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(71) Applicant *(for all designated States except US)*: **THE UNIVERSITY OF BRITISH COLUMBIA** [CA/CA]; University-Industry Liaison Office, 103 - 6190 Agronomy Road, Vancouver, British Columbia V6T 1Z3 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TSUI, Pui Hung Manus** [CA/CA]; 36 - 7691 Moffatt Road, Richmond, British Columbia V6Y 1X9 (CA). **TROCZYNSKI, Tomasz** [CA/CA]; 1050 East 57th Avenue, Vancouver, British Columbia V5X 1T6 (CA).

(74) Agents: **OYEN, Gerald, O., S.** et al.; Oyen Wiggs Green & Mutala LLP, #480 - The Station, 601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).

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(54) **Title:** CALCIUM PHOSPHATE COATED IMPLANTABLE MEDICAL DEVICES, AND ELECTROCHEMICAL DEPOSITION PROCESSES FOR MAKING SAME

- Electrolyte: $Ca(NO_3)_2\ 4H_2O + NH_4H_2PO_4$
- Local pH increases at cathode:

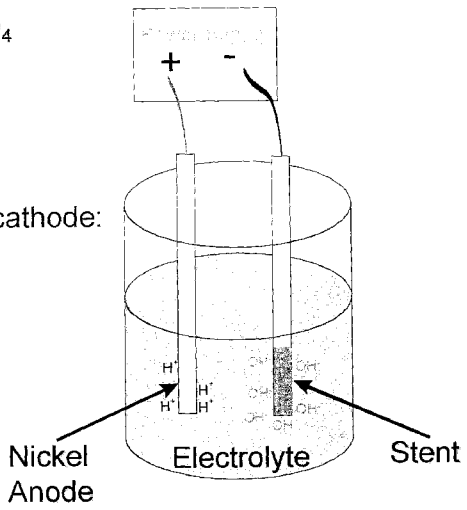
$$2H_2O+2e^- \rightarrow H_2 + 2OH^-$$

- Local concentration of phosphates at cathode:

$$H^+ + PO_4^{3-} \Leftrightarrow HPO_4^{2-}$$
$$HPO_4^{2-} + OH^- \Leftrightarrow H_2O + PO_4^{3-}$$

- When sufficient OH^- produced (pH is sufficiently high), HAP deposits by :

$$10Ca^{2+} + 6PO_4^{3-} + 2OH^- \rightarrow Ca_{10}(PO_4)_6(OH)_2$$



(57) **Abstract:** This invention relates to novel calcium phosphate coated implantable medical devices, and electrochemical deposition processes for making same. A process of coating an implantable medical device with a calcium phosphate coating comprising: (a) subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced; (b) immersing the pretreated substrate in an electrolyte comprising calcium and phosphate species; and (c) coating calcium phosphate onto the substrate by electrochemical deposition.

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

CALCIUM PHOSPHATE COATED IMPLANTABLE MEDICAL DEVICES, AND ELECTROCHEMICAL DEPOSITION PROCESSES FOR MAKING SAME

FIELD OF THE INVENTION

[0001] This invention relates to novel calcium phosphate coated implantable medical devices, and electrochemical deposition processes for making same.

BACKGROUND OF THE INVENTION

[0002] Coronary artery disease (CAD) occurs when fat deposits block the arteries, reducing the oxygen supply to the heart muscle. Angioplasty is a way of opening a narrowed or closed blood vessel without having to do major surgery. Between 70 percent and 90 percent of angioplasty procedures use a stent, a hollow thin-walled wire mesh tube, to keep the vessel open after widening. The stent is placed onto a balloon and pressed firmly against the artery wall during inflation. The balloon is then deflated, leaving the stent in place to act as a scaffold.

[0003] Metallic stents have been used by cardiologists to battle CAD with some success. Though the stent is an effective solution in providing structural support it does not eliminate the recurrence of blockage in the artery (restenosis) in all cases. The release of ions from the bare metal stent may result in the proliferation of smooth muscle cells, a natural inflammatory response to this foreign body. Narrowing or re-closing of the artery often requires a repeat operation within a year. An approach to address this issue is to coat the stent with a polymer coating that contains a drug that prevents the restenosis. A problem with this approach relate to lack of proper biocompatibility of the polymers (many of them trigger inflammatory response of the tissue). This may become an even more severe issue when the drug is entirely released from the coating.

[0004] Due to the excellent biocompatibility of calcium phosphate ceramics, they have received much attention in the fields of orthopedics and dentistry and are clinically applied. Among the various forms of calcium phosphate ceramics, hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] (HAP), a major inorganic component of natural bone, is particularly attractive. HAP, in the form of coatings on rigid implants such as

orthopedic and dental implants, have been applied to achieve biocompatibility. Due to the brittle nature of calcium phosphates, there exists a challenge for calcium phosphates coatings to withstand implant deformation, such as stent expansion during the angioplasty procedure.

SUMMARY OF THE INVENTION

[0005] One aspect of the present invention relates to novel calcium phosphate coated implantable medical devices, and electrochemical deposition processes for making same. A process of coating an implantable medical device with a calcium phosphate coating comprising: (a) subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced; (b) immersing the pretreated substrate in an electrolyte comprising calcium and phosphate species; and (c) coating calcium phosphate onto the substrate by electrochemical deposition.

[0006] Another aspect of the invention relates to a process of coating an implantable medical device with a composite ceramic/polymer coating comprising: (a) subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced; (b) immersing the pretreated substrate in an electrolyte comprising calcium, phosphate and polymer species; and (c) coating a continuous calcium phosphate phase and a continuous polymer phase onto the substrate by electrochemical deposition.

[0007] Yet another aspect of the invention relates to a process of coating an implantable medical device with a composite ceramic/polymer coating comprising: (a) subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced; (b) immersing the pretreated substrate in an electrolyte comprising calcium and phosphate species; (c) coating a continuous calcium phosphate phase onto the substrate by electrochemical deposition; and (d) impregnating the calcium phosphate coated substrate with a polymer to provide a continuous polymer phase.

[0008] A further aspect of the invention relates to an implantable medical device comprising a substrate with a surface micro-etched by alkaline pre-treatment, and a calcium phosphate coating deposited on the substrate by electrochemical deposition.

[0009] A still further aspect of the invention relates to an implantable medical device comprising a substrate with an oxidized surface layer; and a calcium phosphate coating deposited on the substrate by electrochemical deposition.

[0010] Another aspect of the invention relates to an implantable medical device comprising a substrate with aero-sol-gel deposited hydroxyapatite layer, and a calcium phosphate coating deposited on the substrate by electrochemical deposition

[0011] Yet another aspect of the invention relates to an implantable medical device comprising a substrate with a composite coating, the composite coating comprising a continuous ceramic phase and a continuous polymer phase.

[0012] A further aspect of the invention relates to the use of a coated implantable medical device comprising a continuous ceramic phase and a continuous polymer phase in an engineered drug delivery system.

DRAWINGS

[0013] Exemplary embodiments are illustrated in referenced figures of the drawings. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0014] Figures 1(a) to (d) illustrate an ultrasonically cleaned, unmodified stent made of 316L stainless steel. Figures 1(a) to (c) are micrographs of the stent and Figure 1(d) is the stent viewed under an optical microscope.

[0015] Figure 2 is a schematic diagram of an experimental setup for electrochemical deposition of HAP, with relevant chemical reactions, according to one embodiment of the present invention.

[0016]Figure 3 is an X-ray diffraction graph illustrating the composition of electrochemically deposited calcium phosphate.

[0017] Figures 4(a) to (d) are micrographs illustrating an electrochemically deposited HAP coating on a stent according to Example 1.

[0018] Figures 5(a) to (d) are micrographs illustrating an electrochemically deposited HAP coating on a stent according to Example 1.

[0019] Figures 6(a) and (b) are micrographs illustrating an expanded HAP coated stent according to Example 1.

[0020] Figure 7(a) is a micrograph illustrating an expanded HAP coated stent according to Example 1 showing details of coating damage in the compressive stress area.

[0021] Figure 7(b) is a micrograph illustrating an expanded HAP coated stent according to Example 1 showing details of coating damage in the tensile stress area.

[0022] Figures 8(a) and (b) are micrographs illustrating an oxidation pretreated stent surface according to Example 2.

[0023] Figures 9(a) to (d) are micrographs illustrating electrochemically deposited HAP on an oxidation pretreated stent according to Example 2.

[0024] Figures 10(a) to (d) are micrographs illustrating an expanded HAP coated stent with oxidation pretreatment according to Example 2.

[0025] Figures 11(a) and (b) are micrographs illustrating an alkaline pretreated stent surface according to Example 3.

[0026] Figures 12(a) to (d) are micrographs illustrating electrochemically deposited HAP on an alkaline pretreated stent according to Example 3.

[0027] Figures 13(a) to (d) are micrographs illustrating an expanded HAP coated stent with alkaline pretreatment according to Example 3.

[0028] Figures 14(a) to (d) are micrographs illustrating an expanded HAP coated stent with alkaline pretreatment according to Example 4.Figures 15(a) to (d) are micrographs illustrating an expanded HAP coated stent with alkaline pretreatment according to Example 4.

[0029] Figures 16(a) to (d) are micrographs illustrating an expanded HAP coated stent with alkaline pretreatment according to Example 4.

[0030] Figures 17(a) to (d) are micrographs illustrating an expanded HAP coated stent with alkaline pretreatment, coated in 60 seconds with a 0.75 μm coat, according to Example 5.

[0031] Figures 18(a) to (d) are micrographs illustrating an expanded HAP coated stent with alkaline pretreatment, coated in 70 seconds with a 0.90 μm coat, according to Example 5.

[0032] Figures 19(a) to (d) are micrographs illustrating an expanded HAP coated stent with alkaline pretreatment, coated in 90 seconds with a 1.0 μm coat, according to Example 5.

[0033] Figure 19(e) are micrographs illustrating changes in thickness and density of the HAP coating on expanded stents for 40, 50, 60, 70 and 90 seconds of deposition, according to Example 5.

[0034] Figures 20(a) to (d) are micrographs illustrating a stent coated with 0.2 μm aero-sol-gel deposited film of HAP, according to Example 6.

[0035] Figures 21(a) to (d) are micrographs illustrating a stent coated with 0.2 μm aero-sol-gel deposited film of HAP and further coated with 0.5 μm HAP by ECD, according to Example 6.

[0036] Figures 22(a) to (d) are micrographs illustrating an expanded HAP stent coated with 0.2 μm aero-sol-gel deposited film of HAP and further coated with 0.5 μm HAP by ECD, according to Example 6.

[0037] Figures 23(a) to (d) are micrographs illustrating a stent coated by co-deposition of HAP and PVA (of 0.1g in 80ml of the coating solution), according to Example 7.

[0038] Figures 24(a) to (d) are micrographs illustrating an expanded stent coated by co-deposition of HAP and PVA (of 0.1g in 80ml of the coating solution), according to Example 7.

[0039] Figures 25(a) to (d) are micrographs illustrating a stent coated by co-deposition of HAP and PVA (of 0.5g in 80ml of the coating solution), according to Example 7.

[0040] Figures 26(a) to (d) are micrographs illustrating an expanded stent coated by co-deposition of HAP and PVA (of 0.5g in 80ml of the coating solution), according to Example 7.

[0041] Figures 27(a) to (d) are micrographs illustrating an expanded stent coated with
HAP and impregnated with PLGA, according to Example 8.

[0042] Figures 28(a) to (d) are micrographs illustrating an expanded stent coated with
HAP and impregnated with PLGA, according to Example 8.

[0043] Figures 29(a) to (d) are micrographs illustrating the surface morphologies of HAP coated stents impregnated with PLGA solutions at 2, 4 and 6 wt % concentrations, according to Example 8.

DETAILED DESCRIPTION OF THE INVENTION

[0044] Throughout the following description, specific details are set forth in order to provide a more thorough understanding of the invention. However, the invention may be practiced without these particulars. In other instances, well known elements have not been shown or described in detail to avoid unnecessarily obscuring the invention. Accordingly, the specification and drawings are to be regarded in an illustrative, rather than a restrictive, sense.

[0045] In the following description, the term "calcium phosphate" is used generically and includes minerals such as HAP, dicalcium phosphate, tricalcium phosphate, tetracalcium phosphate and amorphous or partially amorphous calcium phosphate.

[0046] The present invention in one aspect relates a process of coating an implantable medical device with a calcium phosphate coating comprising subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced, immersing the pretreated substrate in an electrolyte comprising calcium and phosphate species, and coating calcium phosphate onto the substrate by electrochemical deposition.

[0047] The novel coating process is exemplified below with reference to stents, such as cardiovascular stents (e.g. coronary stents). As shown in the examples below, the coating withstands simulated stent expansion procedures. However, the invention has broad application to virtually any type of implantable device with a metallic surface for use in the human or animal body, and particularly to flexible implantable devices that undergo substantial deformation during use. For example, the coatings are also useful in ureteral stenting and catherterisation.

[0048] The coatings are distinguished by a uniform and optimum thickness (< 1μm), and the coating adhesion is high enough to avoid separation of the coating from the substrate during implantation and expansion of the stent. The coatings are porous, typically in the range of 30-60 vol% porosity. The open porosity of the coatings may be filled with secondary materials such as polymers, proteins, drugs, and others.

[0049] Electrochemical deposition (ECD) is accomplished by using an electrolyte that contains calcium phosphate precursors and by application of a current that triggers precipitation of the calcium phosphate of a desirable phase (e.g. HAP) on one of the electrodes. The substrate deposition is preceded by surface pretreatment. As a result of the surface pretreatment, there is a surprising and significant increase in adhesion of the calcium phosphate coating to stents.

[0050] The increase in adhesion is believed to take place due to (i) surface nano-roughness created during pretreatment which enhances the mechanical interlocking of the hydroxyapatite coating; and/or (ii) a change of surface chemistry that promotes formation of chemical bonds between the modified surface and the coating during the ECD process. Surface modification is achieved by using (a) alkaline (micro-etching) treatment, (b) pre-oxidation treatment of the metallic stent surface or (c) pre-coating of the stent surface with sol-gel derived HAP. A combination of these surface modification methods may also be practiced.

[0051] During alkaline treatment, a nano-rough surface microstructure forms on the substrate, which is believed to promote mechanical interlocking and thus physical bonding. Additionally during alkaline treatment, an interfacial compound of Na_4CrO_4 forms, which may act as a chemical bonding bridge between metal and ceramic.

[0052] Specifically, pretreated 316L stainless steel stent substrates (using the above surface treatment methods (a), (b) and (c); refer to the examples below for the specifics) are subsequently coated by ECD using a specially designed electrolysis cell. The electrochemical deposition of calcium phosphates, e.g. hydroxyapatite, on the substrates are conducted in a mixed aqueous solution of calcium and phosphate species, such as $Ca(NO_3)_2 \cdot 4H_2O$ and $NH_4H_2PO_4$. The stainless steel stent substrate is the cathode (negative electrode), and a nickel ring, for example, is used as the anode (positive electrode). The pH of the electrolyte may be controlled at pH = 4.0± 0.1 with dynamic addition of suitable amount sodium hydroxide to the solution. The environment temperature may be controlled at T = 50°C ± 1°C.

[0053] Substrates are coated using specified parameters of current and duration of deposition. The specific parameters depend on the overall surface area of the substrate, and the desired thickness of the coating. For example, in one frequently used process with stents we have used a 0.90 mA applied current, and a deposition time of 50 seconds. The total current is specific to assure suitable current density of the stent surface. The deposition time is adjusted to achieve desired thickness of the deposit, i.e. about 1 um for the 50 second deposition for the above conditions. The combination of current, time, and electrolyte parameters control the coating uniformity, porosity, thickness, and phase composition. After achieving the desired coating thickness, the coated stents are rinsed in distilled water and dried.

[0054] The present invention in another aspect relates to improvements to the functional properties and reliability of implantable medical device coatings impregnated with polymers, or polymers containing drugs, for long-term controlled drug release. Porous calcium phosphate coatings (e.g. HAP coatings) can be used as a scaffold for carrying organic material, forming a novel organo-ceramic composite. A unique and distinctive feature of such a scaffold carrying the organic material is the physical continuity of the scaffold. In this regard, the present invention provides for implantable medical devices, and process for making same, wherein calcium phosphate coatings (i.e. the physically continuous scaffold) are combined with organic material (e.g. bio-polymers) either through co-deposition, or post-deposition impregnation.

[0055] Mechanical performance of the coated stents are tested by the stent expansion test. The expansion test determines the effect of surface treatment on damage to the HAP coating. During the test, stents expand to about three times their original diameter of about 1 mm. All expansion tests are performed with the commercial Encore^{TM} 26 Inflation Device Kit. The catheter pressure used for expansion is 170 psi. After expansion, the adhesion of the HAP coating is investigated. Surface morphology and elemental analysis of the deposited specimens are observed by a Hitachi S-3000 scanning electron microscopy (SEM), with magnification of up to 10,000x.

[0056] We have observed that the calcium phosphate coatings according to the present invention are able to survive large strain (>10%) of the underlying substrate. Tiny fractures observed in some such coatings to accommodate the strain is *distributed* and *localized*, i.e. the nano-cracks are limited to small (< 100 nm) areas adjacent to the pores. Although frequently not visible even under 10,000x magnification, collective opening of these nano-cracks accommodates the substrate strain. These nano-cracks may link to form larger (visible), 1-10 μm long cracks, but generally do not cause macro-cracking (> 100 μm) leading to separation of the coating from the substrate. Denser (porosity < 40%) and thicker (> 1 μm) calcium phosphate coatings show macro-cracking during stent deformation. These kinds of calcium phosphate coatings are suitable for non-deforming substrates. However, these denser and thicker films are still suitable for deforming substrates (e.g. stents) if combined with viscoelastically deforming filler such as organic polymers.

