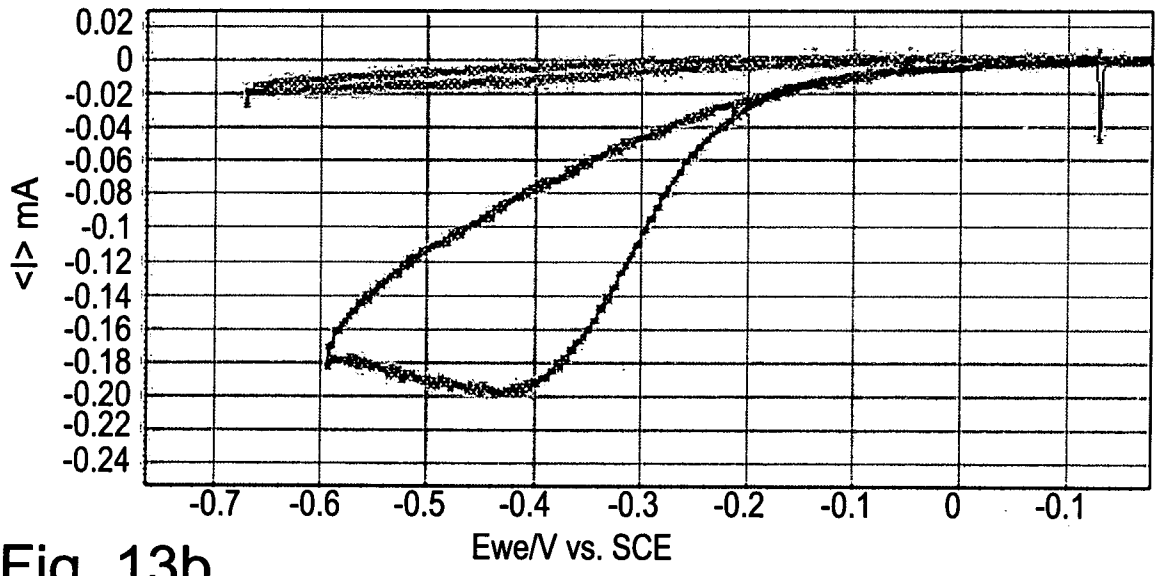



Fig. 13b

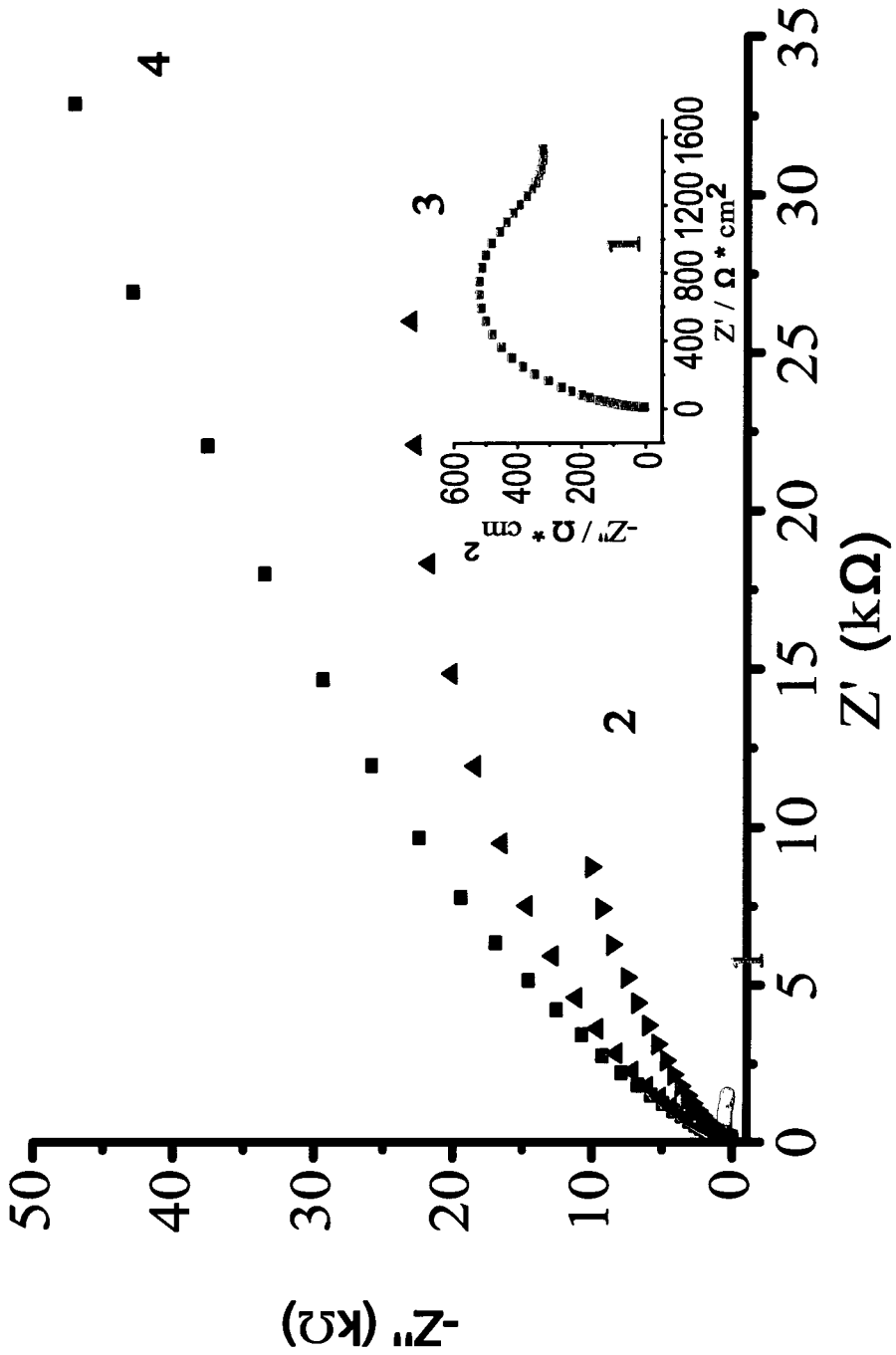

-Z'' (kΩ)
Z' (kΩ)
0
5
10
15
20
25
30
35
0
10
20
30
40
50
1
2
3
4
-Z'' / Ω * cm²
Z' / Ω * cm²
0
200
400
600
0
400
800
1200
1600

Fig. 14

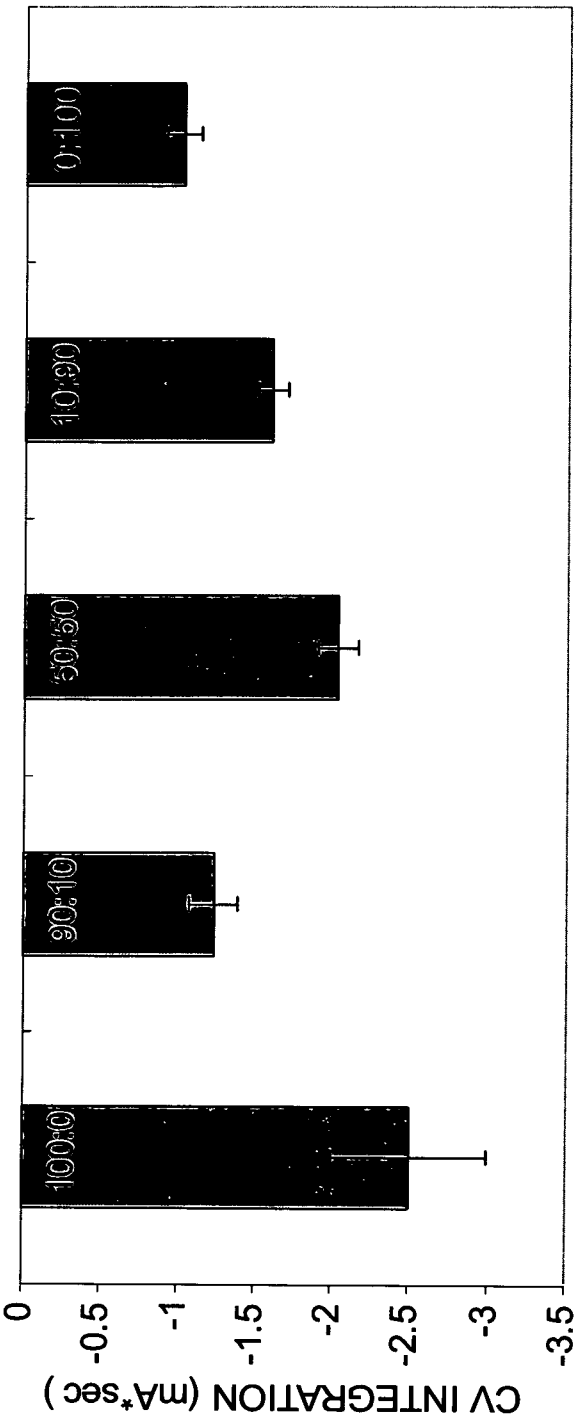

CV INTEGRATION (mA*sec)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
100:0
90:10
50:50
10:90
0:100
DS06:DS04 ratio

Fig. 15

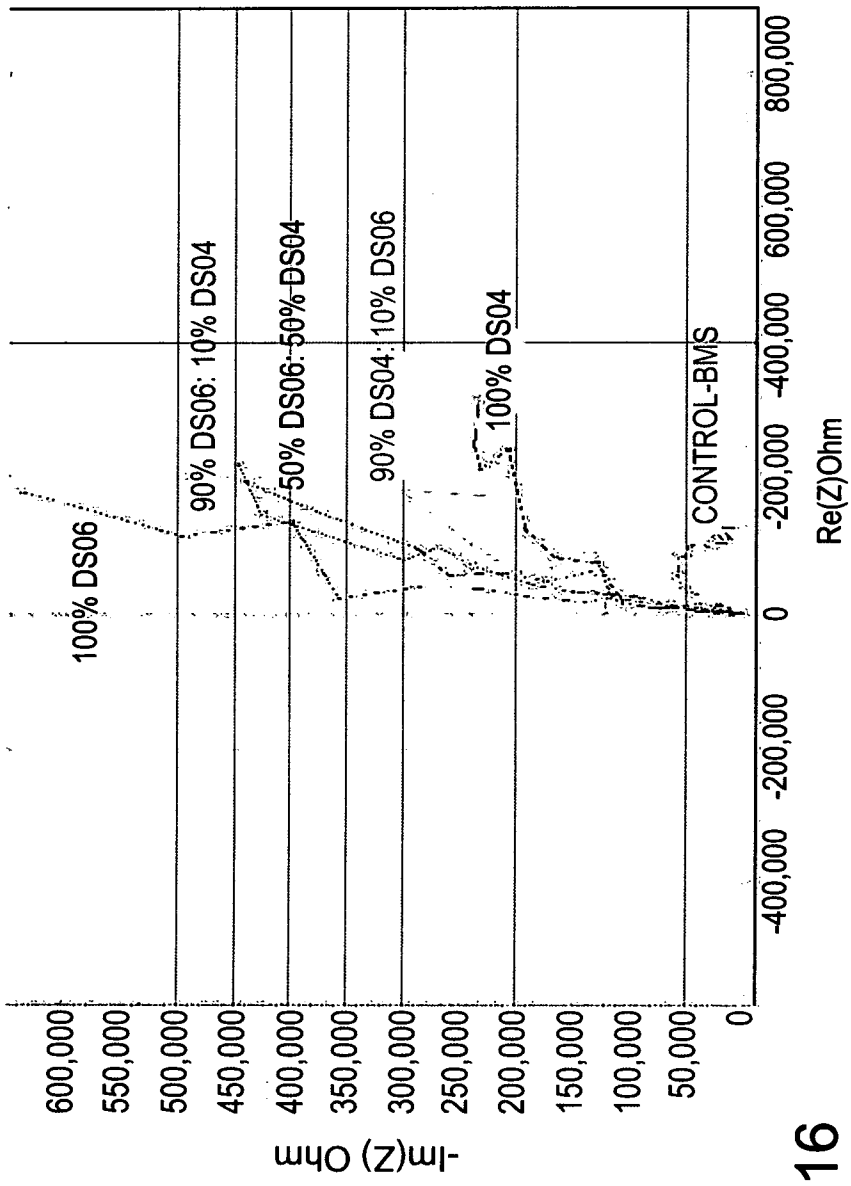

-Im(Z) Ohm
600,000
550,000
500,000
450,000
400,000
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
-400,000
-200,000
0
-200,000
-400,000
600,000
800,000
Re(Z)Ohm
100% DS06
90% DS06: 10% DS04
50% DS06: 50% DS04
90% DS04: 10% DS06
100% DS04
CONTROL-BMS

Fig. 16

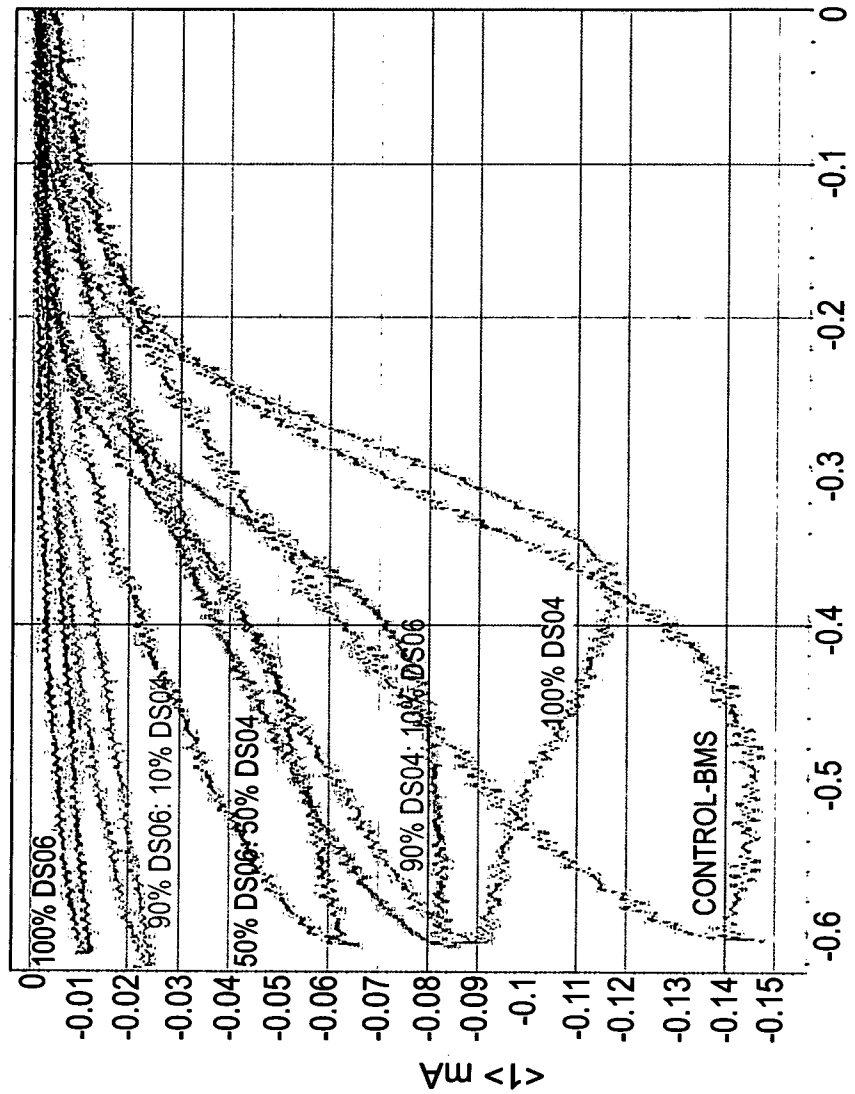
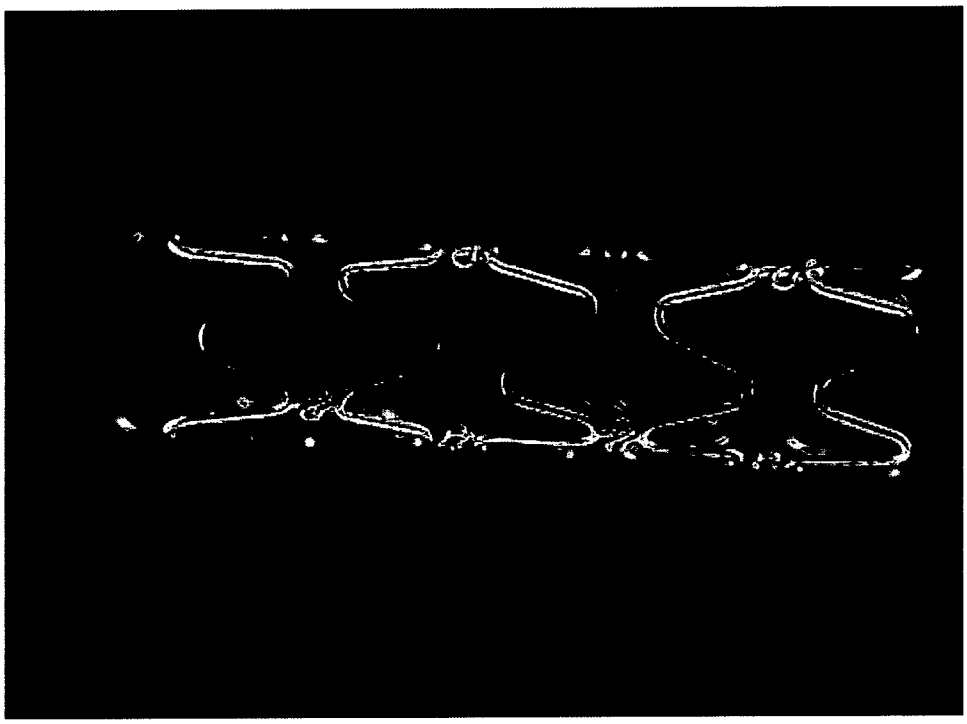

0
-0.01
-0.02
-0.03
-0.04
-0.05
-0.06
-0.07
-0.08
-0.09
-0.1
-0.11
-0.12
-0.13
-0.14
-0.15
<1> mA
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
Ewe/V vs. SCE
100% DS06
90% DS06: 10% DS04
50% DS06: 50% DS04
90% DS04: 10% DS06
100% DS04
CONTROL-BMS

Fig. 17

Figure 18:

a)



b)