EXAMPLES

[0057] To demonstrate the feasibility of the novel processing concepts outlined above, the following examples are described below for a stainless steel substrate, in particular, coronary stents. The procedures outlined below can be applied to other implantable medical devices.

Example 1 – General ECD Process

[0058] A 316L stainless steel stent, 14mm in length and 0.85mm outer radius was used. The stent surface was electro-polished, then cleaned in ultrasonic bath, with distilled water and then with ethyl alcohol. Figures 1(a) to (d) show the stent surface before coating. The radial surface non-uniformity is an artifact of laser cutting the stent from a steel tube during manufacture.

[0059] Electrochemical deposition was performed in 80 mL of electrolyte consisting of 0.02329M of $Ca(NO_3)_2 \cdot 4H_2O$ and 0.04347M of $NH_4H_2PO_4$, maintained at 50 °C. The schematic ECD setup and relevant chemical reactions taking place during the process are shown in Figure 2. The X-ray diffraction pattern from the material collected at the conclusion of ECD process is shown in Figure.3, demonstrating the predominant presence of HAP in the material.

[0060] The "as-received" stent (i.e. without any additional surface preparation) was used as the cathode and a nickel ring was used as the anode. When a 0.90 mA current is applied for 50 seconds, an approximately 0.5 μm thin film HAP coating is deposited on the stent. Immediately, the coated stent was washed with running distilled water for 1 minute and air dried for 5 minutes. The coating had uniform coating approximately 0.5 μm thick that covered all surfaces of the stent, as shown in Figures 4(a) to (d). Figures 5(a) to (d) show the second sample processed in a separate repeat experiment.

[0061] An expansion test was performed after the coated stent has been air dried. An Encore™ 26 Inflation Device Kit was used, and the catheter inserted into the stent was inflated to 170 psi. The expanded stent was observed under SEM. Figures 6 and 7 illustrate the results. The HAP coating separated from the stent surface in the areas of significant strain due to stent expansion. The flaked coating allowed assessment of the coating thickness, which was about 0.6 μm. The coating was retained on the stent in areas experiencing low strain or no strain.

Example 2 – ECD on Pre-Oxidized Stent

[0062] A 316L stainless steel stent was selected as in Example 1. The stent was cleaned in an ultrasonic bath, with distilled water and then with ethyl alcohol. Subsequently, the stent was subjected to an oxidation pretreatment to modify the surface for enhanced adhesion of coating. The stent was placed in a furnace at 500 °C for 20 minutes to create an oxidized surface layer on the stent. The oxide film thickness was estimated to be <50 nm thick. Figures 8(a) and (b) show the stent surface after oxidation pretreatment. The surface exhibits nano-roughness on the order of 50 to100 nm.

[0063] Electrochemical deposition was performed as in Example 1, with immersion of the stent in 80mL of electrolyte consisting of 0.02329M $Ca(NO_3)_2$ $4H_2O$ and 0.04347M $NH_4H_2PO_4$ at 50 °C. The oxidation pretreated stent was used as the cathode and a nickel ring was used as the anode. When a 0.90 mA current was applied for 50 seconds, a thin film HAP coating was deposited on the stent.

Immediately, the coated stent was washed with running distilled water for 1 minute and air dried for 5 minutes.

[0064] The coating uniformly covered the stent and the thickness was approximately 0.5 μm, as shown in Figures 9(a) to (d). The surface morphology of the coating remained unchanged from the HAP coating on the un-modified stent of Example 1 (Figures 4 and 5). An expansion test was performed as in Example 1 after HAP coated pre-oxidized stent had been air dried. As in Example 1, the expanded stent was observed under SEM, and Figures 10(a) to (d) illustrate the results. No separation of the coating was visible even in the areas of the highest strain due to the expansion, at magnifications up to 10,000x. The stent strain was accommodated by the coating through nano-size localized cracking, which was not visible under the microscope.

Example 3 – ECD on Micro-Etched Stent

[0065] A 316L stainless steel stent was selected as in Example 1. The stent was cleaned in an ultrasonic bath, with distilled water and then with ethyl alcohol. In addition, the stent was subjected to a micro-etching pretreatment in an alkaline environment, followed by heat treatment in an oxidizing atmosphere. Alkaline treatment involved immersion in a 10N NaOH solution at 60 °C for 24 hours. The stent was then ultrasonically cleaned with distilled water and heat treated at 500 °C for 1 hour.

[0066] Figures 11(a) and (b) show the stent surface after alkaline micro-etching and oxidizing pretreatment. The surface exhibits nano-roughness on the order of 50 to 100 nm. Electrochemical deposition was performed done as in Example 1, with immersion of the stent in 80 mL of electrolyte consisting of 0.02329M $Ca(NO_3)_2$ $4H_2O$ and 0.04347M $NH_4H_2PO_4$ at 50°C. The alkaline pretreated stent was used as the cathode and a nickel ring was used as the anode.

[0067] When a 0.90mA current was applied for 50 seconds, a thin film HAP coating was deposited on the stent. Immediately, the coated stent was washed with running distilled water for 1 minute and air dried for 5 minutes. The coating uniformly

covered the stent and the thickness was approximately 0.5 μm, as shown in Figures 12(a) to (d). The surface morphology of the coating remained unchanged from the HAP coating on the un-modified stent of Example 1 (Figures 4 and 5). An expansion test was performed as in Example 1 after HAP coated pre-oxidized stent had been air dried. As in Example 1, the expanded stent was observed under SEM, and Figures 13(a) to (d) illustrate the results. No separation of the coating was visible even in the areas of the highest strain due to the expansion. The plastic shear of the metal surface produced surface relief on the coating, without damage to the coating integrity. The stent strain was accommodated by the coating through nano-size localized cracking. In the highest strain areas, the nano-cracks linked to form 1 to 5 μm long microcracks; however, these microcracks did not trigger separation of the coating from the substrate.

Example 4 – Reproducibility of ECD on Micro-Etched Stents

[0068] The experiment described in Example 3 was repeated exactly many times, and several randomly selected samples are presented here to verify process reproducibility. The expanded stents were observed under SEM, as shown in Figures 14 to 16. No separation of the coating was visible even in the areas of the highest strain due to the expansion. In one case (Fig. 15) microcracks appeared in the highest tensile strain area. Surface contamination of the coating was also visible, due to pick-up of foreign particles, likely during the drying of the coated stent. Figure 16 illustrates extremely severe deformation of an over-expanded stent, including bending and twisting. However, even in this case, no damage of the coating was observed at magnifications up to 10,000x.

Example 5 - ECD Deposition Time Effects

[0069] As in Example 1, three 316L stainless steel stents were electro-polished, and cleaned in an ultrasonic bath, first with distilled water and then with ethyl alcohol. As in Example 3, each stent was subjected to an alkaline micro-etch pretreatment. Electrochemical deposition was performed as in Example 1. A 0.90 mA current was applied for 60, 70 and 90 seconds to stents #1, #2 and #3 respectively, and a thin film HAP coating was deposited on the stents. The coating uniformly covered the stents and the thickness of the coating on stents #1, #2 and #3 was approximately 0.75 μm,

approximately 0.90 μm and approximately 1.0 μm, respectively, as shown in Figures 17, 18 and 19 respectively. Some damage of the coatings starts to appear for the 60 second process (Figure 17), although no separation of the coating from the substrate was observed. Longer processes (70 and 90 seconds) resulted in denser and thicker coatings, which were also stiffer and therefore produced larger stresses (at same strain) during stent expansion, as compared to the shorter deposition time / thinner / more porous coatings (Figures 13 to 17). It is therefore noted that the longer deposition times produce coatings which are not suitable for deforming substrates such as stents, but may be applied to non-deforming substrates such as dental or hip implants.

[0070] Figure 19(e) comparatively illustrates the changing morphology of the HAP coated stents for different times of deposition. As deposition time increases, coating density increased and the coating was more uniform. 50 and 60 second depositions exhibited the most uniform coating structure, and the most desire porosity. 90 second deposition caused local delamination of the coating.

Example 6 - ECD on Aero-Sol-Gel HAP Coated Stent

[0071] A 316L stainless steel stent was selected as in Example 1. The stent was cleaned in an ultrasonic bath, with distilled water and then with ethyl alcohol. The stent was coated with ~0.2 μm thick coating of HAP using sol-gel technology as described in T. Troczynski and Dean-Mo Liu, "Novel Sol-Gel Hydroxyapatite Ceramic Coatings and Method of Making Same", US Patent No. 6,426,114; Canadian Patent No. 2,345,552. The aero-sol-gel deposition (ASGD) method was used to uniformly deposit droplets of sol particles on the stent surface. A smooth, uniform, well-adhering film of HAP was produced on the stent surface as illustrated in Figures 20(a) to (d).

[0072] As this type (i.e., AGSD) of HAP film is very thin and adhesive, it survives the stent expansion test well. However, these types of very thin, dense films are not suitable for carrying additional materials such as bio-polymers, protein, and/or drugs. In this example we illustrate combination of the ASGD method with ECD method, in order to achieve a composite adherent film which is porous and thus capable to carry additional material such as bio-polymers, protein, and/or drugs. At the same time

such ASGD-HAP pre-coated stent do not require any additional surface treatment (e.g. pre-oxidation or micro-etching) as the pre-existing film of ASGD-HAP has been found to provide a good nucleation surface for the precipitating HAP. This is illustrated in Figures 21(a) to (d) showing HAP deposited by ECD according to the process in Example 1, on an ASGD-HAP pre-coated stent, and Figures 22(a) to (d) illustrating the same stent after the expansion test performed according to Example 1. The surface morphology of the double-coated stent (Figures 21(a) to (d)) is the same as the directly-coated stent shown in Examples 1-4. The expanded double-coated stent (Figures 22(a) to (d)) shows dramatically improved performance of the coating (e.g. in terms of coating retention), as compared to the previously shown coatings on non-modified stents (Figures 7(a) to (b)). The stent strain was accommodated by the double coating through nano-size localized cracking. In the highest strain areas, the nano-cracks linked to form 1 to 5 μm long microcracks; however, these microcracks did not trigger separation of the coating from the substrate.

[0073] The ASGD-HAP nano-thin film provided sufficient surface modification to retain the subsequent ECD-HAP film on the stent during the expansion test. In this respect, the ASGD-HAP performs a similar function as stent pre-oxidation or micro-etching/oxidation as illustrated in Examples 2 and 3 respectively.

Example 7 – ECD-HAP/PVA Bioceramic/Biopolymer Composite Coatings through Co-Deposition

[0074] The principal advantages of the ECD process for HAP coatings (high porosity and room-temperature deposition) make them ideal carriers for organic materials such as polymers (preferably bio-polymers), proteins and DNA, and drugs. As an illustrative example of such composite coatings, the process described in Example 3 was modified by dissolving 0.1 g of polyvinyl alcohol (PVA) in the electrolyte (i.e. the coating solution, as described in Example 1), and the coating process was repeated as in Example 3. The resulting coating is shown in Figures 23 (a) to (d) (as-deposited) and Figures 24 (a) to (d) (after the expansion test).

[0075] The composite coating morphology appears more porous and more rough, as compared to the coatings produces without PVA (e.g. in Example 1). The expansion

test exposes a fraction of the stent surface in the areas of highest strain (Figures 24(a) to (d)) but the coating was retained on the stent.

[0076] Increasing the amount of PVA dissolved in the bath to 0.5 g gave the results illustrated, before and after expansion, in Figures 25(a) to (d) and Figures 26(a) to (d), respectively. The surface morphology is more smooth (as compared to the 0.1 g PVA coating in Figures 23(a) to (d)), and the retention of the coating is also better. This may be attributed to the higher amount of PVA entrapped in the ECD-HAP coating, which helps to relax the expansion-related stresses through visco-elastic deformation (and thus stress relaxation).

Example 8 - ECD-HAP/PLGA Bioceramic/Biopolymer Composite Coatings through Impregnation

[0077] This example illustrates an alternate route to bioceramics / biopolymer composite coating, through post-deposition impregnation with a polymer solution. The experiment described in Example 3 is repeated. In addition, the HAP coated stent is impregnated with poly(DL-lactide-co-glycolide) (PLGA) solution of 2 wt% or 4 wt% PLGA and acetone, by simple dipping, followed by drying in air.

[0078] The over-expanded stent (i.e., strain up to two times greater than a normal implantation procedure) is illustrated in Figures 27(a) to (d) and 28(a) to (d) for the 2 wt% and 4 wt% PLGA solutions respectively. No separation of the coating is visible even in the areas of the highest strain due to the expansion in both cases, although a few microcracks may be observed for the coating impregnated with the 2 wt% solution of PLGA.

[0079] Figures 29(a) to (d) illustrate the surface morphology of the composite coatings, with an additional no-impregnation sample and a 6 wt% PLGA solution impregnation sample. Figures 29(a) to (d) show that PLGA filled in most of the pores of the HAP coatings with the 2 wt% PLGA solution, and PLGA filled in all pores of the HAP coating for 4 wt% PLGA solution; however, for these cases the surface features of the HAP coating can still be observed. The 6 wt% PLGA solution filled in

all pores of the HAP coating and uniformly covered the surface of HAP coating to the extent that the features of HAP coating surface were no longer visible.

[0080] The illustrated bioceramics / biopolymer composite coatings have an important distinguishing feature. Namely, the ceramic (HAP) phase is a continuous phase, i.e. there is continuity between the ceramic, AND the polymer phase is also a continuous phase. The continuity of the ceramic phase makes the coating system stable and inhibits fast dissolution of the polymer phase into environment (e.g. tissue and body fluids). Such stable composite coatings are suitable for engineered drug delivery systems, for example.

What is claimed is:

1. A process of coating an implantable medical device with a calcium phosphate coating comprising:
   (a) subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced;
   (b) immersing the pretreated substrate in an electrolyte comprising calcium and phosphate species; and
   (c) coating calcium phosphate onto the substrate by electrochemical deposition.

2. A process according to claim 1 wherein step (a) comprises heating the substrate to create an oxidized surface layer on the substrate.

3. A process according to claim 2 wherein the substrate is heated at 500 °C for 20 minutes.

4. A process according to claim 1 wherein step (a) comprises treating the substrate with an alkaline solution.

5. A process according to claim 4 wherein the alkaline solution is a sodium hydroxide solution.

6. A process according to claim 4 wherein treating the substrate with an alkaline solution comprises immersing the substrate in a 10N sodium hydroxide solution at 60 °C for 24 hours.

7. A process according to any of claims 4 to 6 wherein step (a) further comprises heating the substrate after the alkaline treatment step.

8. A process according to claim 7 wherein the substrate is heated at 500 °C for 1 hour.

9. A process according to claim 1 wherein step (a) comprises subjecting the substrate to aero-sol-gel deposition of hydroxyapatite.

10. A process according to claim 9 wherein the aero-sol-gel deposited hydroxyapatite has a thickness of approximately 0.2 μm.

11. A process according to any of claims 1 to 10 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 1.0 μm.

12. A process according to claim 11 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.75 μm.

13. A process according to claim 12 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.5 μm.

14. A process according to any of claims 1 to 13 wherein the calcium phosphate coating is a coating selected from the group consisting of hydroxyapatite, dicalcium phosphate, tricalcium phosphate and tetracalcium phosphate.

15. A process according to any of claims 1 to 13 wherein the calcium species is $Ca(NO_3)_2 \cdot 4H_2O$ and the phosphate species is $NH_4H_2PO_4$.

16. A process according to any of claims 1 to 13 wherein the calcium phosphate coating is a coating of hydroxyapatite.

17. A process according to any of claims 1 to 16 wherein the electrolyte comprises an organic material.

18. A process according to claim 17 wherein the organic material is selected from the group consisting of a bioceramic, a biopolymer, a protein, a drug, DNA or combinations thereof.

19. A process according to claim 17 wherein the organic material is polyvinyl alcohol.

20. A process according to any of claims 1 to 19 comprising step (d) impregnating the calcium phosphate coated substrate with a polymer.

21. A process according to claim 20 wherein the polymer is a bioceramic or a biopolymer.

22. A process according to claim 20 wherein the polymer is poly(DL-lactide-co-glycolide).

23. A process according to any of claims 1 to 22 wherein the substrate is flexible.

24. A process according to any of claims 1 to 23 wherein the substrate is a stent.

25. A process according to claim 24 wherein the stent is a cardiovascular stent.

26. A process of coating an implantable medical device with a composite ceramic/polymer coating comprising:

(a) subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced;

(b) immersing the pretreated substrate in an electrolyte comprising calcium, phosphate and polymer species; and

(c) coating a continuous calcium phosphate phase and a continuous polymer phase onto the substrate by electrochemical deposition.

27. A process according to claim 26 wherein the calcium species is $Ca(NO_3)_2 \cdot 4H_2O$, the phosphate species is $NH_4H_2PO_4$, and the polymer species is polyvinyl alcohol.