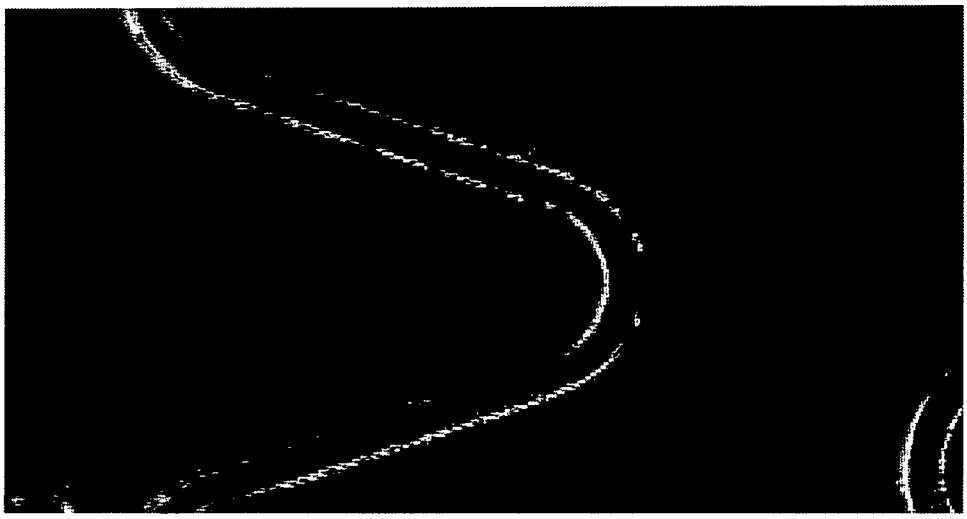
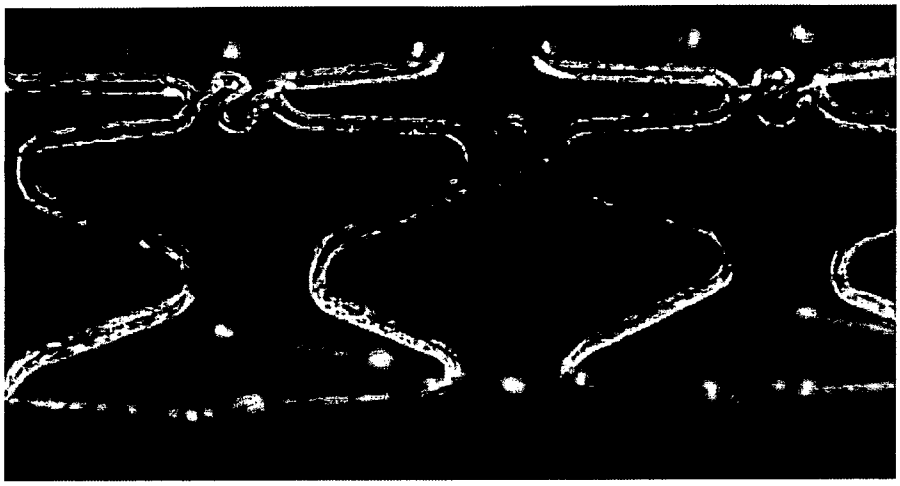


Figure 19:

a)



b)

c)

Figure 20:

a)

b)

c)

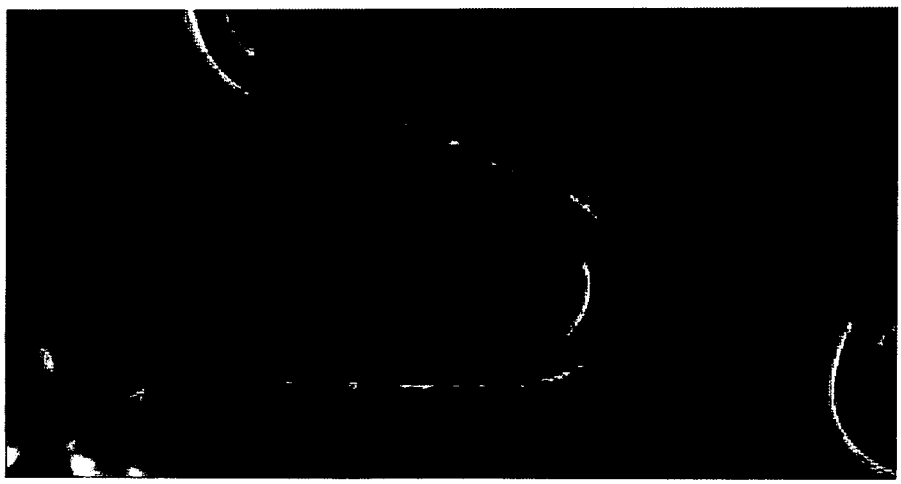
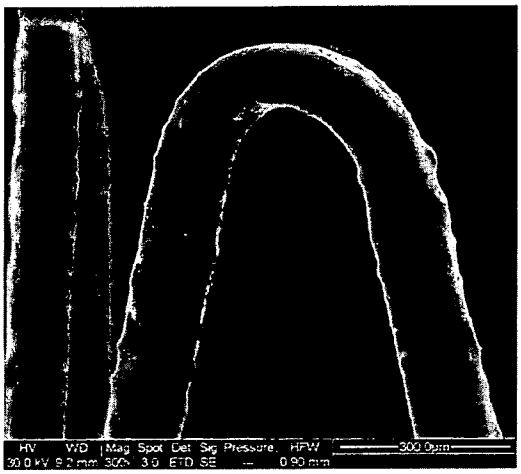
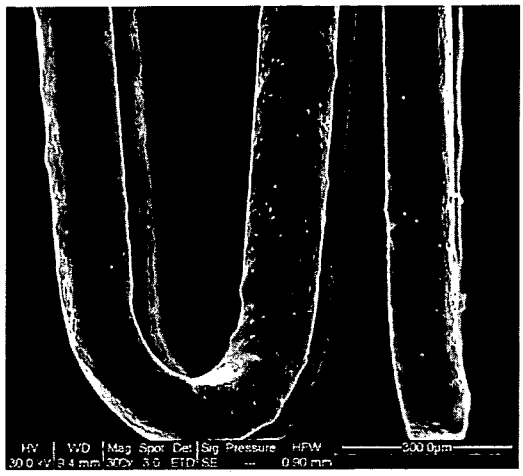


Figure 21:

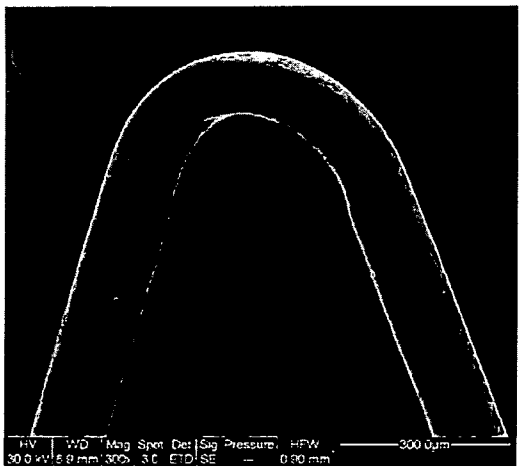
a)



b)



c)



d)

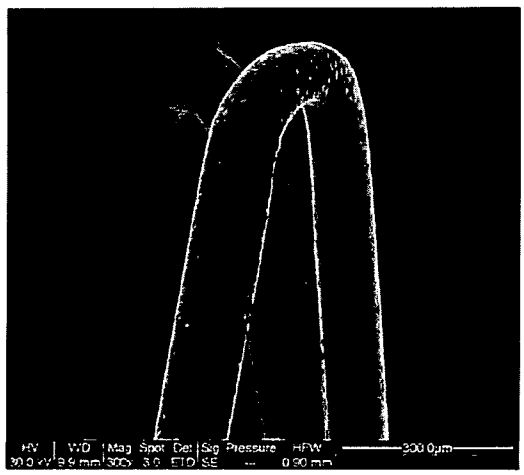


Figure 22:

a)


6/16/2007 | Det | Mag | HV | Spot | WD
9:41:43 AM | ETD | 300x | 30.0 kV | 3.0 | 16.6 mm
400.0µm

b)

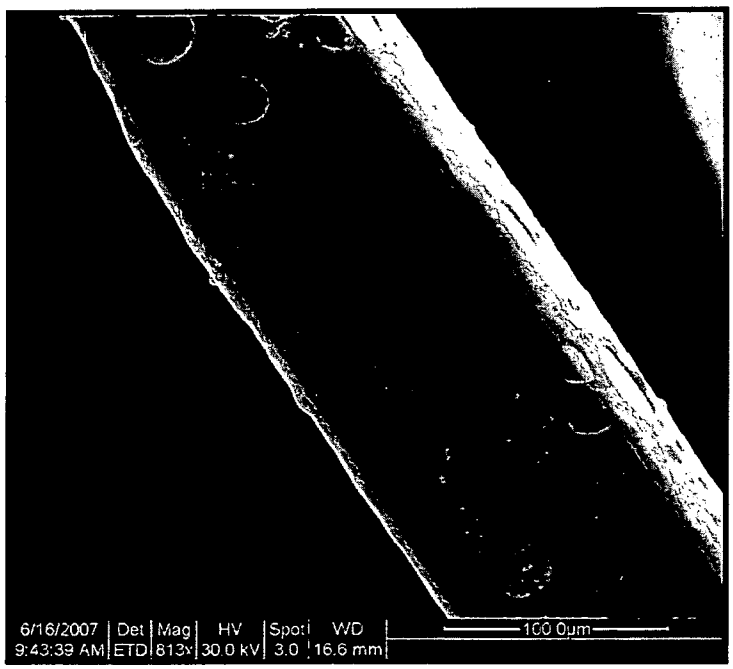
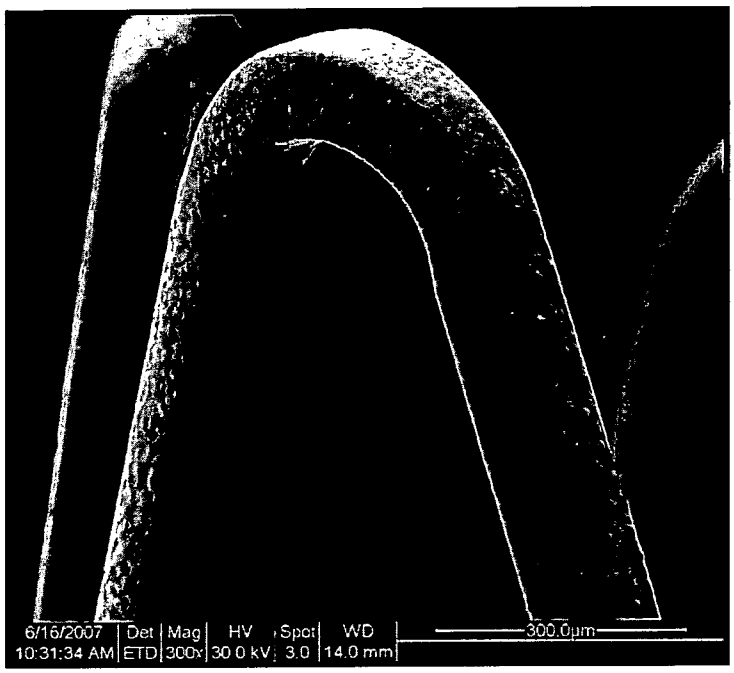

6/16/2007 | Det | Mag | HV | Spot | WD
9:43:39 AM | ETD | 813x | 30.0 kV | 3.0 | 16.6 mm
100.0µm

Figure 23:

a)


6/16/2007 | Det | Mag | HV | Spot | WD
10:31:34 AM | ETD | 300x | 30.0 kV | 3.0 | 14.0 mm
300.0µm

b)

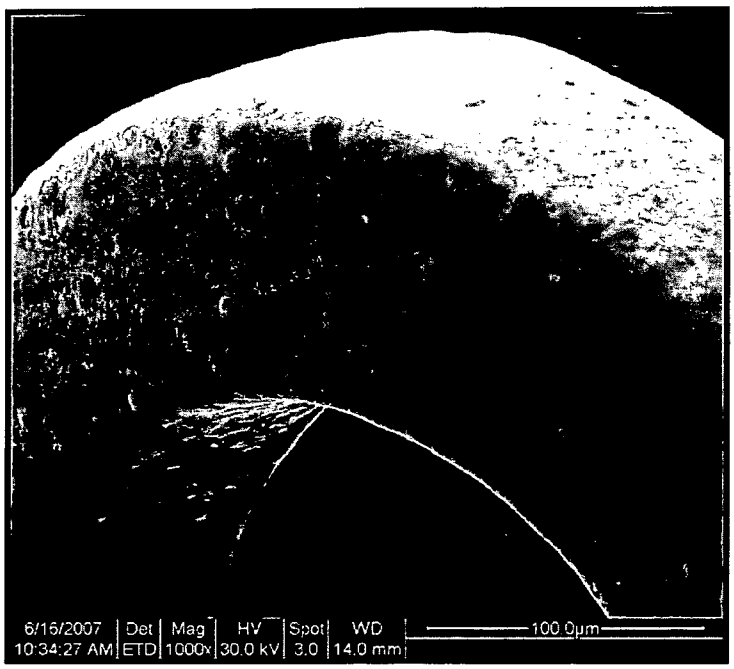
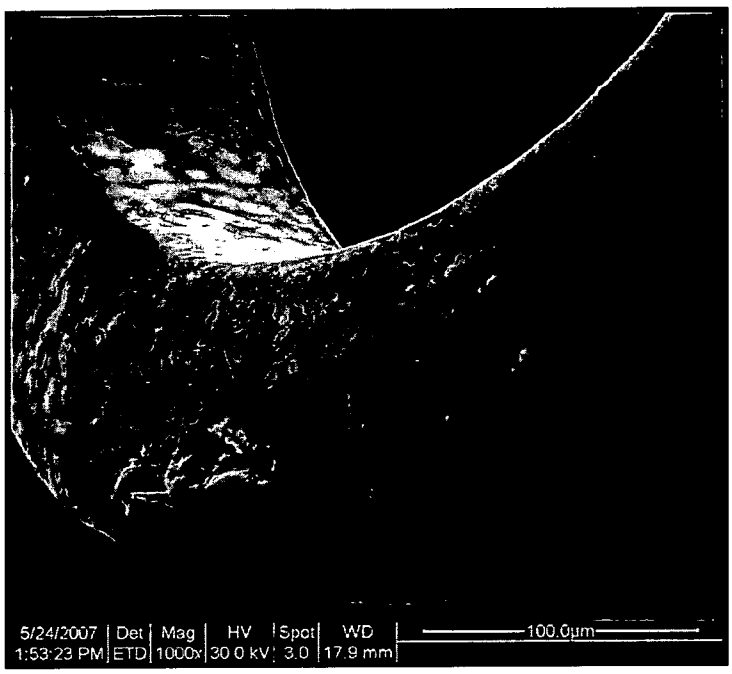

6/16/2007 | Det | Mag | HV | Spot | WD
10:34:27 AM | ETD | 1000x | 30.0 kV | 3.0 | 14.0 mm
100.0µm

Figure 24:

a)


5/24/2007 | Det | Mag | HV | Spot | WD
1:53:23 PM | ETD | 1000x | 30.0 kV | 3.0 | 17.9 mm
100.0µm

b)

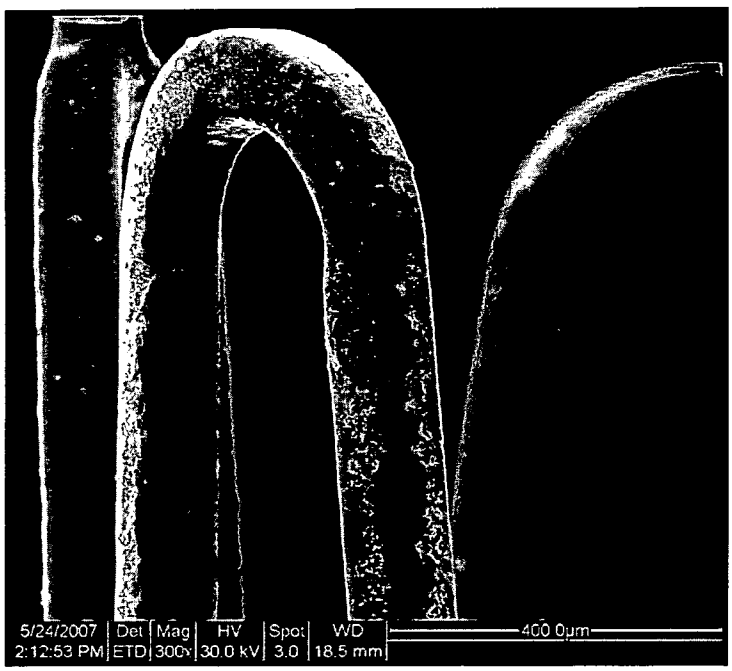
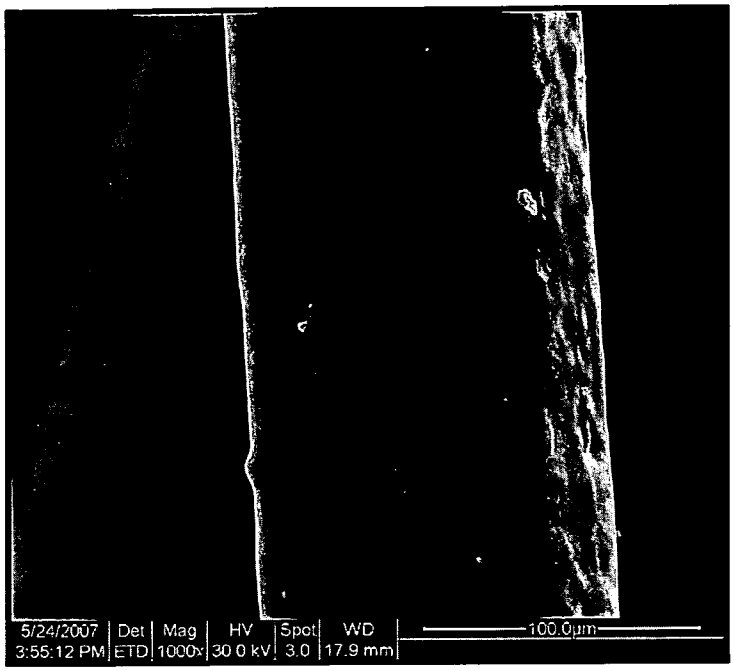

5/24/2007 | Det | Mag | HV | Spot | WD
2:12:53 PM | ETD | 300x | 30.0 kV | 3.0 | 18.5 mm
400.0µm

Figure 25:

a)


5/24/2007 | Det | Mag | HV | Spot | WD
3:55:12 PM | ETD | 1000x | 30.0 kV | 3.0 | 17.9 mm
100.0µm

b)