28. A process of coating an implantable medical device with a composite ceramic/polymer coating comprising:

(a) subjecting a substrate to a surface pretreatment whereby adhesion of the calcium phosphate coating to the substrate is enhanced;

(b) immersing the pretreated substrate in an electrolyte comprising calcium and phosphate species;

(c) coating a continuous calcium phosphate phase onto the substrate by electrochemical deposition; and

(d) impregnating the calcium phosphate coated substrate with a polymer to provide a continuous polymer phase.

29. A process according to claim 28 wherein the calcium species is $Ca(NO_3)_2 \cdot 4H_2O$, the phosphate species is $NH_4H_2PO_4$, and the polymer is poly(DL-lactide-co-glycolide).

30. An implantable medical device comprising:

(a) a substrate with a surface micro-etched by alkaline pre-treatment; and

(b) a calcium phosphate coating deposited on the substrate by electrochemical deposition.

31. An implantable medical device according to claim 30 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 1.0 μm.

32. An implantable medical device according to claim 31 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.75 μm.

33. An implantable medical device according to claim 32 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.5 μm.

34. An implantable medical device according to any of claims 30 to 33 wherein the calcium phosphate coating is a coating selected from the group consisting

of hydroxyapatite, dicalcium phosphate, tricalcium phosphate and tetracalcium phosphate.

35. An implantable medical device according to any of claims 30 to 33 wherein the calcium phosphate coating is a coating of hydroxyapatite.

36. An implantable medical device according to any of claims 30 to 35 wherein the substrate is flexible.

37. An implantable medical device according to any of claims 30 to 36 wherein the substrate is a stent.

38. An implantable medical device according to claim 37 wherein the stent is a cardiovascular stent.

39. An implantable medical device comprising:

(a) a substrate with an oxidized surface layer; and

(b) a calcium phosphate coating deposited on the substrate by electrochemical deposition.

40. An implantable medical device according to claim 39 wherein the oxidized surface layer has a thickness less than or equal to 50 nm.

41. An implantable medical device according to claim 39 or 40 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 1.0 μm.

42. An implantable medical device according to claim 41 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.75 μm.

43. An implantable medical device according to claim 42 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.5 μm.

44. An implantable medical device according to any of claims 39 to 43 wherein the calcium phosphate coating is a coating selected from the group consisting of hydroxyapatite, dicalcium phosphate, tricalcium phosphate and tetracalcium phosphate.

45. An implantable medical device according to any of claims 39 to 33 wherein the calcium phosphate coating is a coating of hydroxyapatite.

46. An implantable medical device according to any of claims 39 to 45 wherein the substrate is flexible.

47. An implantable medical device according to any of claims 39 to 46 wherein the substrate is a stent.

48. An implantable medical device according to claim 47 wherein the stent is a cardiovascular stent.

49. An implantable medical device comprising:

(a) a substrate with aero-sol-gel deposited hydroxyapatite layer; and

(b) a calcium phosphate coating deposited on the substrate by electrochemical deposition.

50. An implantable medical device according to claim 49 wherein the aero-sol-gel deposited hydroxyapatite layer has a thickness of approximately 0.2 μm.

51. An implantable medical device according to claim 49 or 50 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 1.0 μm.

52. An implantable medical device according to claim 51 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.75 μm.

53. An implantable medical device according to claim 52 wherein the calcium phosphate coating has a thickness of less than or equal to approximately 0.5 μm.

54. An implantable medical device according to any of claims 49 to 53 wherein the calcium phosphate coating is a coating selected from the group consisting of hydroxyapatite, dicalcium phosphate, tricalcium phosphate and tetracalcium phosphate.

55. An implantable medical device according to any of claims 49 to 53 wherein the calcium phosphate coating is a coating of hydroxyapatite.

56. An implantable medical device according to any of claims 49 to 55 wherein the substrate is flexible.

57. An implantable medical device according to any of claims 49 to 56 wherein the substrate is a stent.

58. An implantable medical device according to claim 57 wherein the stent is a cardiovascular stent.

59. An implantable medical device comprising a substrate with a composite coating, the composite coating comprising:
(a) a continuous ceramic phase; and
(b) a continuous polymer phase.

60. An implantable medical device according to claim 59 wherein the continuous ceramic phase comprises a calcium phosphate coating.

61. An implantable medical device according to claim 60 wherein the calcium phosphate coating is a coating selected from the group consisting of hydroxyapatite, dicalcium phosphate, tricalcium phosphate and tetracalcium phosphate.

62. An implantable medical device according claim 60 wherein the calcium phosphate coating is a coating of hydroxyapatite.

63. An implantable medical device according to any of claims 59 to 62 wherein the continuous polymer phase comprises an organic material selected from the group consisting of a bioceramic, a biopolymer, a protein, a drug, DNA or combinations thereof.

64. An implantable medical device according to any of claims 59 to 62 wherein the continuous polymer phase comprises polyvinyl alcohol.

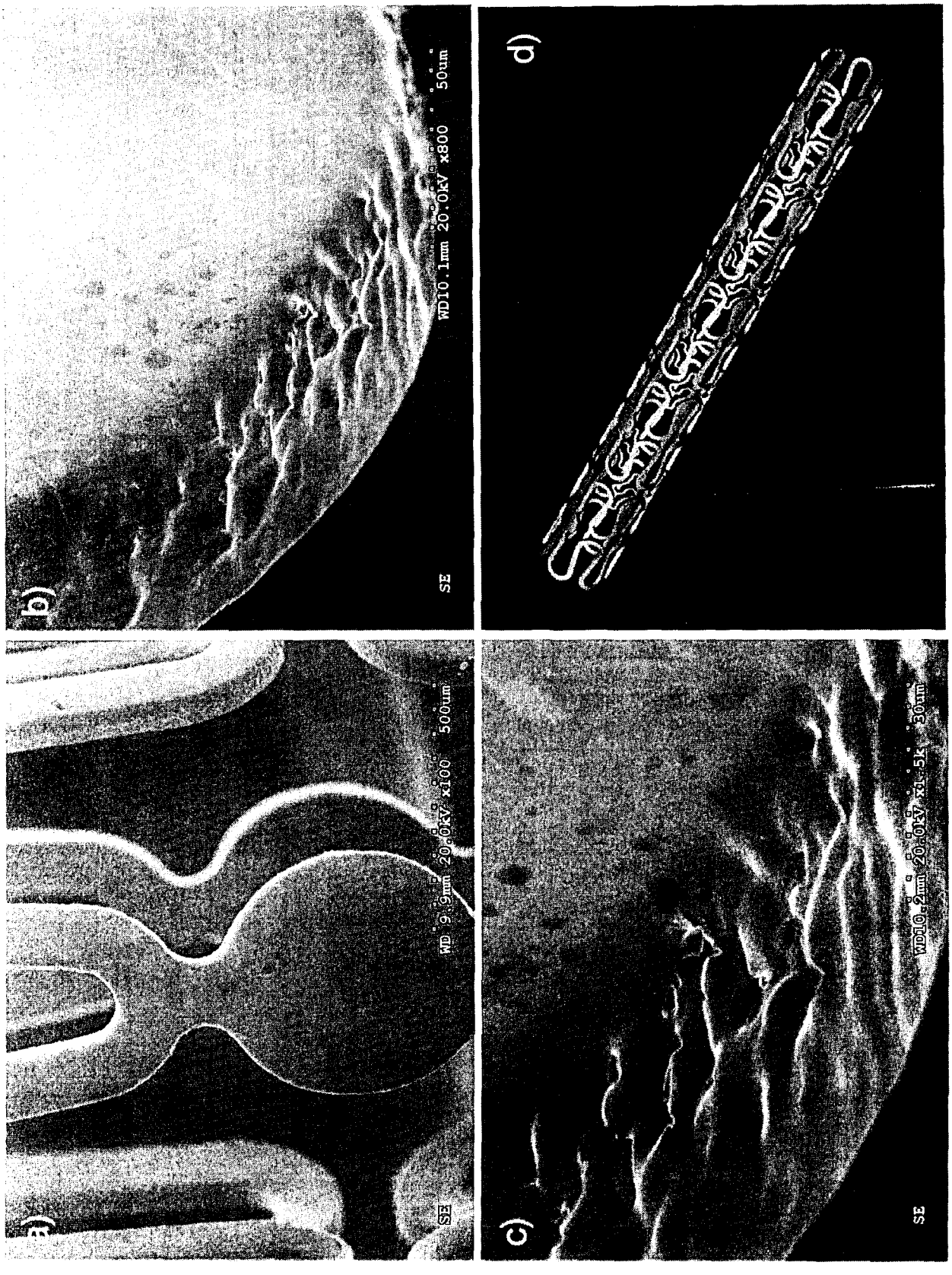
65. An implantable medical device according to any of claims 59 to 62 wherein the continuous polymer phase comprises poly(DL-lactide-co-glycolide).

66. An implantable medical device according to any of claims 59 to 65 wherein the substrate is flexible.

67. An implantable medical device according to any of claims 59 to 65 wherein the substrate is a stent.

68. An implantable medical device according to claim 67 wherein the stent is a cardiovascular stent.

69. The use of a coated implantable medical device comprising a continuous ceramic phase and a continuous polymer phase in an engineered drug delivery system.


a)
WD 9.9mm 20.0kV x100 500um
SE
b)
WD10.1mm 20.0kV x800 50um
SE
c)
WD10.2mm 20.0kV x5k 20um
SE
d)

FIGS. 1(a) - (d)

- Electrolyte: $Ca(NO_3)_2\ 4H_2O + NH_4H_2PO_4$
- Local pH increases at cathode:

$$2H_2O+2e^- \rightarrow H_2 + 2OH^-$$

- Local concentration of phosphates at cathode:

$$H^+ + PO_4^{3-} \Leftrightarrow HPO_4^{2-}$$
$$HPO_4^{2-} + OH^- \Leftrightarrow H_2O + PO_4^{3-}$$

- When sufficient OH^- produced (pH is sufficiently high), HAP deposits by :

$$10Ca^{2+} + 6PO_4^{3-} + 2OH^- \rightarrow Ca_{10}(PO_4)_6(OH)_2$$

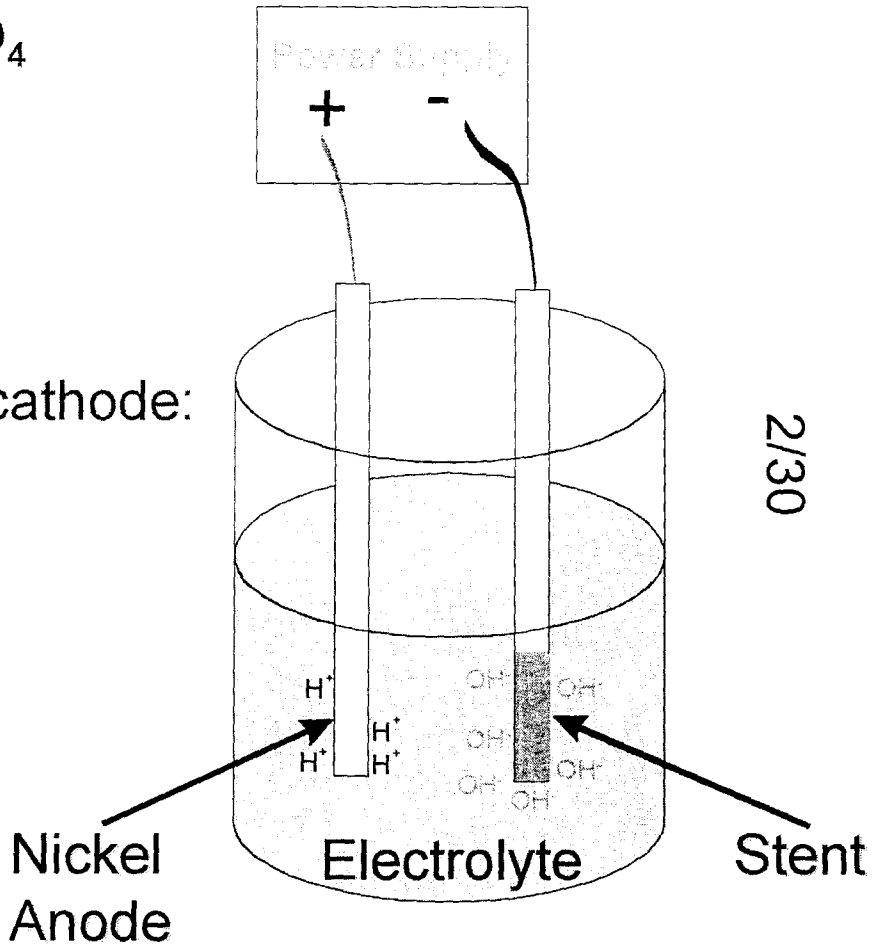


FIG. 2

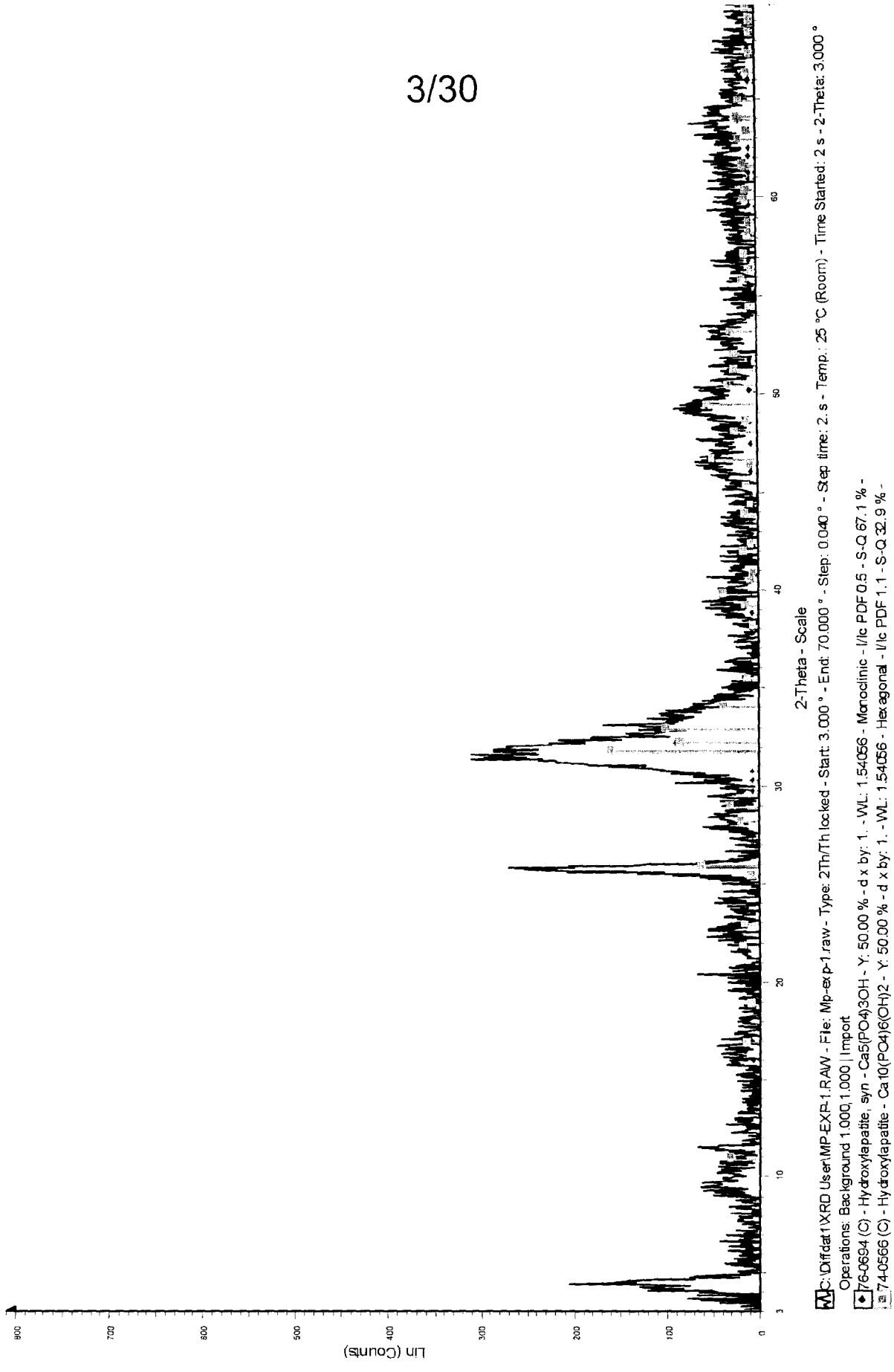
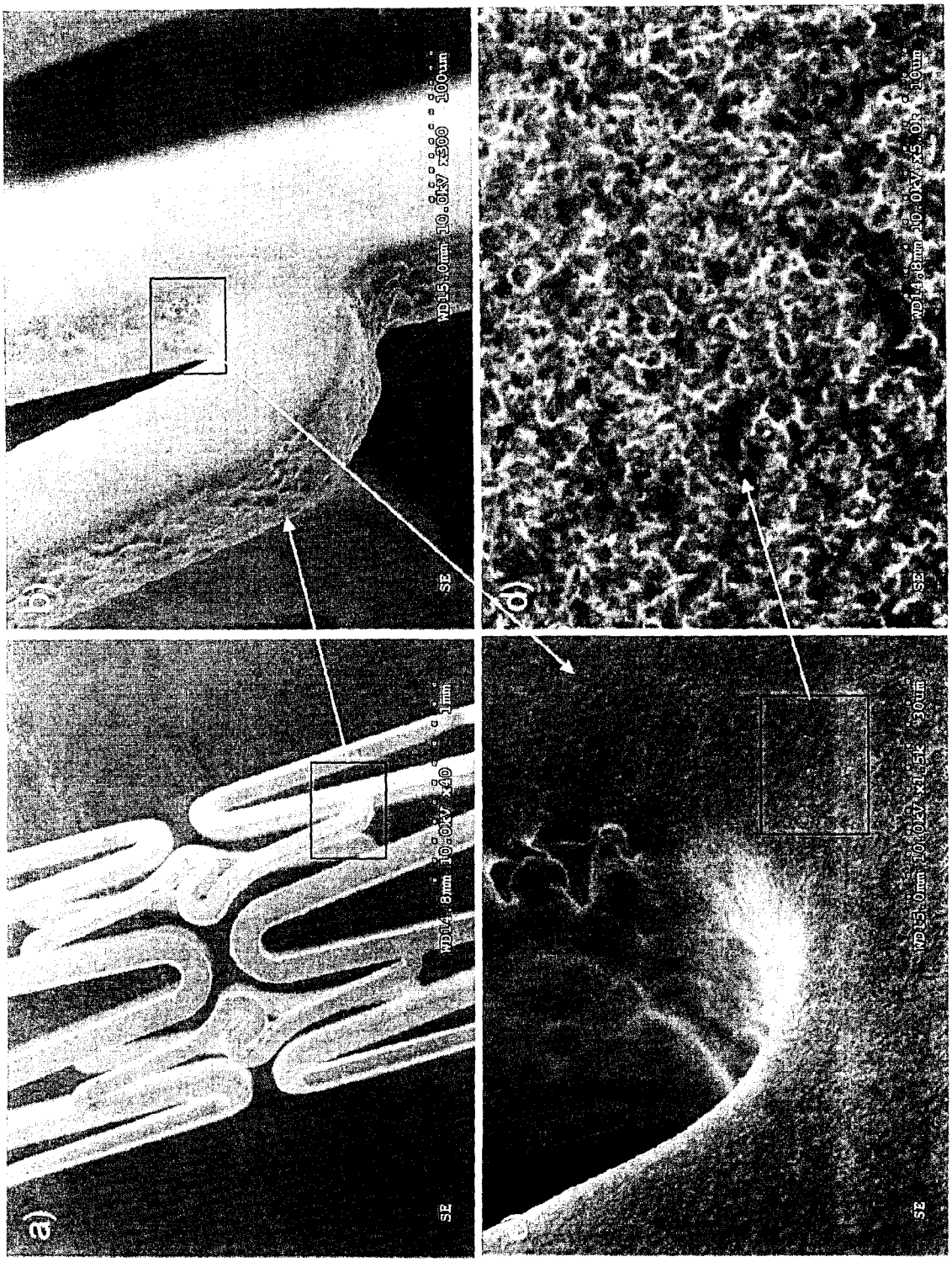