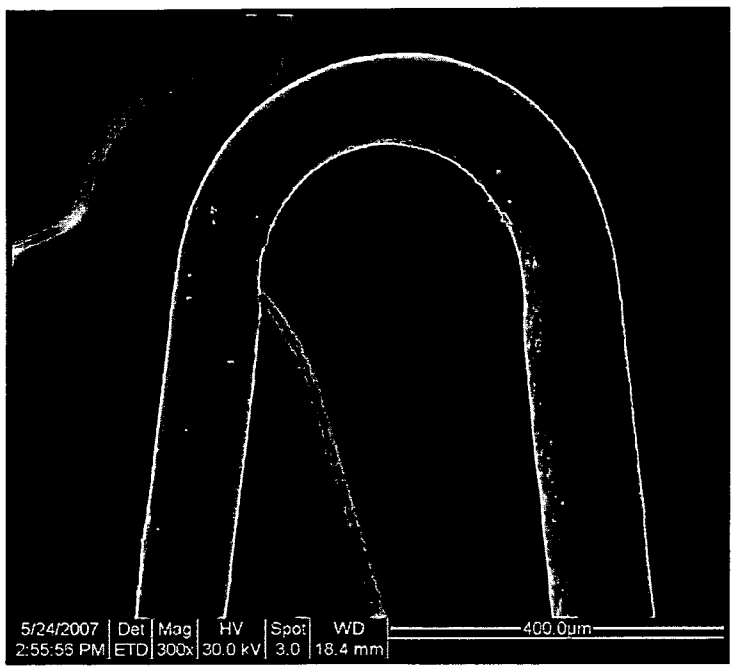
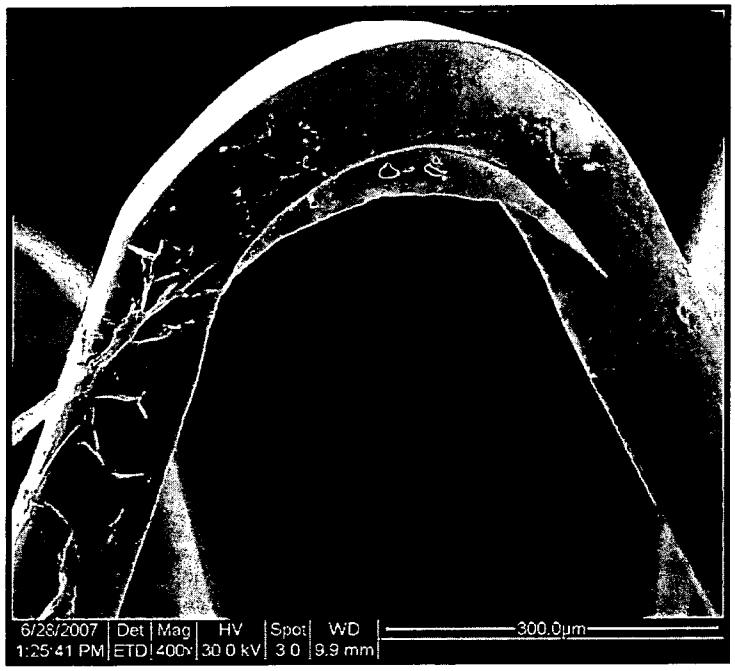

5/24/2007 | Det | Mag | HV | Spot | WD
2:55:55 PM | ETD | 300x | 30.0 kV | 3.0 | 18.4 mm
400.0µm

Figure 26:

a)


6/28/2007 | Det | Mag | HV | Spot | WD
1:25:41 PM | ETD | 400x | 30.0 kV | 3.0 | 9.9 mm
300.0µm

b)


6/28/2007 | Det | Mag | HV | Spot | WD
7:05:18 PM | ETD | 300x | 30.0 kV | 3.0 | 10.4 mm
400.0µm

Figure 27:

a)


6/28/2007 | Det | Mag | HV | Spot | WD
1:57:10 PM | ETD | 300x | 30.0 kV | 3.0 | 12.9 mm
400.0µm

b)

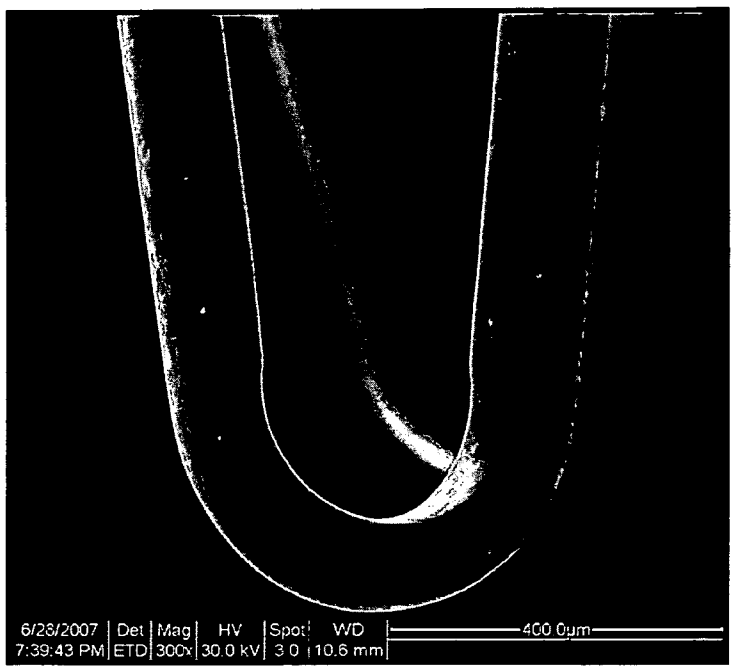
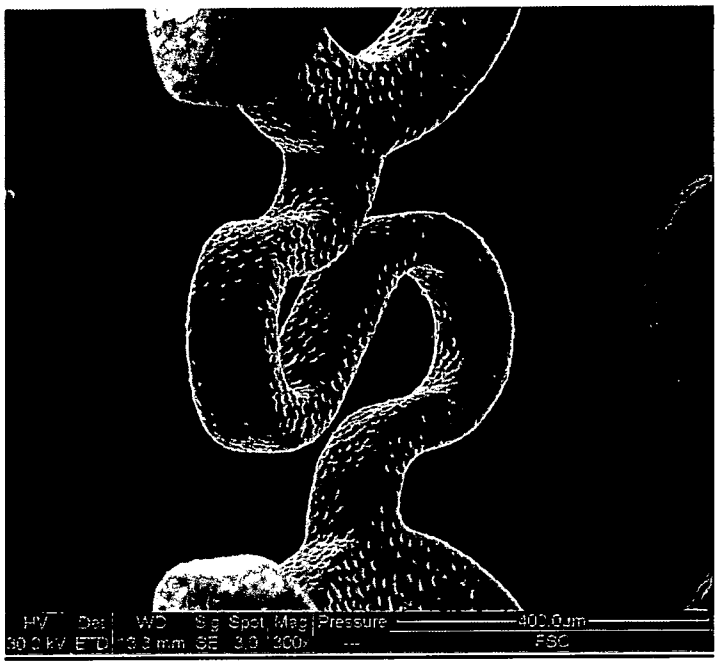

6/28/2007 | Det | Mag | HV | Spot | WD
7:39:43 PM | ETD | 300x | 30.0 kV | 3.0 | 10.6 mm
400.0µm

Figure 28:

a)


HV Det WD Sig Spot Mag Pressure
400.0um
FSC

b)

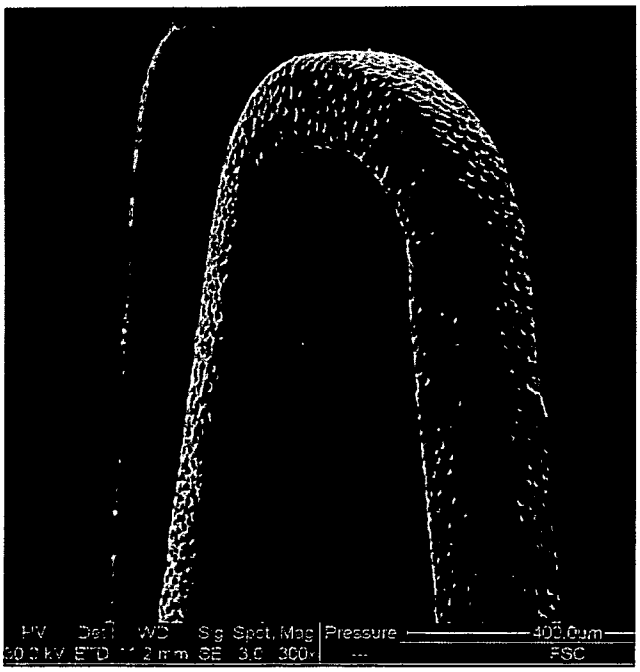
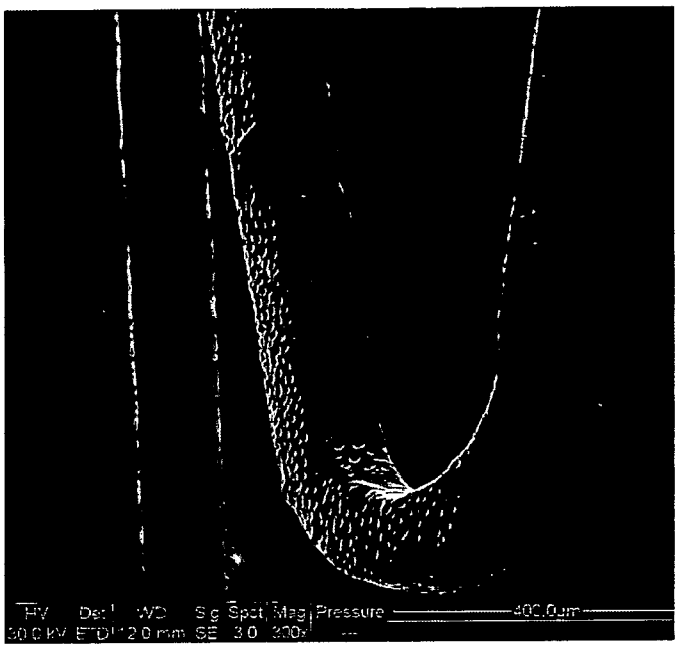

HV Det WD Sig Spot Mag Pressure
400.0um
FSC

Figure 29:

a)


HV Det WD Sig Spot Mag Pressure
400.0µm
30.0 kV ETD 12.0 mm SE 3.0 300x

b)

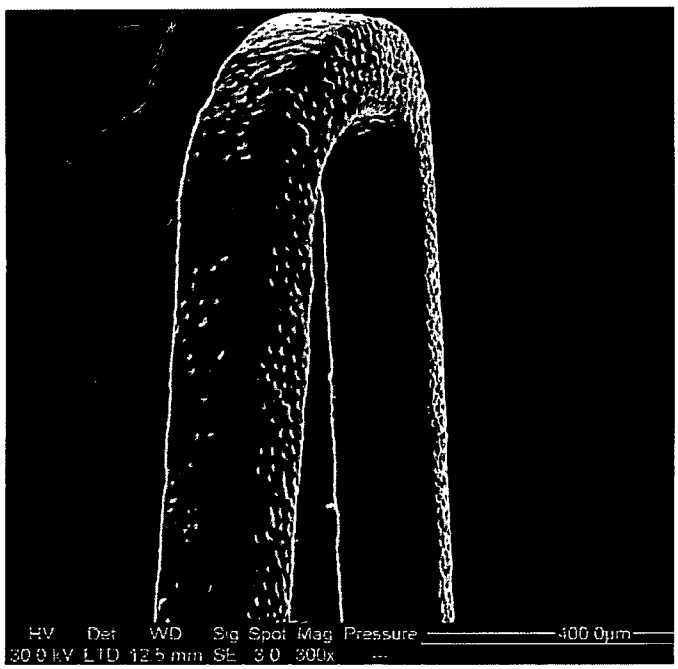

HV Det WD Sig Spot Mag Pressure
400.0µm
30.0 kV LTD 12.5 mm SE 3.0 300x

Figure 30:

a)

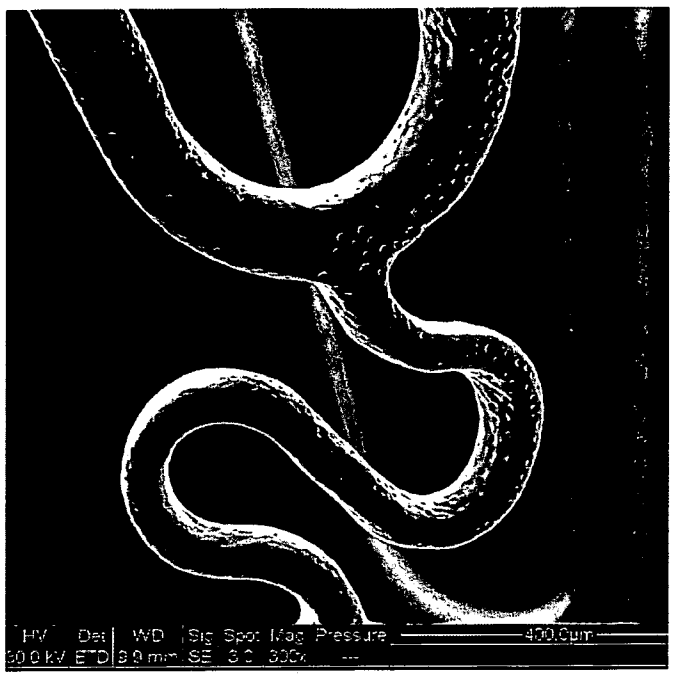

HV Det WD Sig Spot Mag Pressure
400.0µm
30.0 kV ETD 9.9 mm SE 3.0 300x ---
Spec 5 ZIRSTAR 0.6-0.8 15 kV

b)


HV Det WD Sig Spot Mag Pressure
400.0µm
30.0 kV ETD 10.5 mm SE 3.0 300x ---
Spec 5 ZIRSTAR 0.6-0.8 15 kV

Figure 31:

a)


HV Det WD Sig Spot Mag Pressure
400.0µm
30.0 kV ETD 9.9 mm SE 3.0 300x

b)

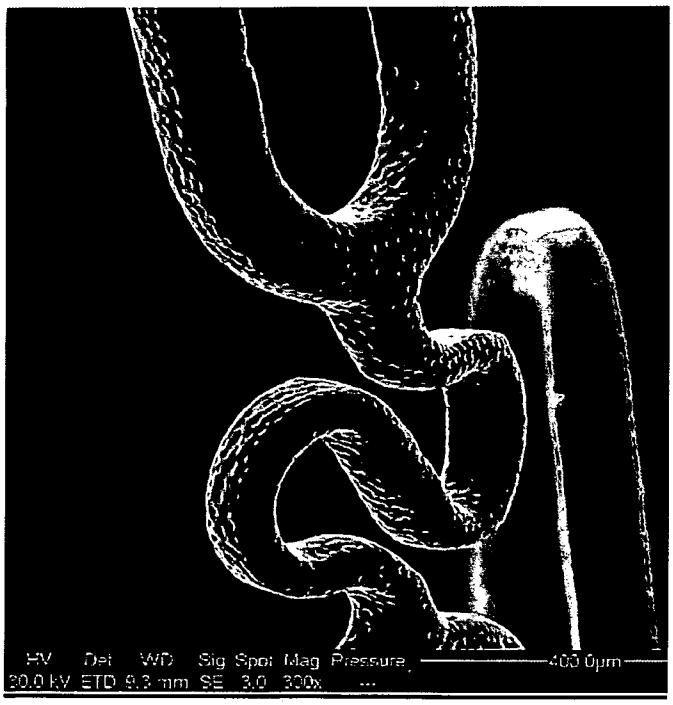

HV Det WD Sig Spot Mag Pressure
400.0µm
20.0 kV ETD 9.3 mm SE 3.0 300x

Figure 32:

a)


HV Det WD Sig Spot Mag Pressure
400.0µm
Spec 5 ZIRSTAR

b)

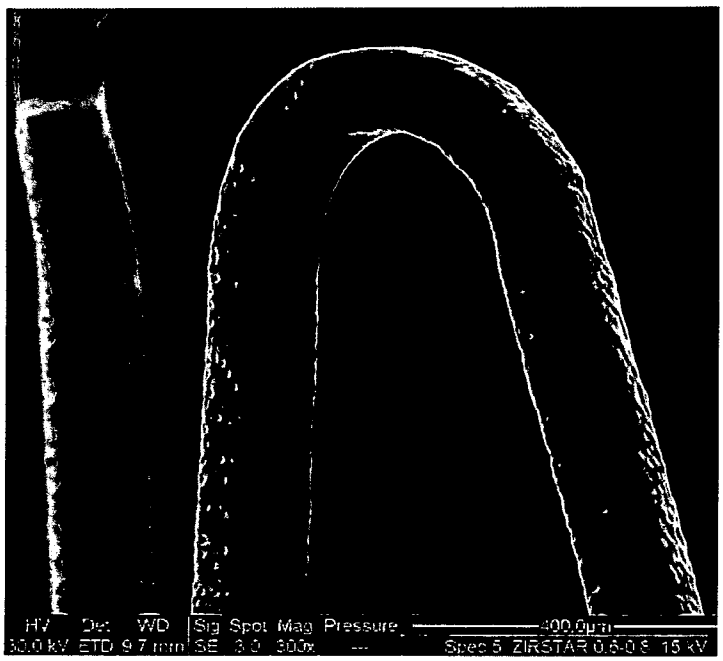

HV Det WD Sig Spot Mag Pressure
400.0µm
Spec 5 ZIRSTAR

Figure 33:

a)

b)

c)

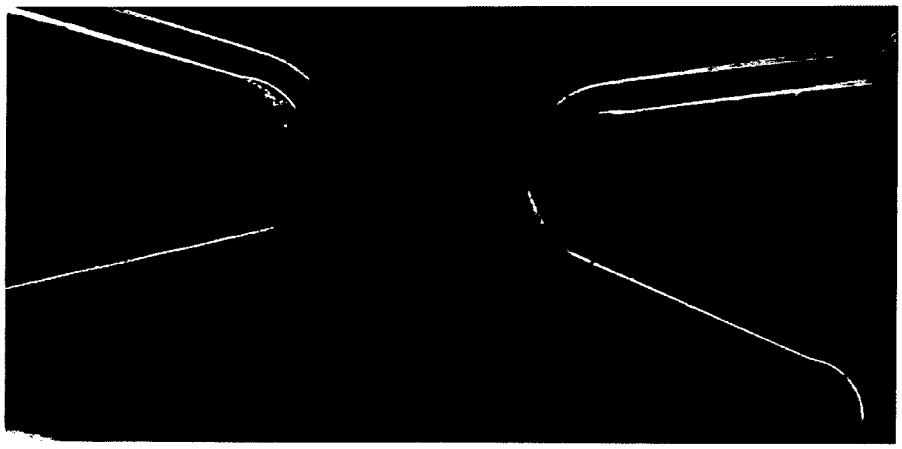


Figure 34:

a)

b)

c)