Lin (Counts)
2-Theta - Scale
C:\Diffdat1\XRD User\MP_EXP-1.RAW - File: Mp-exp-1.raw - Type: 2Th/Th locked - Start: 3.000 ° - End: 70.000 ° - Step: 0.040 ° - Step time: 2. s - Temp.: 25 °C (Room) - Time Started: 2 s - 2-Theta: 3.000 °
Operations: Background 1.000,1.000 | Import
76-0694 (C) - Hydroxylapatite, syn - Ca5(PO4)3OH - Y: 50.00 % - d x by: 1. - WL: 1.54056 - Monoclinic - I/Ic PDF 0.5 - S-Q 67.1 % -
74-0566 (C) - Hydroxylapatite - Ca10(PO4)6(OH)2 - Y: 50.00 % - d x by: 1. - WL: 1.54056 - Hexagonal - I/Ic PDF 1.1 - S-Q 32.9 % -

FIG. 3



FIGS. 4(a) - (d)

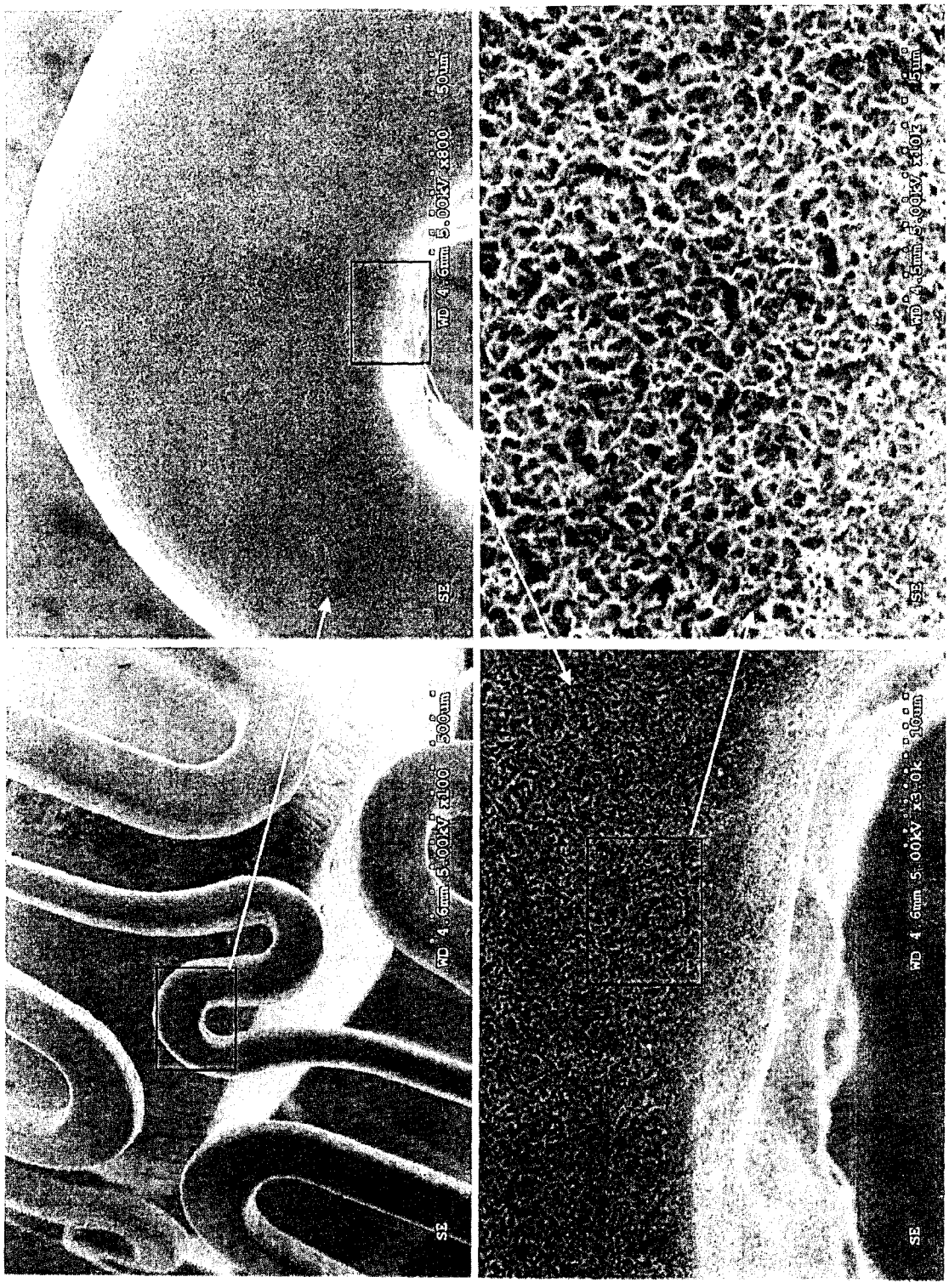

SE
WD 4.6mm 5.00kV x100 300um
SE
WD 4.5mm 5.00kV x300 50um
SE
WD 4.5mm 5.00kV x10k 1um
SE
WD 4.6mm 5.00kV x3.01k 10um

FIG. 5

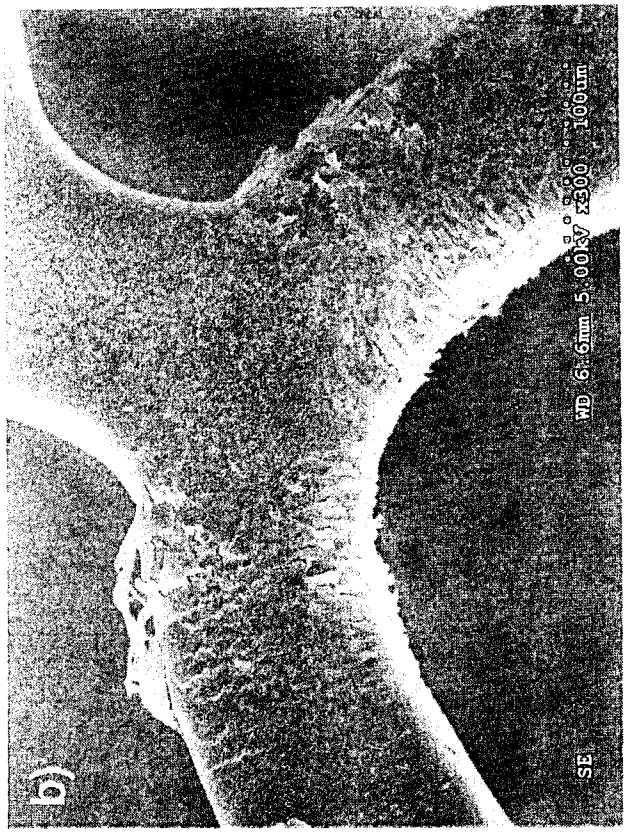


FIG. 6(b)

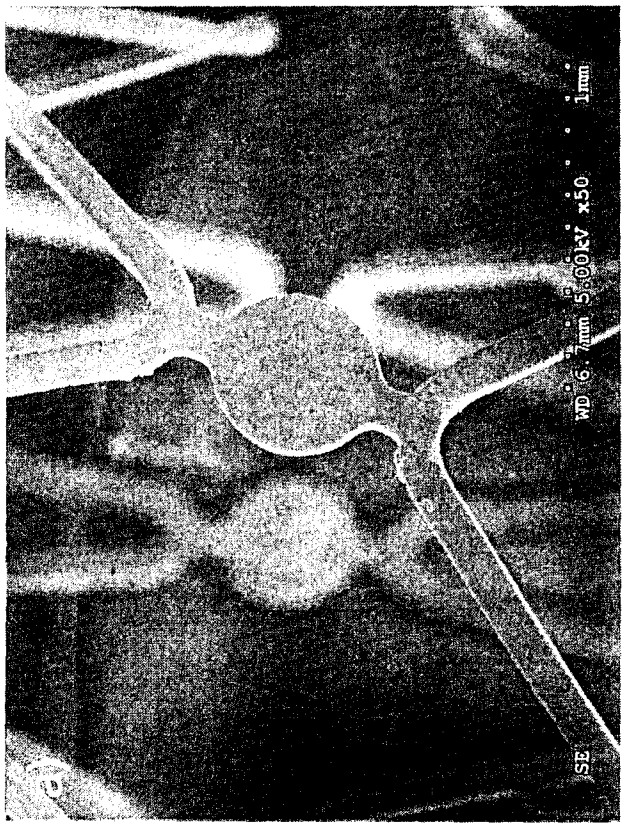


FIG. 6(a)

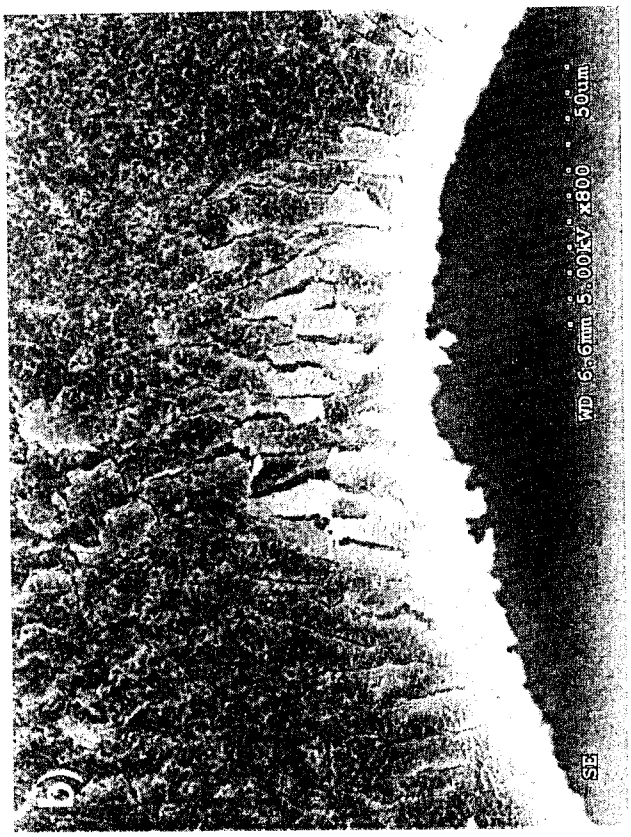


FIG. 7(b)

FIG. 7(a)

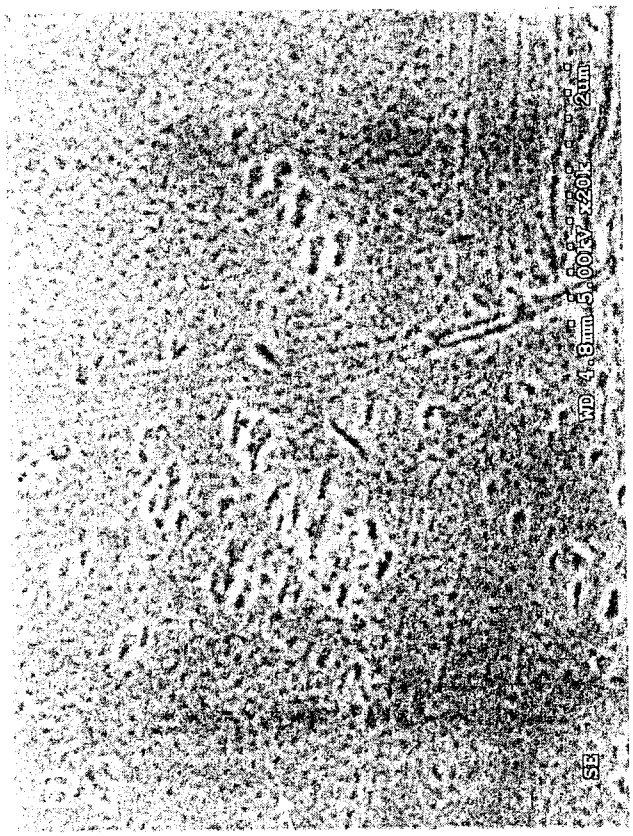


FIG. 8(b)

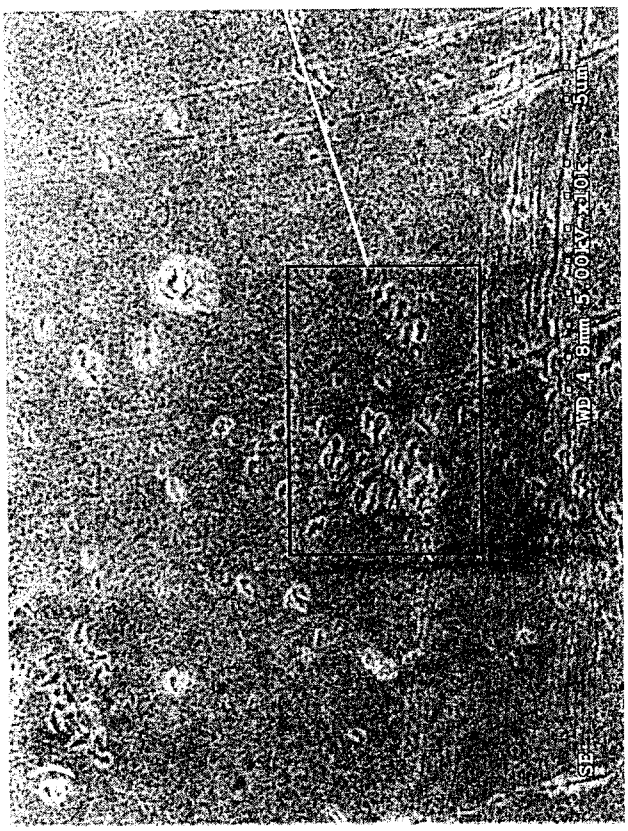
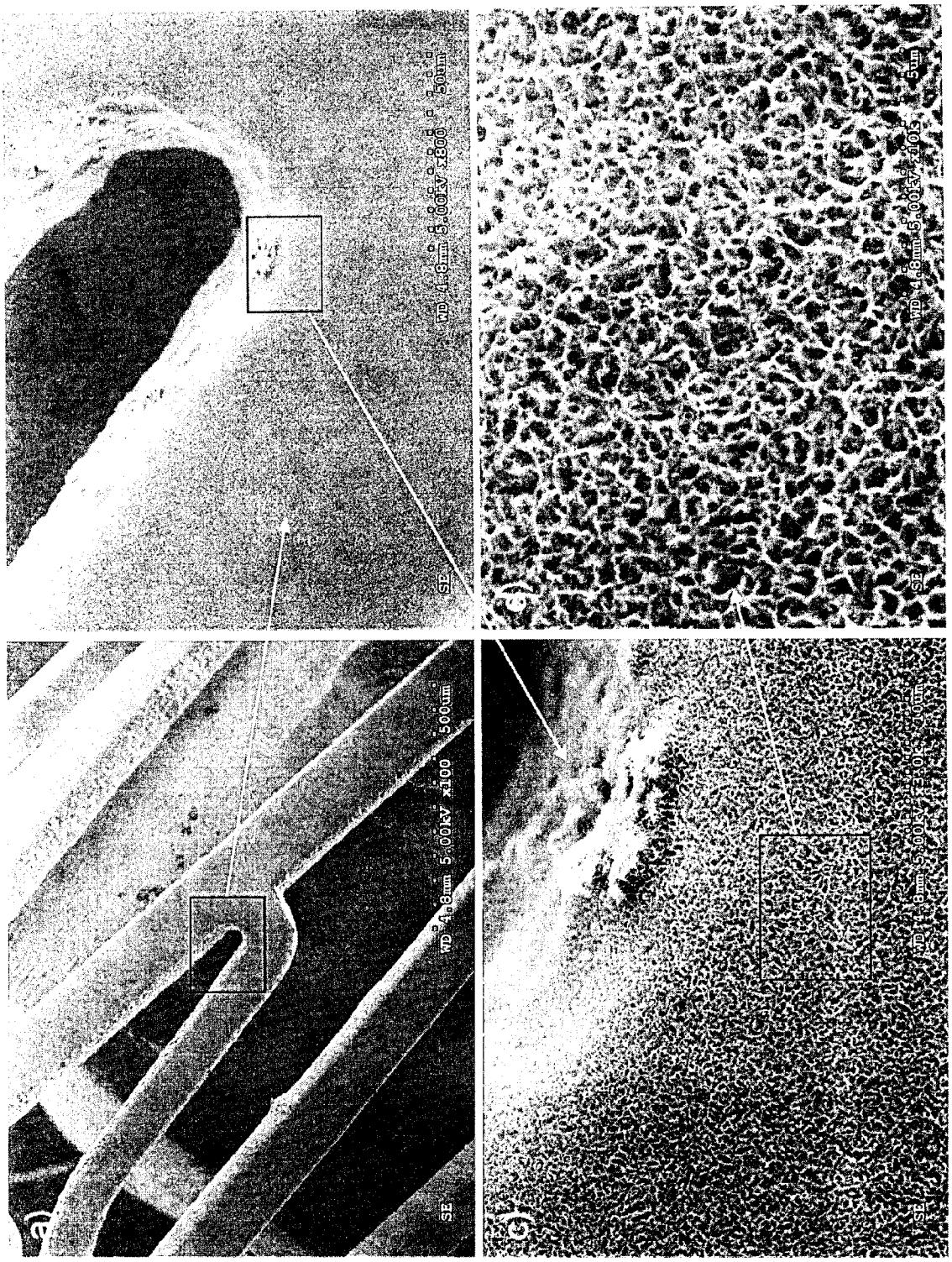
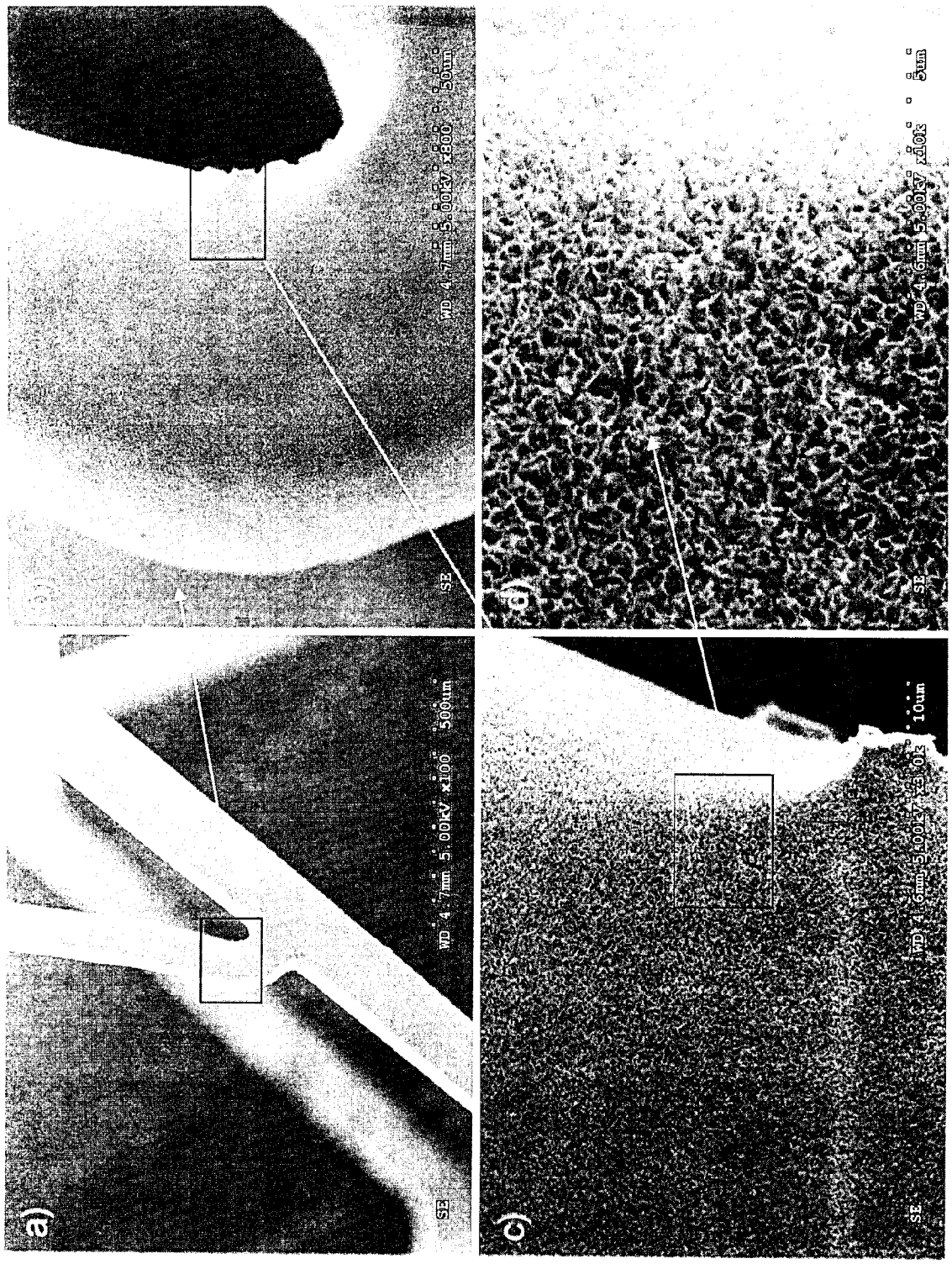


FIG. 8(a)



FIGS. 9(a) - (d)


a)
WD 4.7mm 5.00kV x100 500um
SE
b)
WD 4.7mm 5.00kV x200 50um
SE
c)
WD 4.6mm 5.00kV x1.0k 10um
SE
d)
WD 4.6mm 5.00kV x1.0k 5um
SE

FIGS. 10(a) - (d)

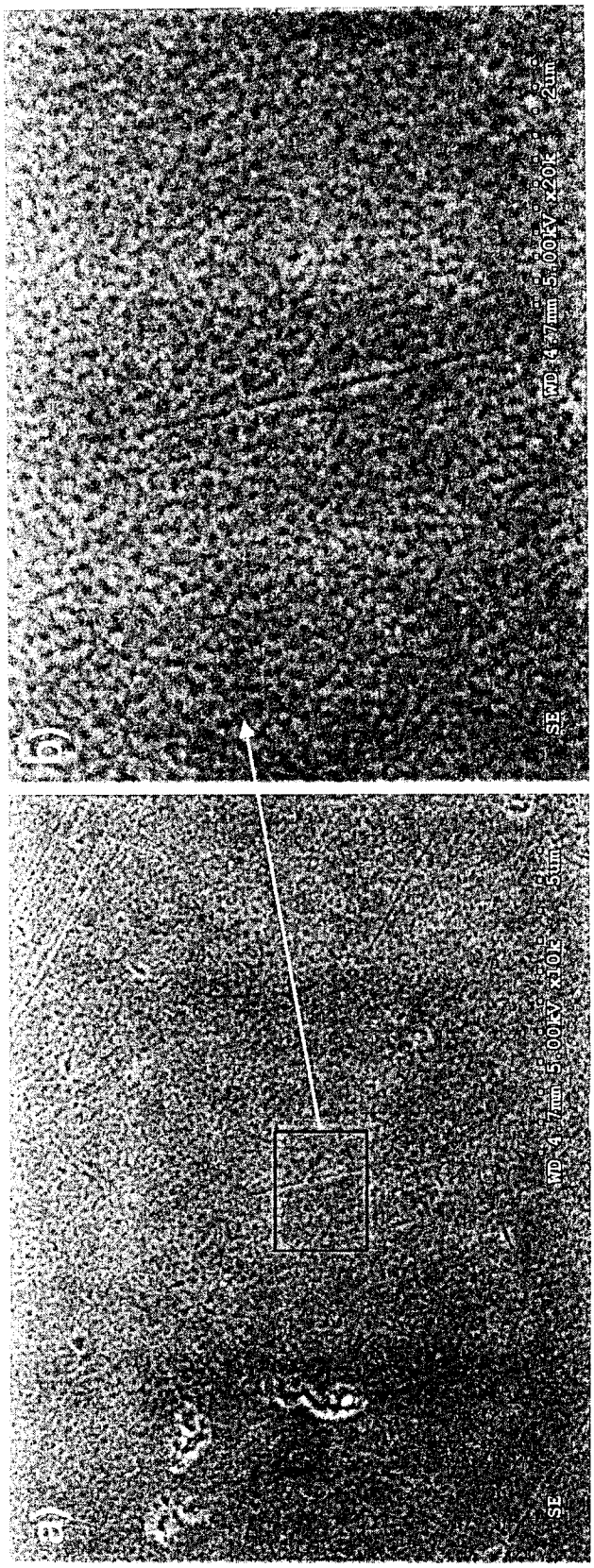
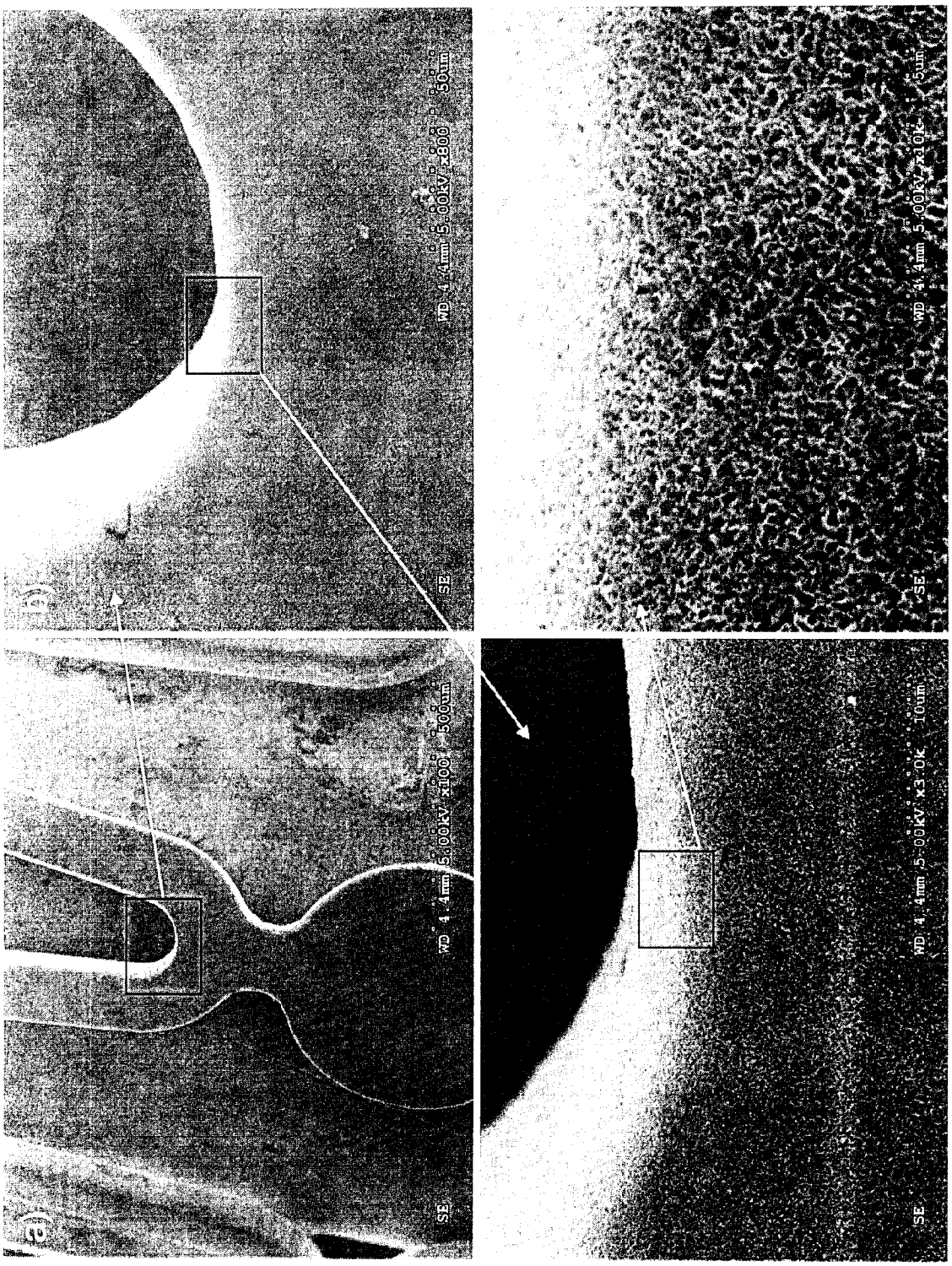


FIG. 11(b)