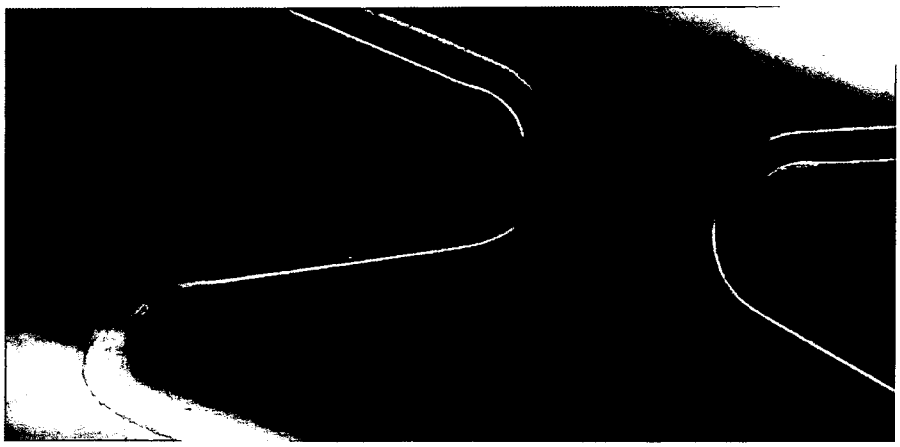
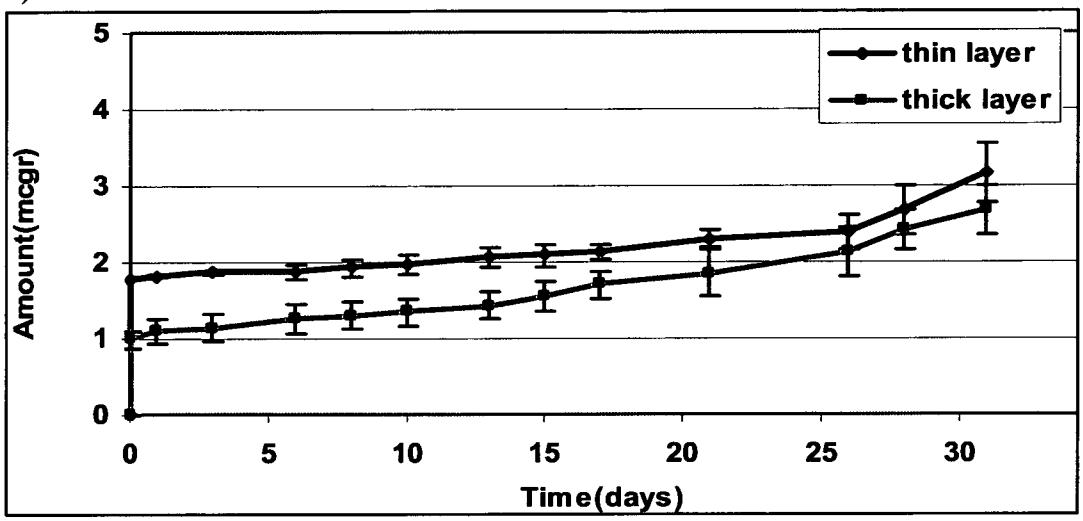


Figure 35:

a)


thin layer
thick layer
Amount(mcgr)
Time(days)
0
1
2
3
4
5
0
5
10
15
20
25
30

b)

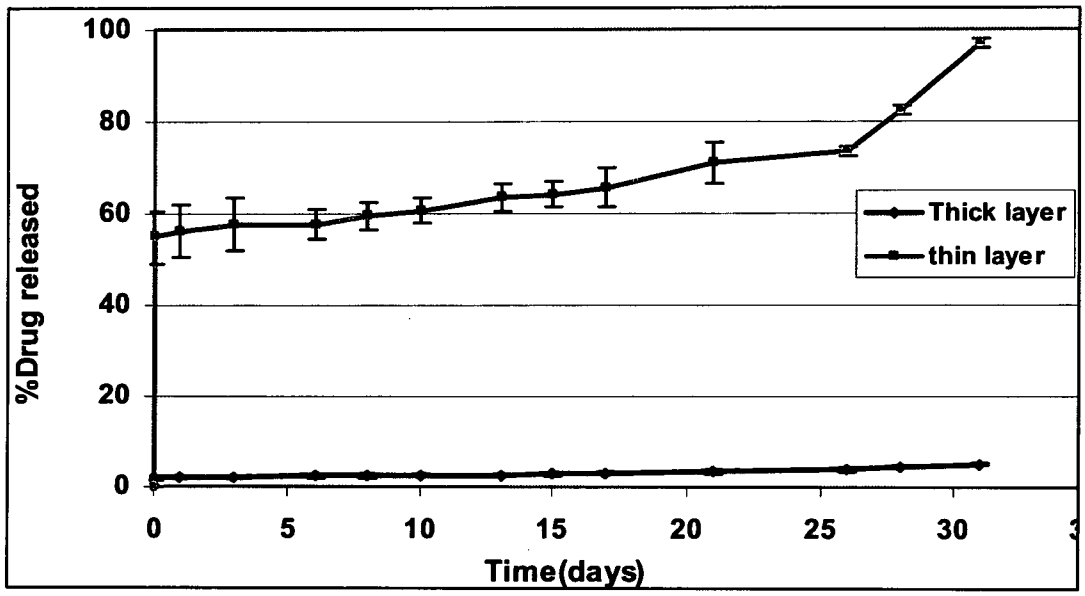

Thick layer
thin layer
%Drug released
Time(days)
0
20
40
60
80
100
0
5
10
15
20
25
30

Figure 36:

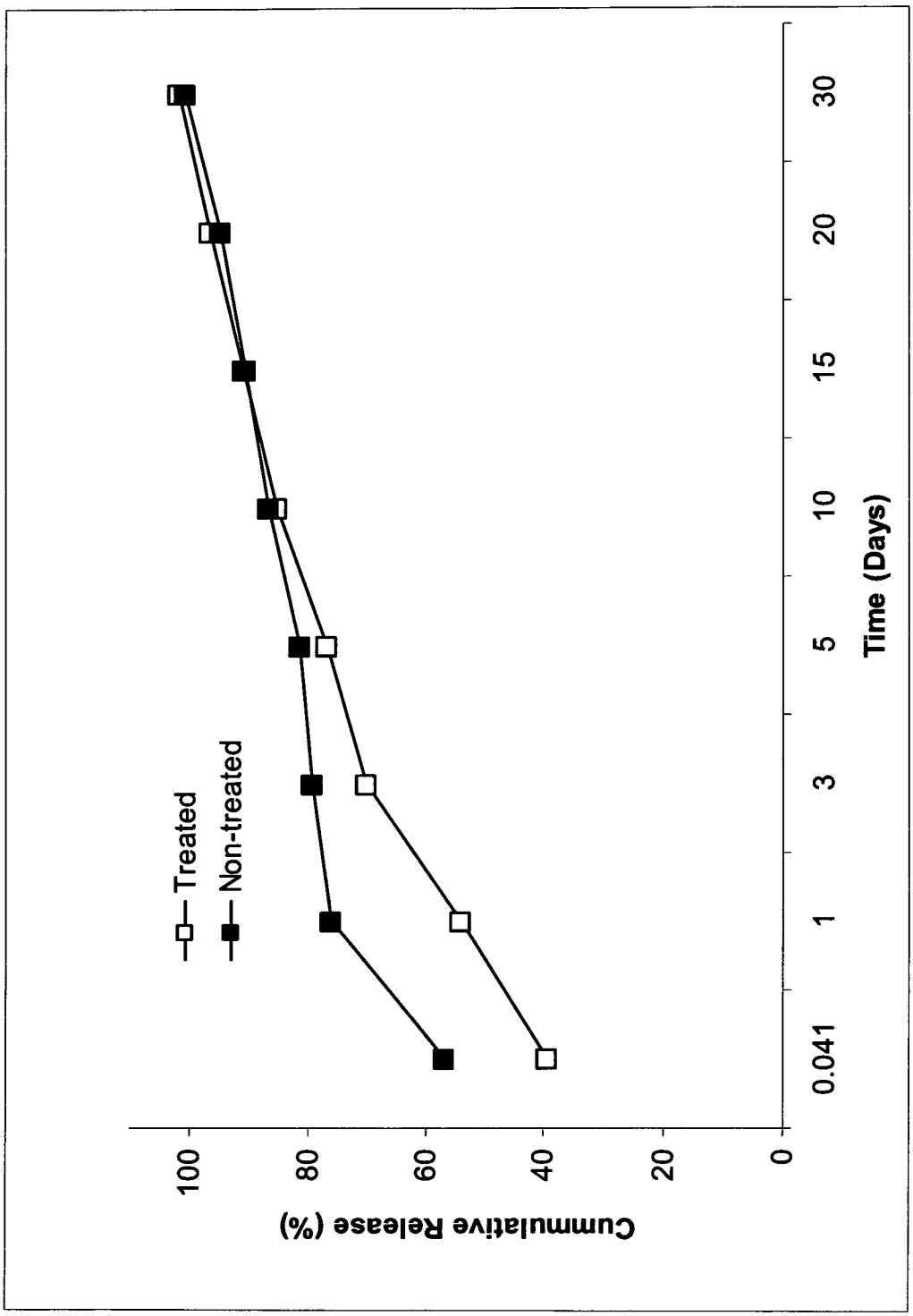
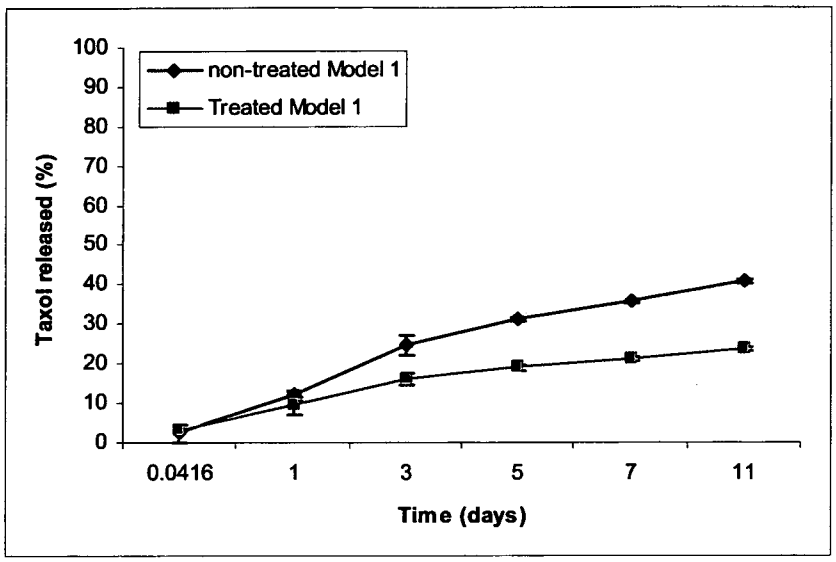