FIG. 11(a)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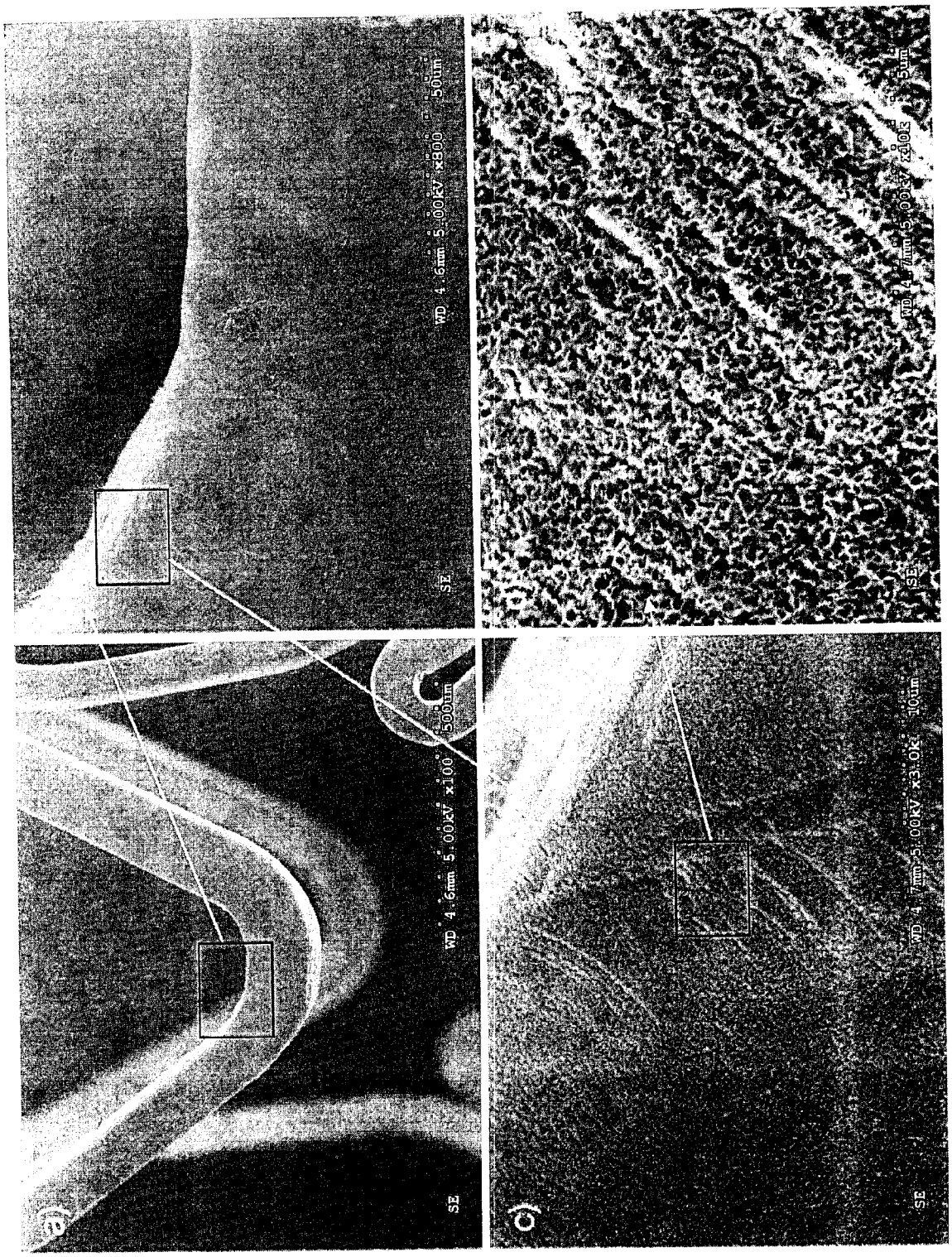
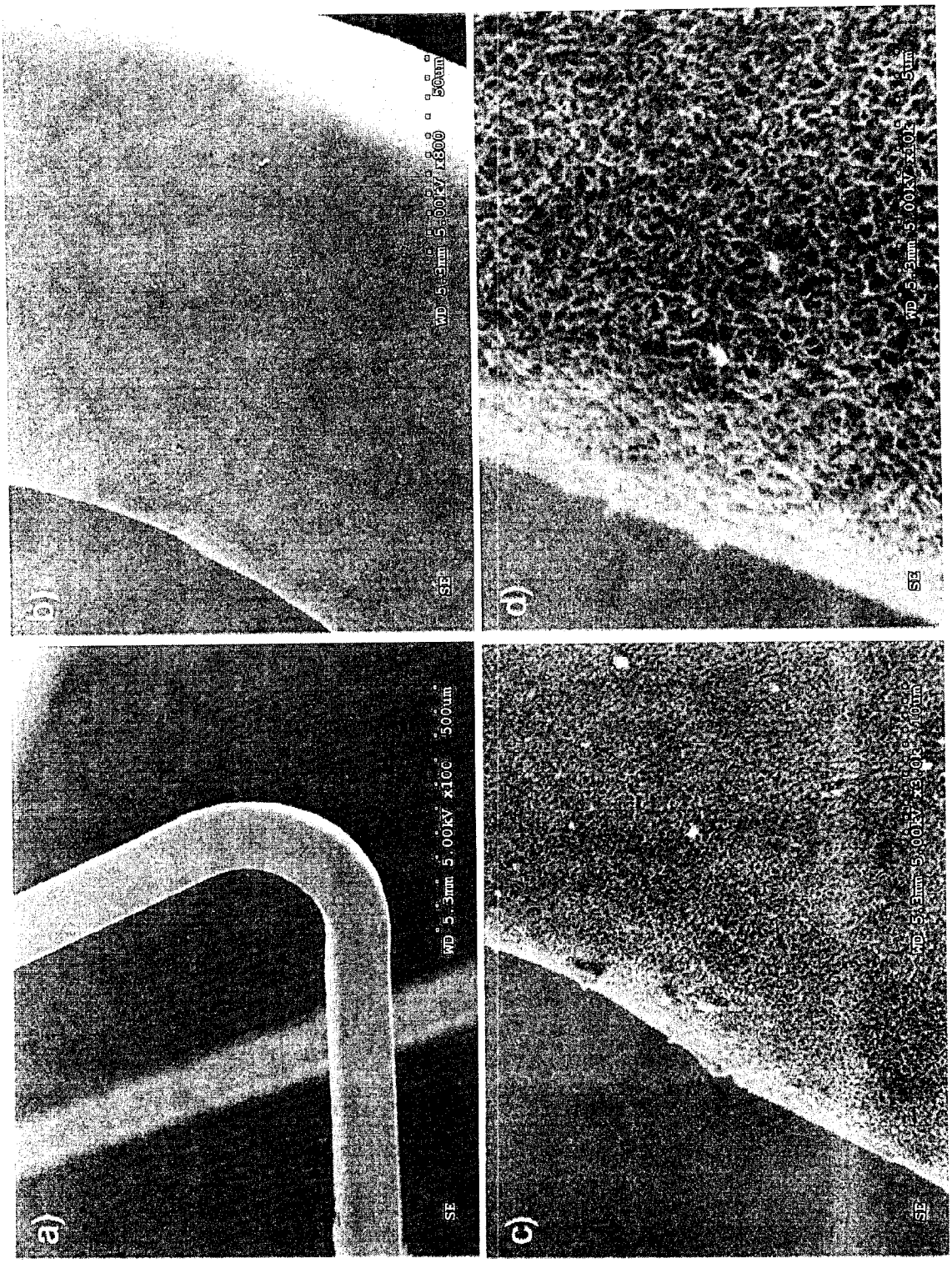
SE
WD 4.4mm 5.00kV x10k 5um
SE
WD 4.4mm 5.00kV x100 500um
SE
WD 4.4mm 5.00kV x3.0k 10um
SE

FIGS. 12(a) - (d)


WD 4.6mm 5.00kV x300 50um
SE
WD 4.6mm 5.00kV x100 500um
SE
WD 4.7mm 5.00kV x3.0k 10um
SE
WD 4.7mm 5.00kV x10k 5um
SE

FIGS. 13(a) - (d)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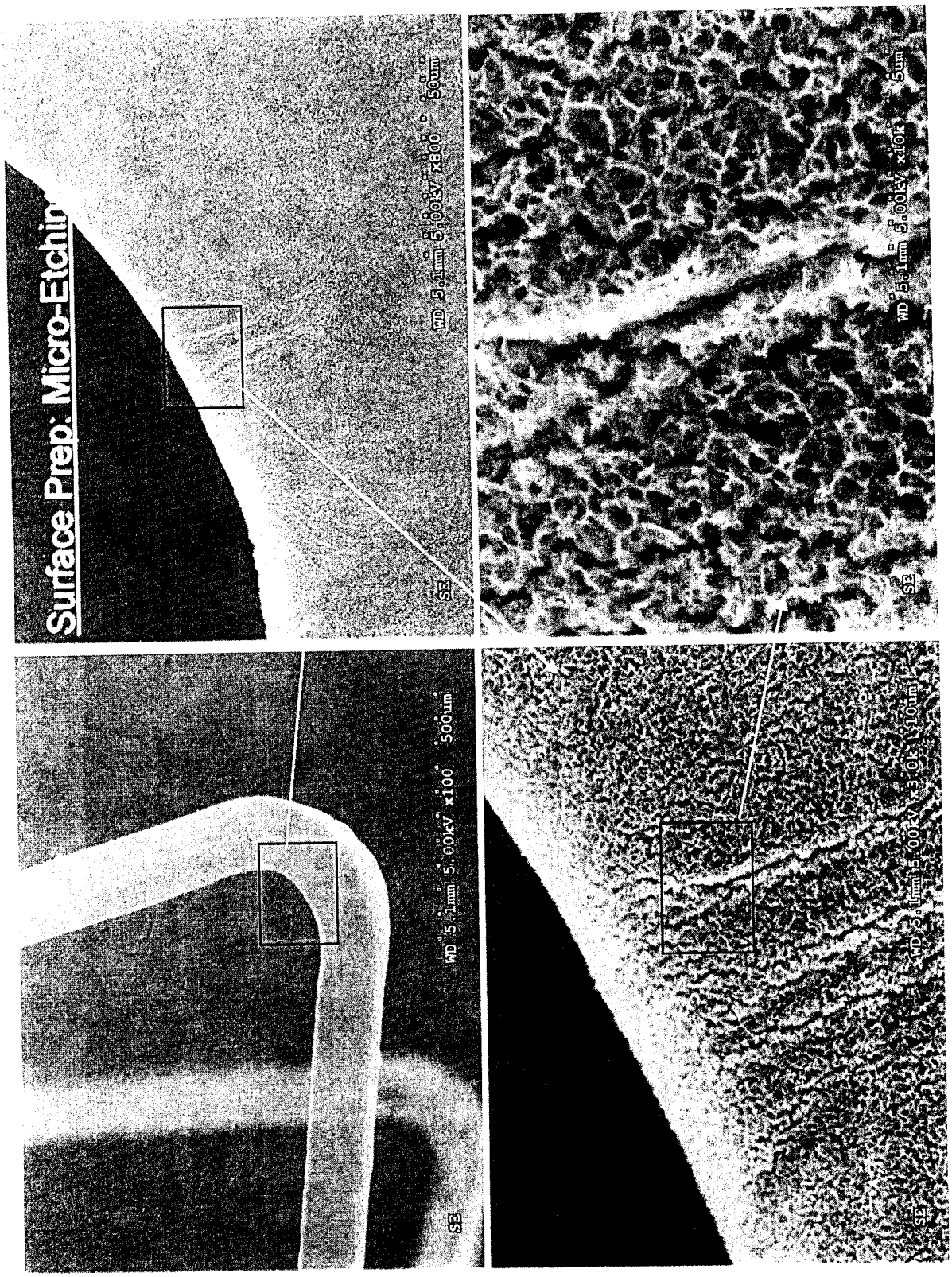
b)
SE
WD 5.3mm 5.00kV x800 50um
c)
SE
WD 5.3mm 5.00kV x3.0k 10um
d)
SE
WD 5.2mm 5.00kV x10k 5um

FIGS. 14(a) - (d)


Surface Prep: Micro-Etchin
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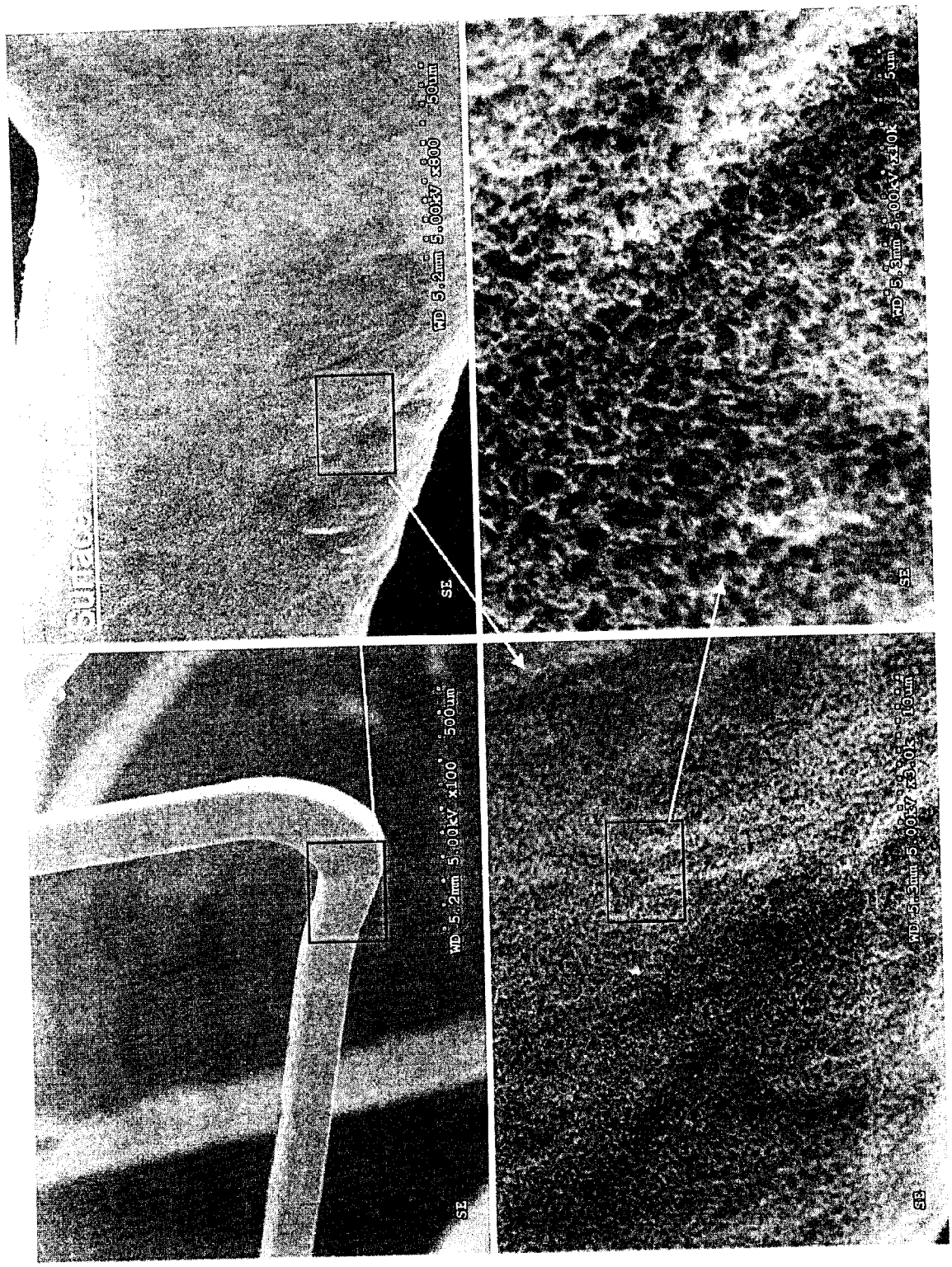
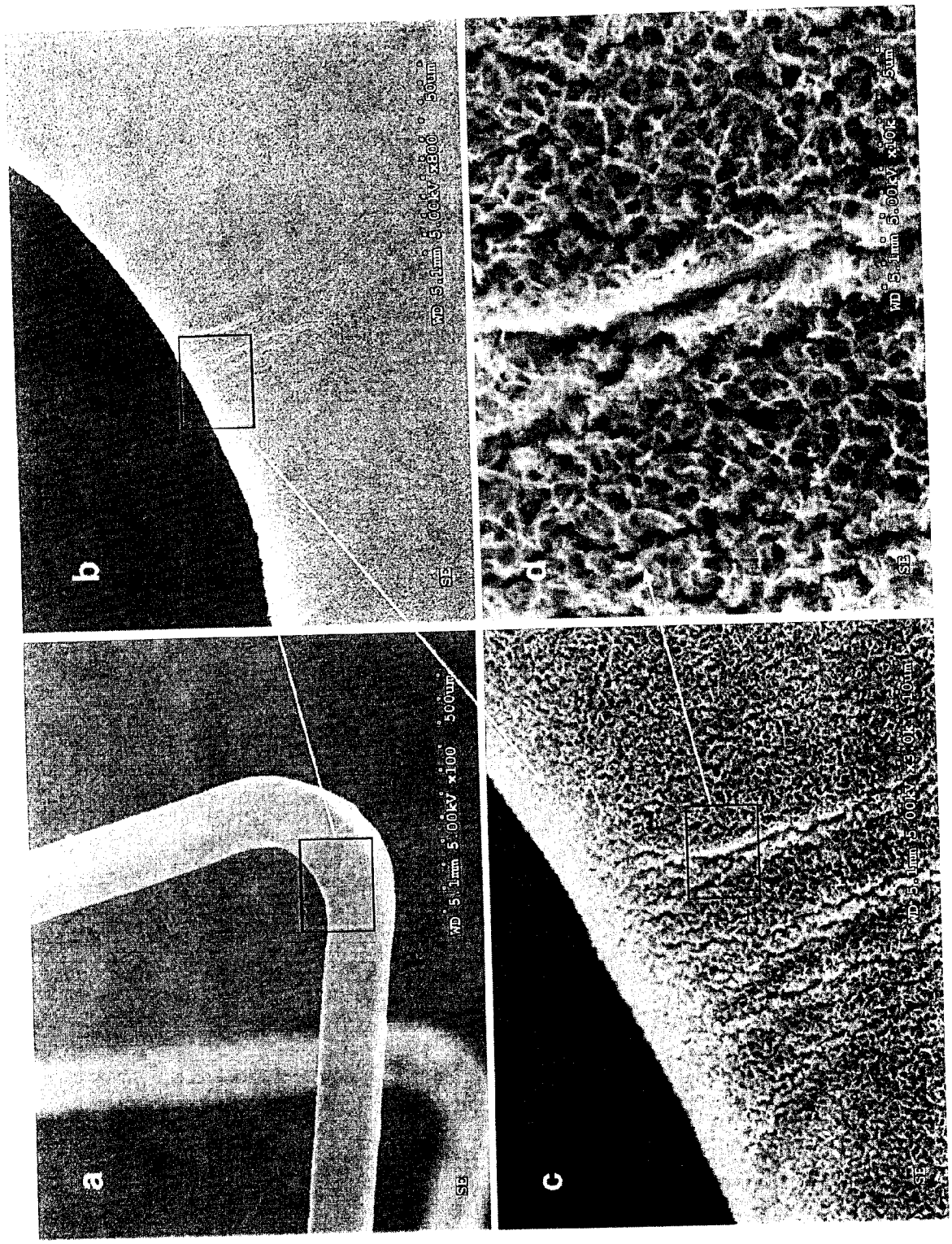
SE
WD 5.1mm 5.00kV x10k 5um
SE
WD 5.1mm 5.00kV x100 500um
SE
WD 5.1mm 5.00kV x3.0k 10um
SE

FIGS. 15(a) - (d)


WD 5.2mm 5.00kV x100 500um
SE
WD 5.2mm 5.00kV x800 50um
SE
WD 5.3mm 5.00kV x10k 5um
SB
WD 5.3mm 5.00kV x30k 10um
SB

FIGS. 16(a) - (d)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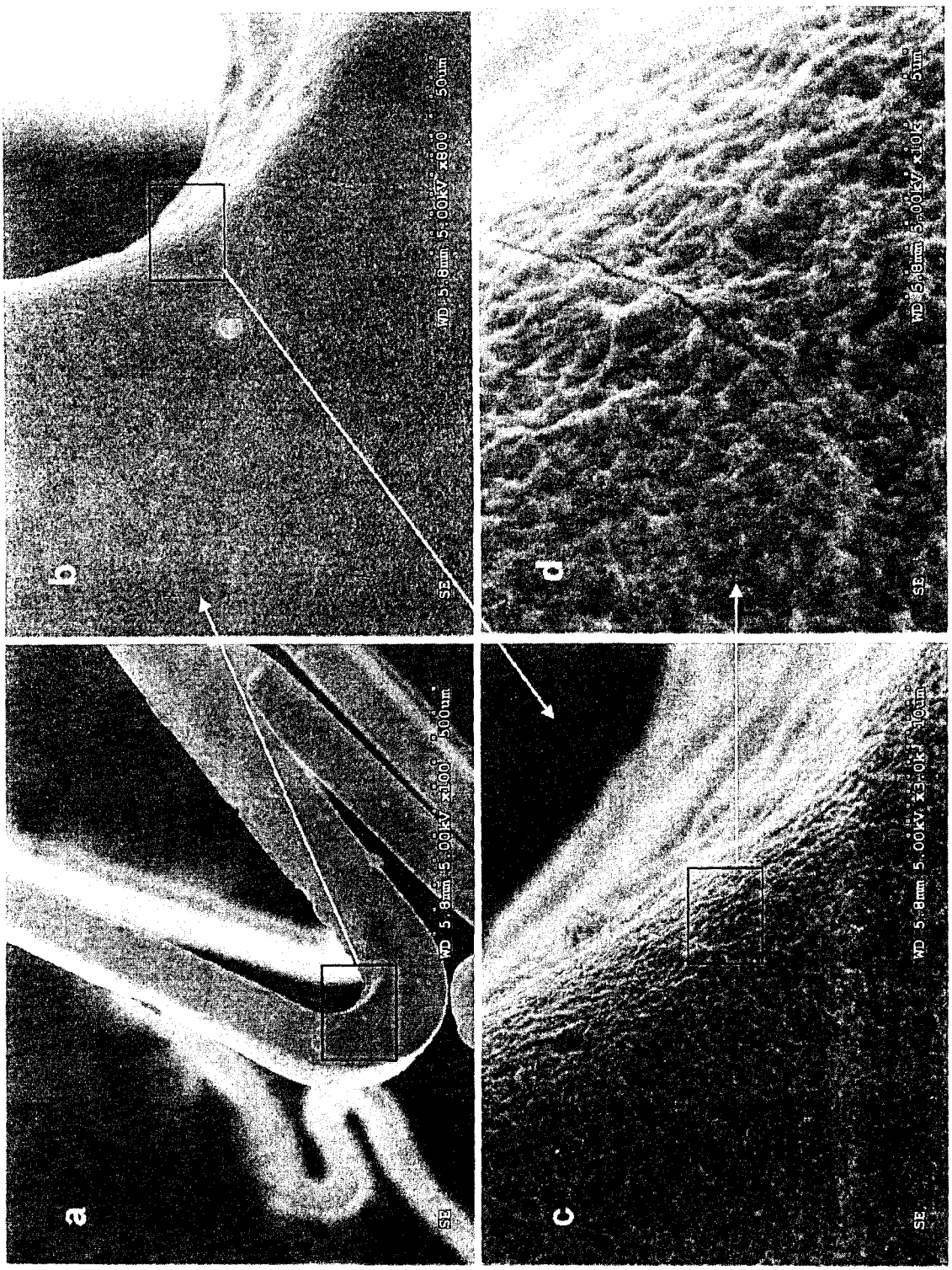
b
WD 5.4mm 5.00kV x800 50um
SE
c
WD 5.1mm 5.00kV x3.0K 10um
SE
d
WD 5.1mm 5.00kV x10K 5um
SE

FIGS. 17(a) - (d)


a
WD 5.8mm 5.00kV x100 500um
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b
WD 5.8mm 5.00kV x800 50um
SE
c
WD 5.8mm 5.00kV x3.0k 10um
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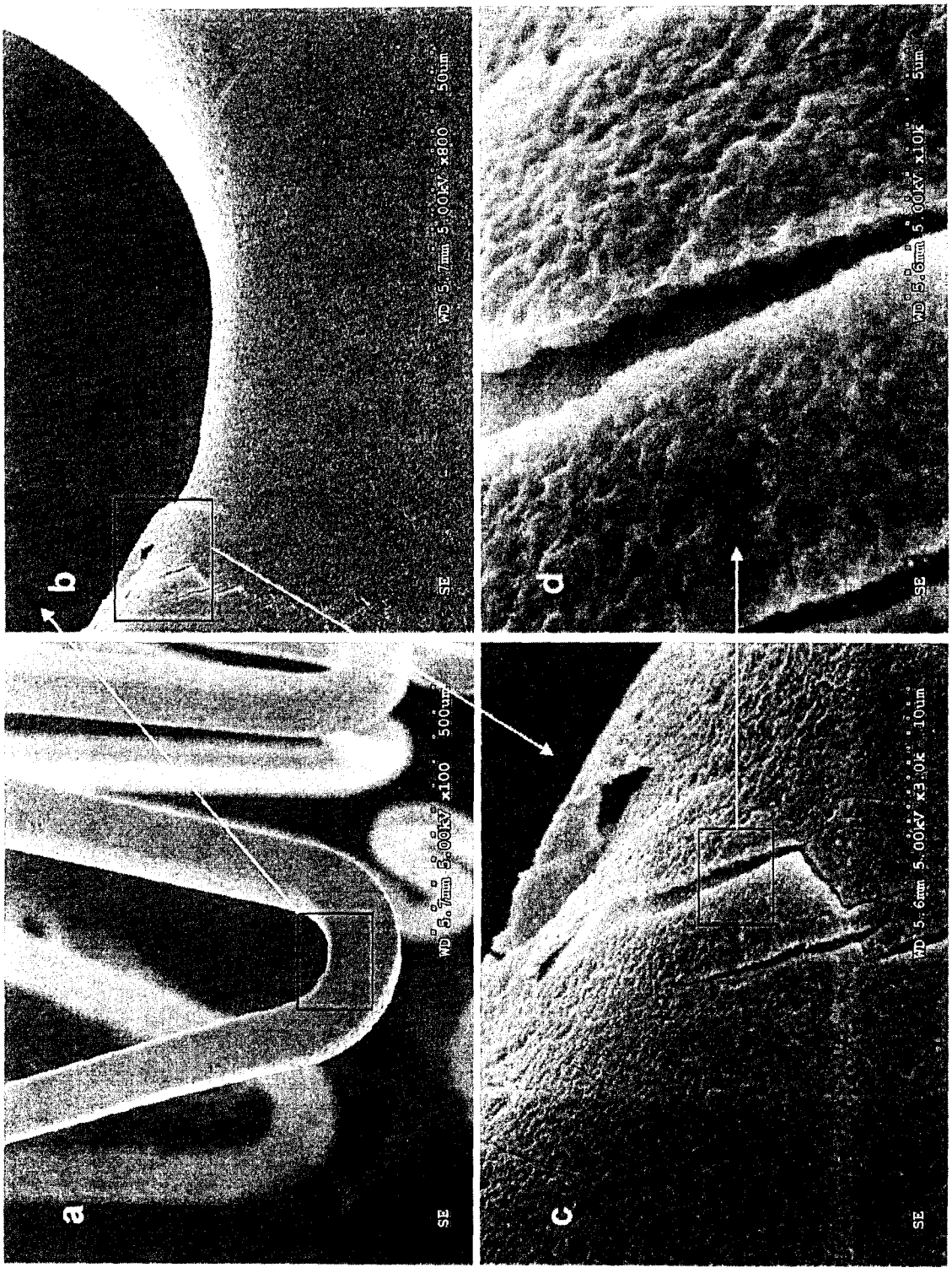
d
WD 5.8mm 5.00kV x10k 5um
SE

FIGS. 18(a) - (d)


a
WD 5.7mm 5.00kV x100 500um
SE
b
WD 5.7mm 5.00kV x800 50um
SE
c
WD 5.6mm 5.00kV x3.0k 10um
SE
d
WD 5.6mm 5.00kV x10k 5um
SE

FIGS. 19(a) - (d)

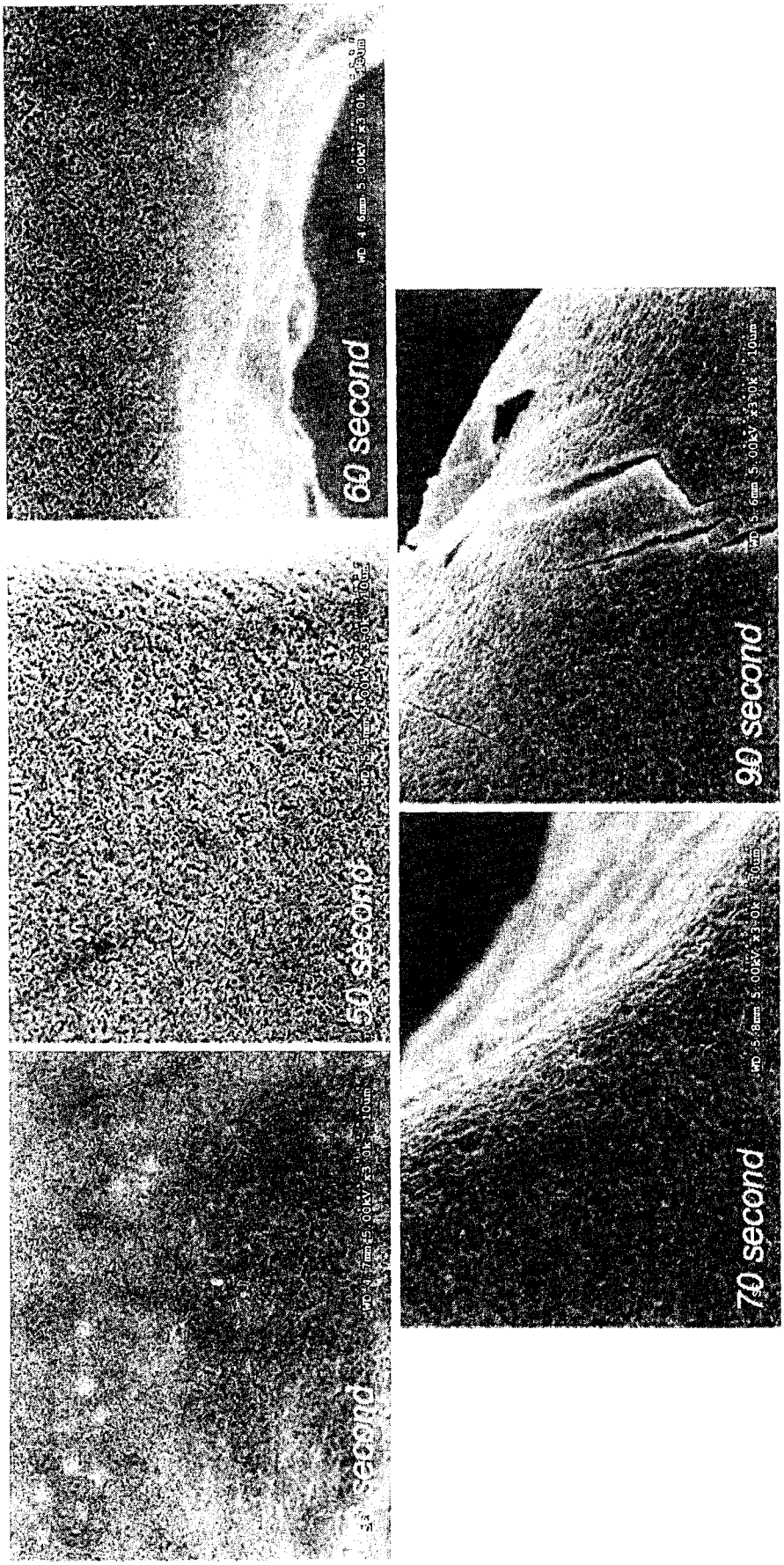
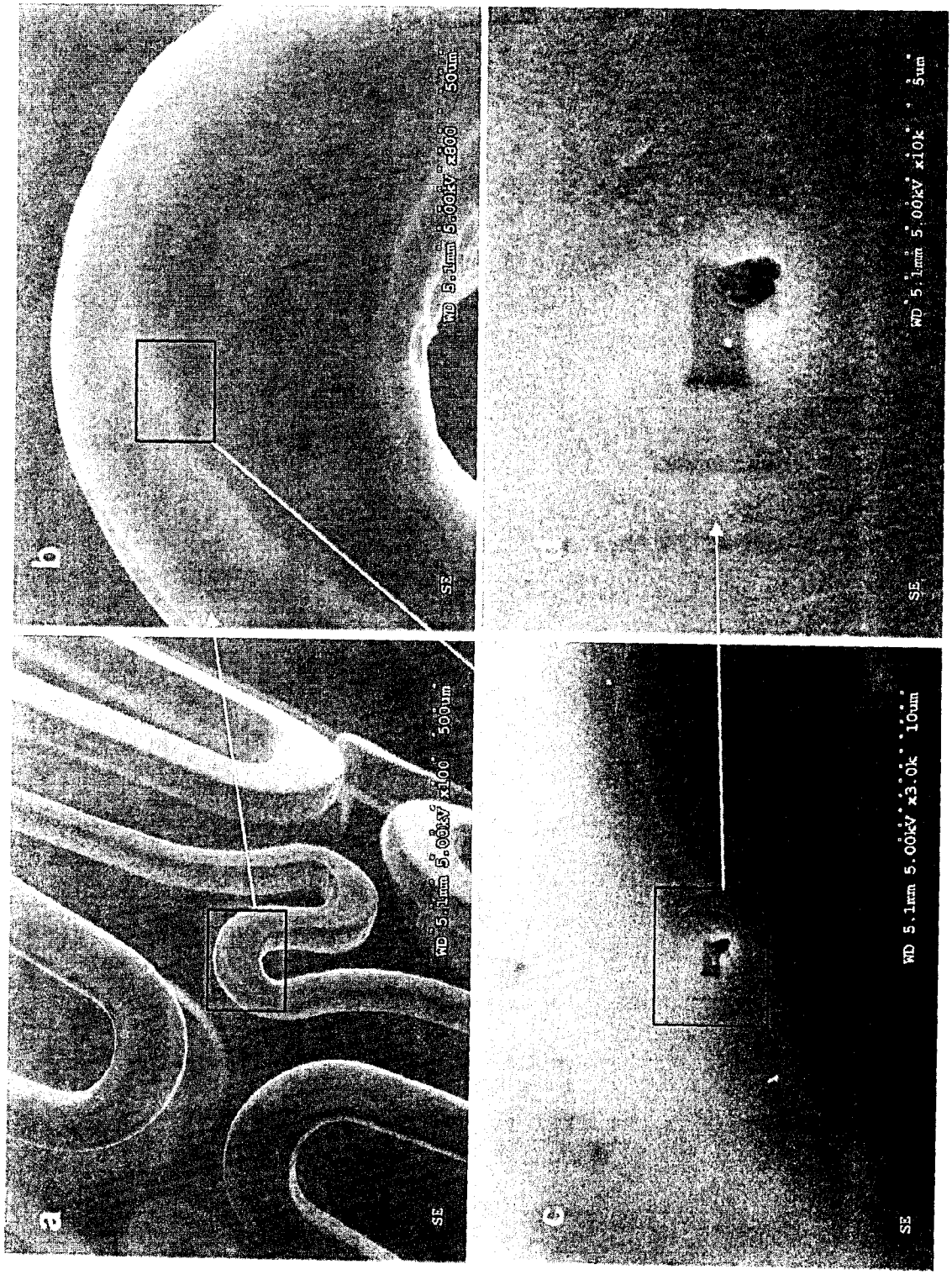
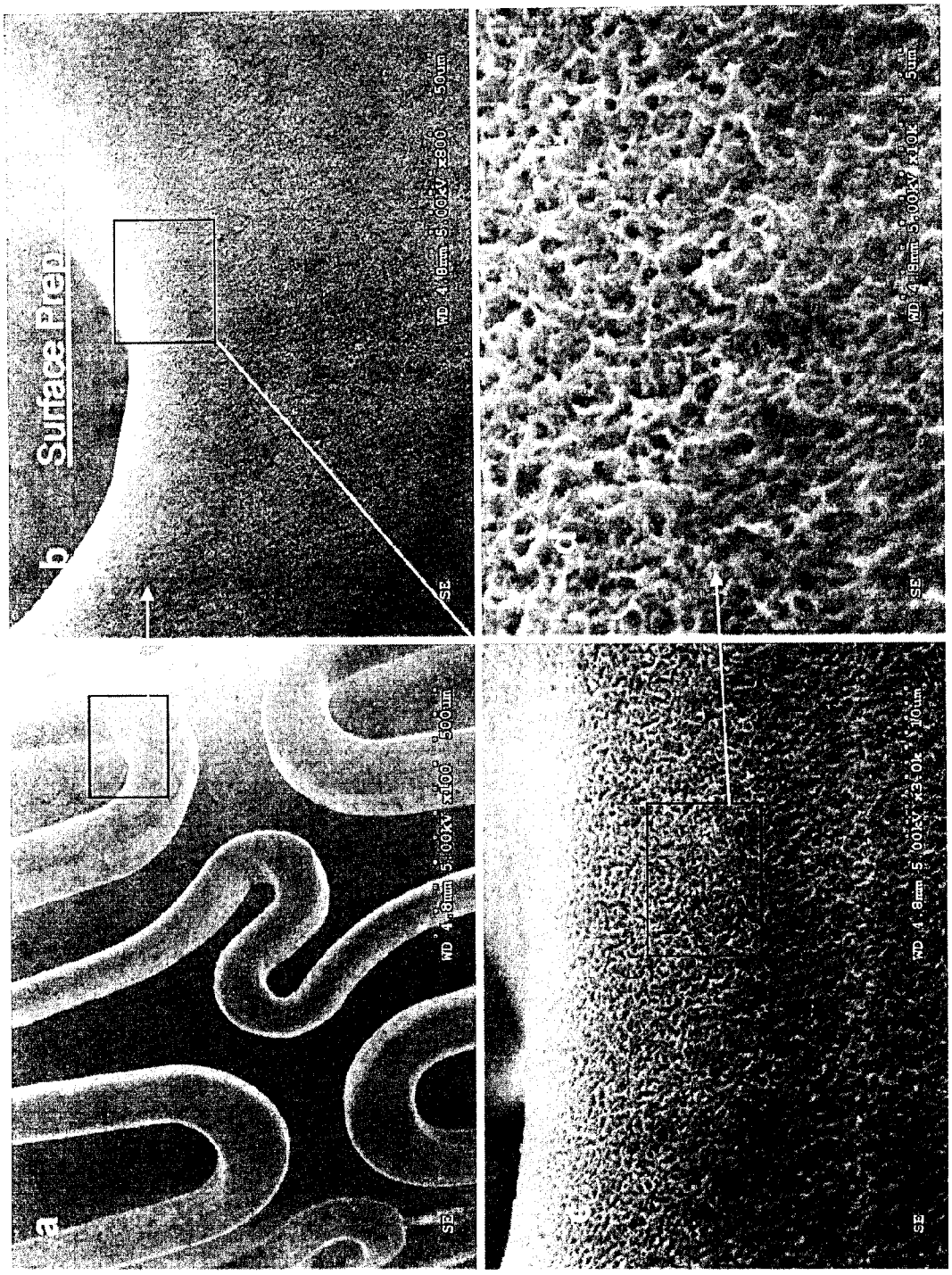