Cummulative Release (%)
0
20
40
60
80
100
0.041
1
3
5
10
15
20
30
Time (Days)
Treated
Non-treated

Figure 37:

a)


non-treated Model 1
Treated Model 1
Taxol released (%)
100
90
80
70
60
50
40
30
20
10
0
0.0416
1
3
5
7
11
Time (days)

b)

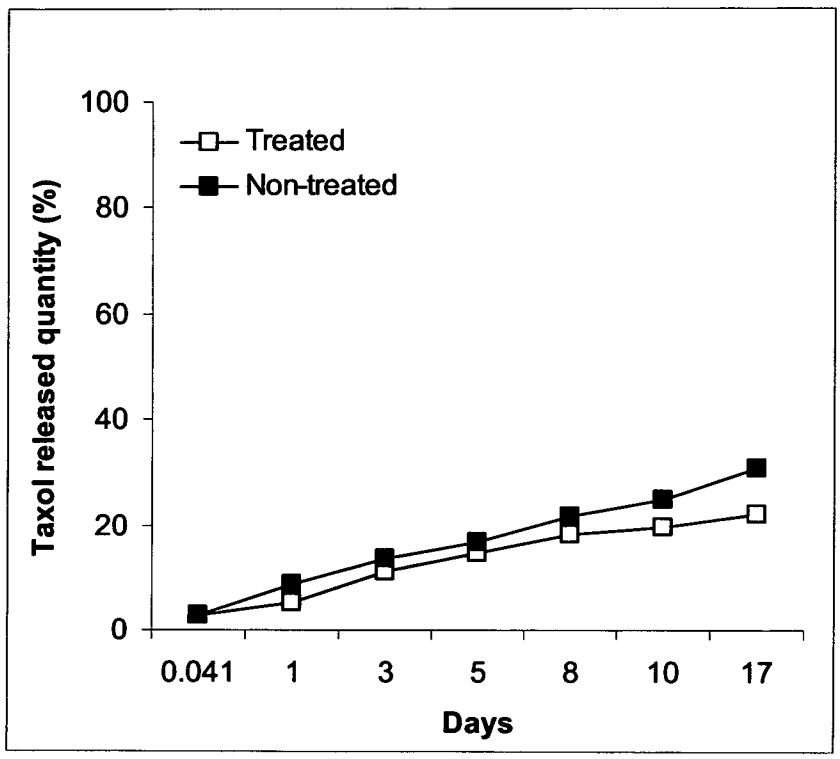

Treated
Non-treated
Taxol released quantity (%)
100
80
60
40
20
0
0.041
1
3
5
8
10
17
Days

Figure 38:

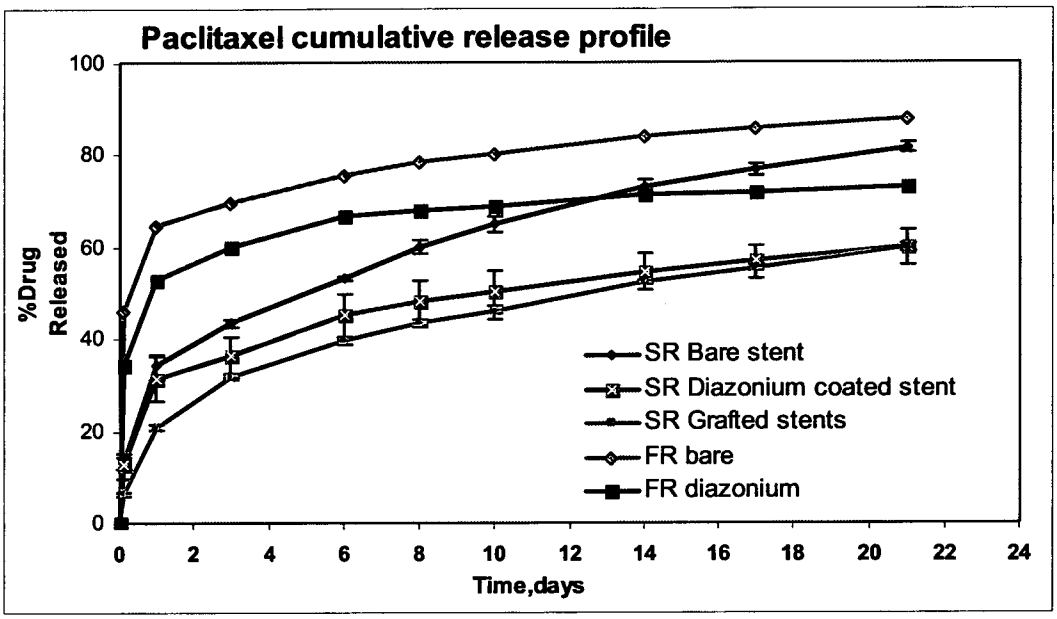
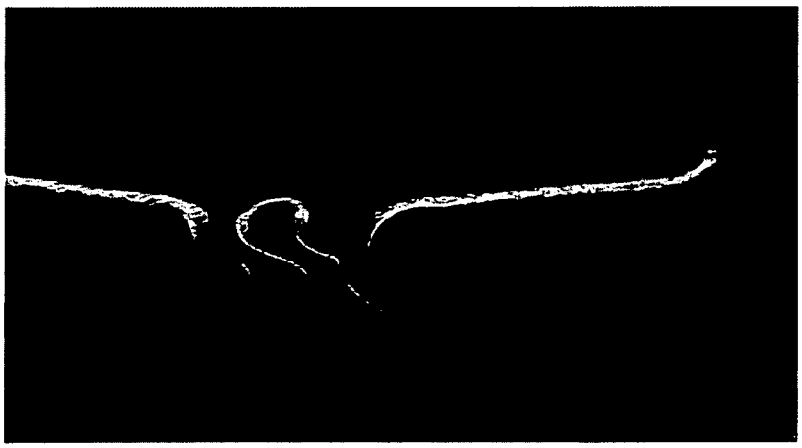

Paclitaxel cumulative release profile
%Drug Released
Time,days
SR Bare stent
SR Diazonium coated stent
SR Grafted stents
FR bare
FR diazonium
0
20
40
60
80
100
0
2
4
6
8
10
12
14
16
18
20
22
24

Figure 39:

a)

b)



c)

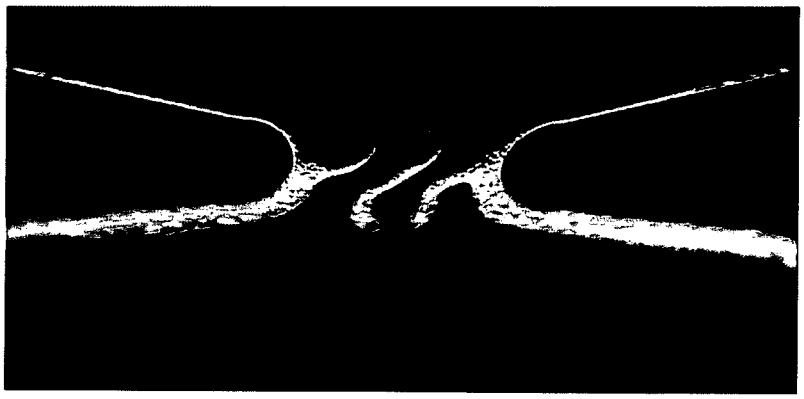


Figure 40:

a)

b)

c)

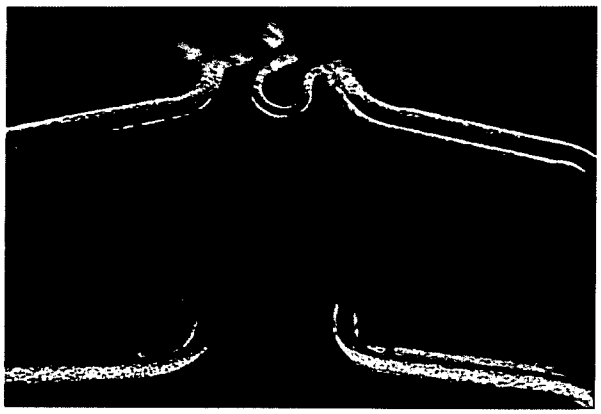


Figure 41:

a)

b)

Figure 42:

a)

b)