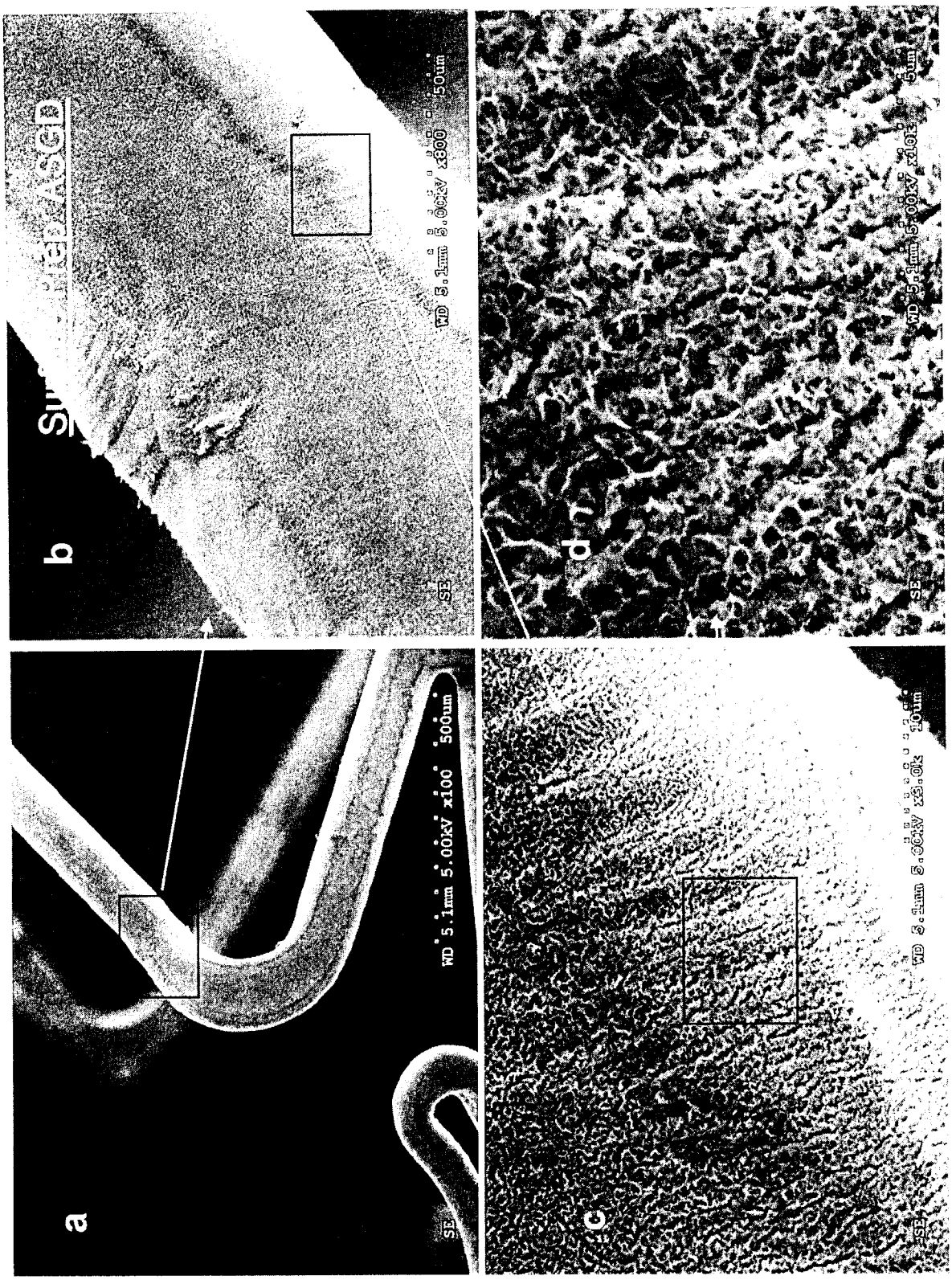
FIG. 19(e)


a
WD 5.1mm 5.00kV x100 500um
SE
b
WD 5.1mm 5.00kV x800 50um
SE
c
WD 5.1mm 5.00kV x3.0k 10um
SE
d
WD 5.1mm 5.00kV x10k 5um
SE

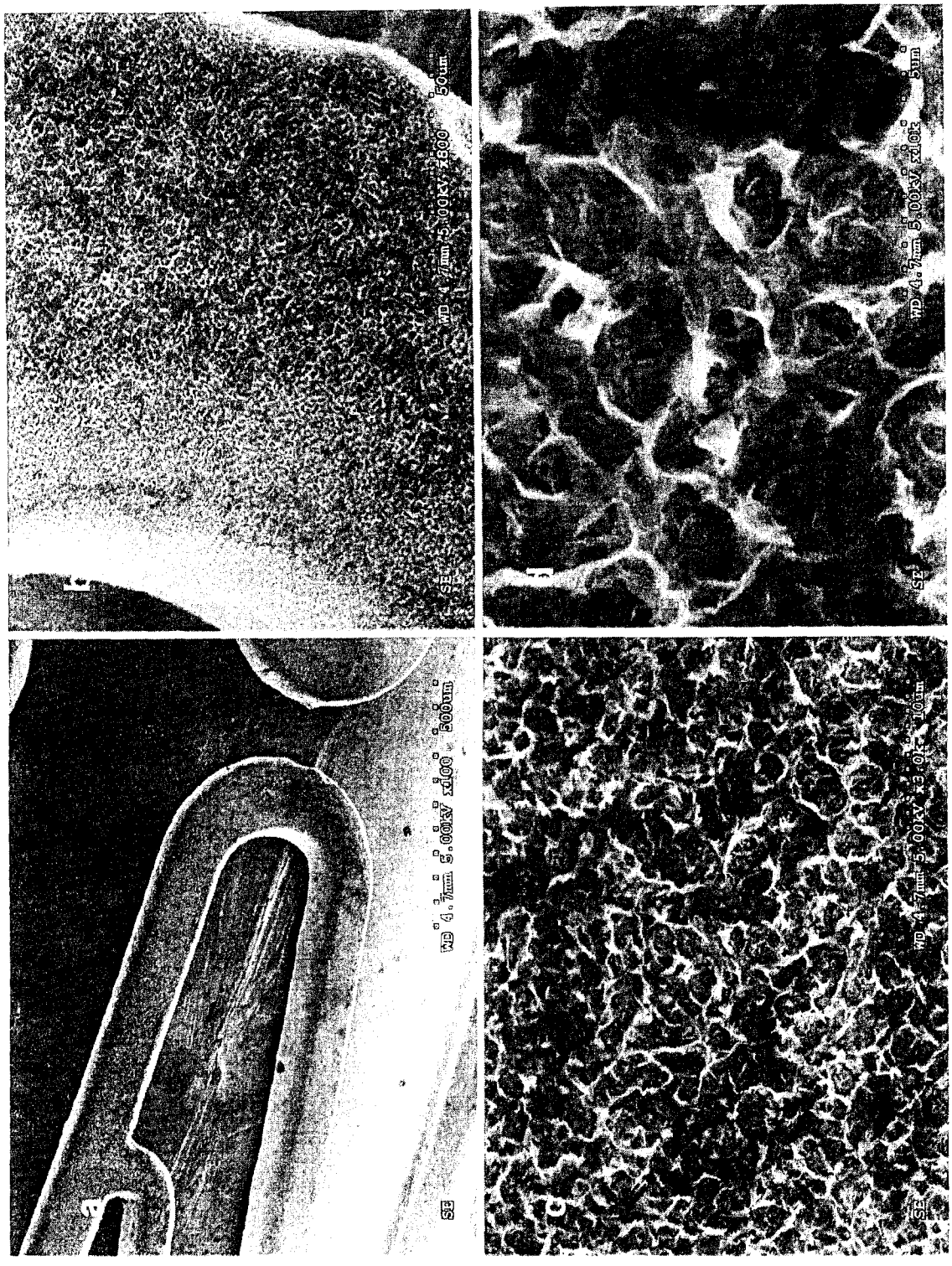
FIGS. 20(a) - (d)



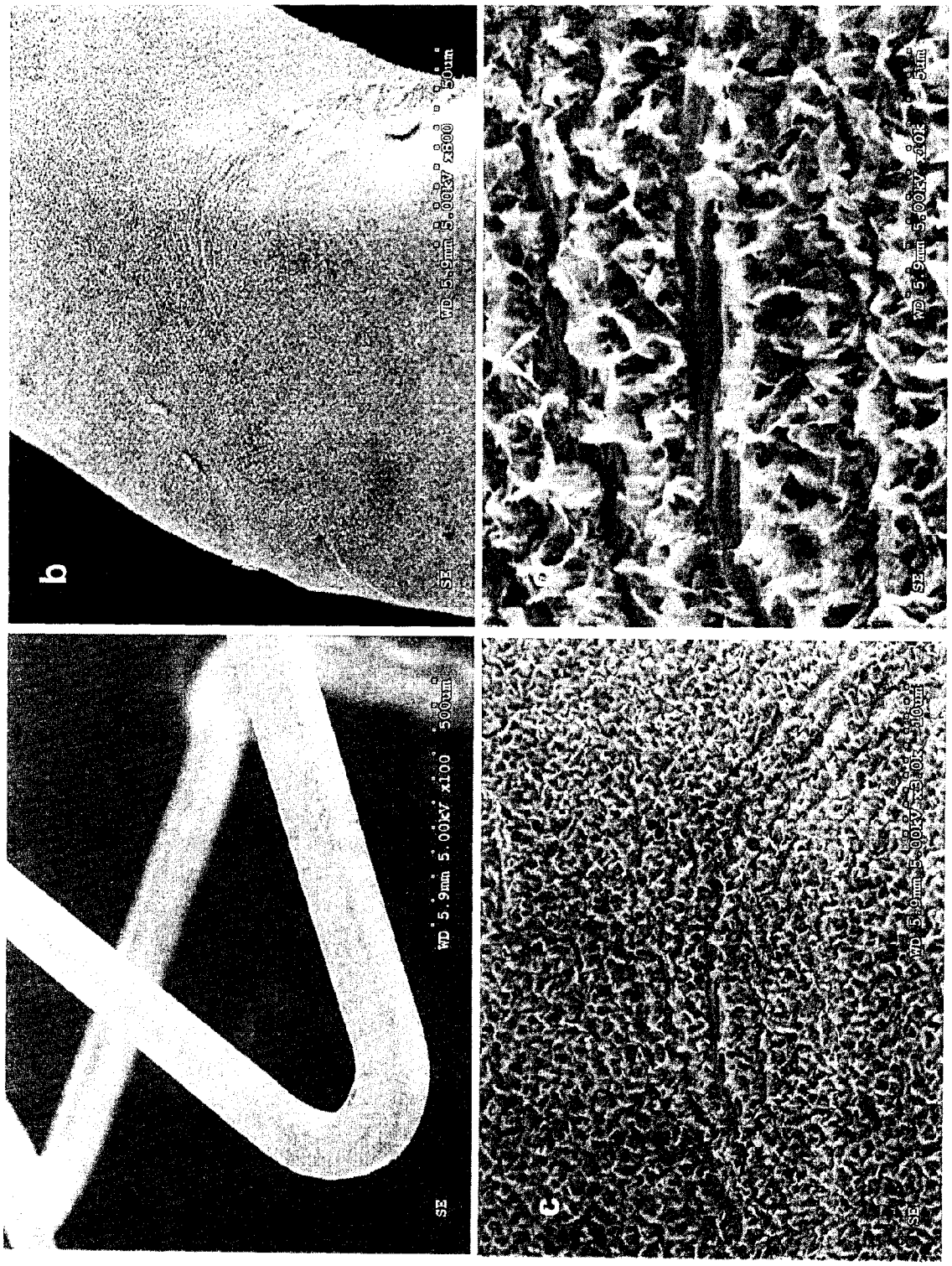
FIGS. 21(a) - (d)


a
WD 5.1mm 5.00kV x100 500um
SE
b
WD 5.1mm 5.00kV x800 50um
SE
c
WD 5.1mm 5.00kV x5.0k 10um
SE
d
WD 5.1mm 5.00kV x10.0k 5um
SE

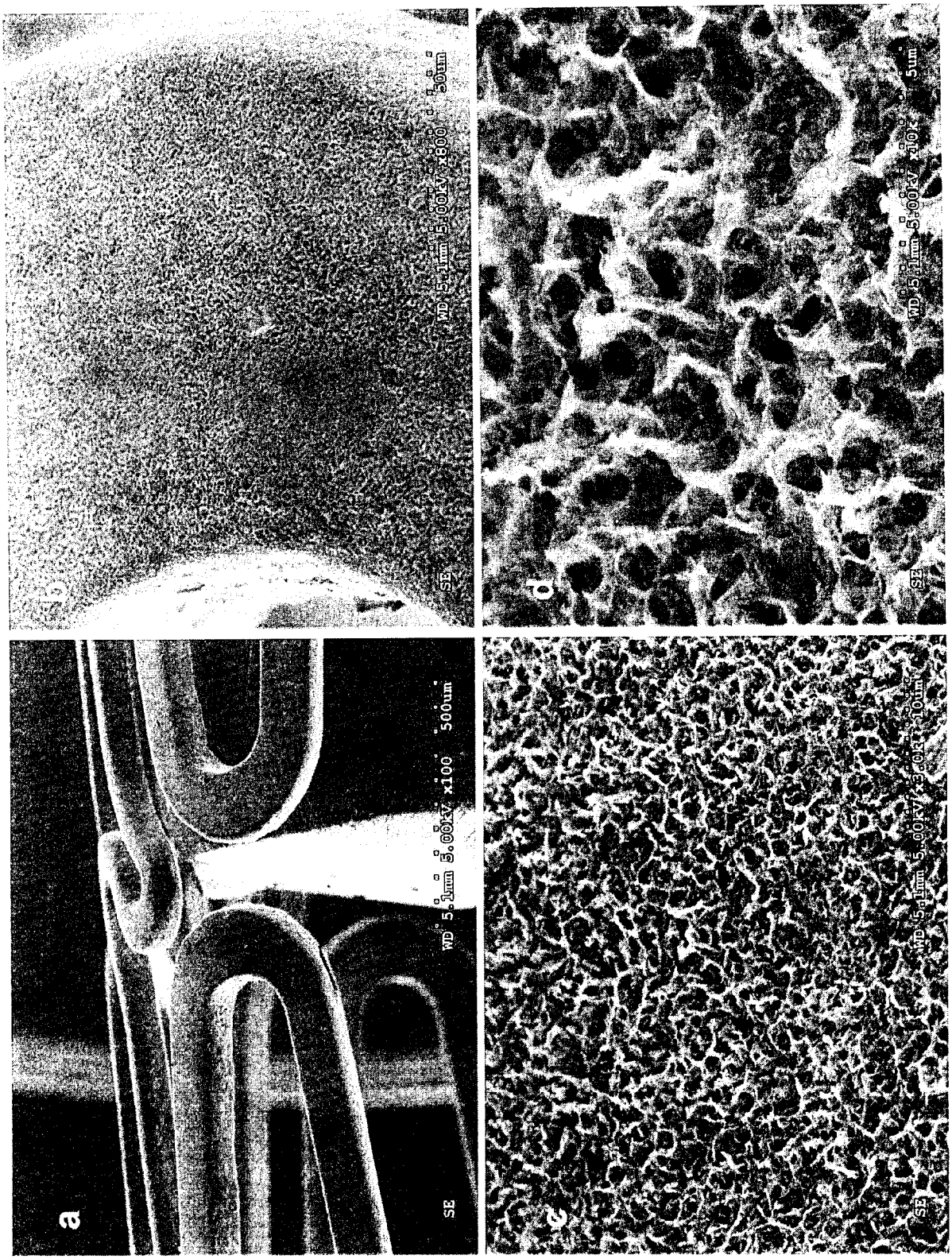
FIGS. 22(a) - (d)



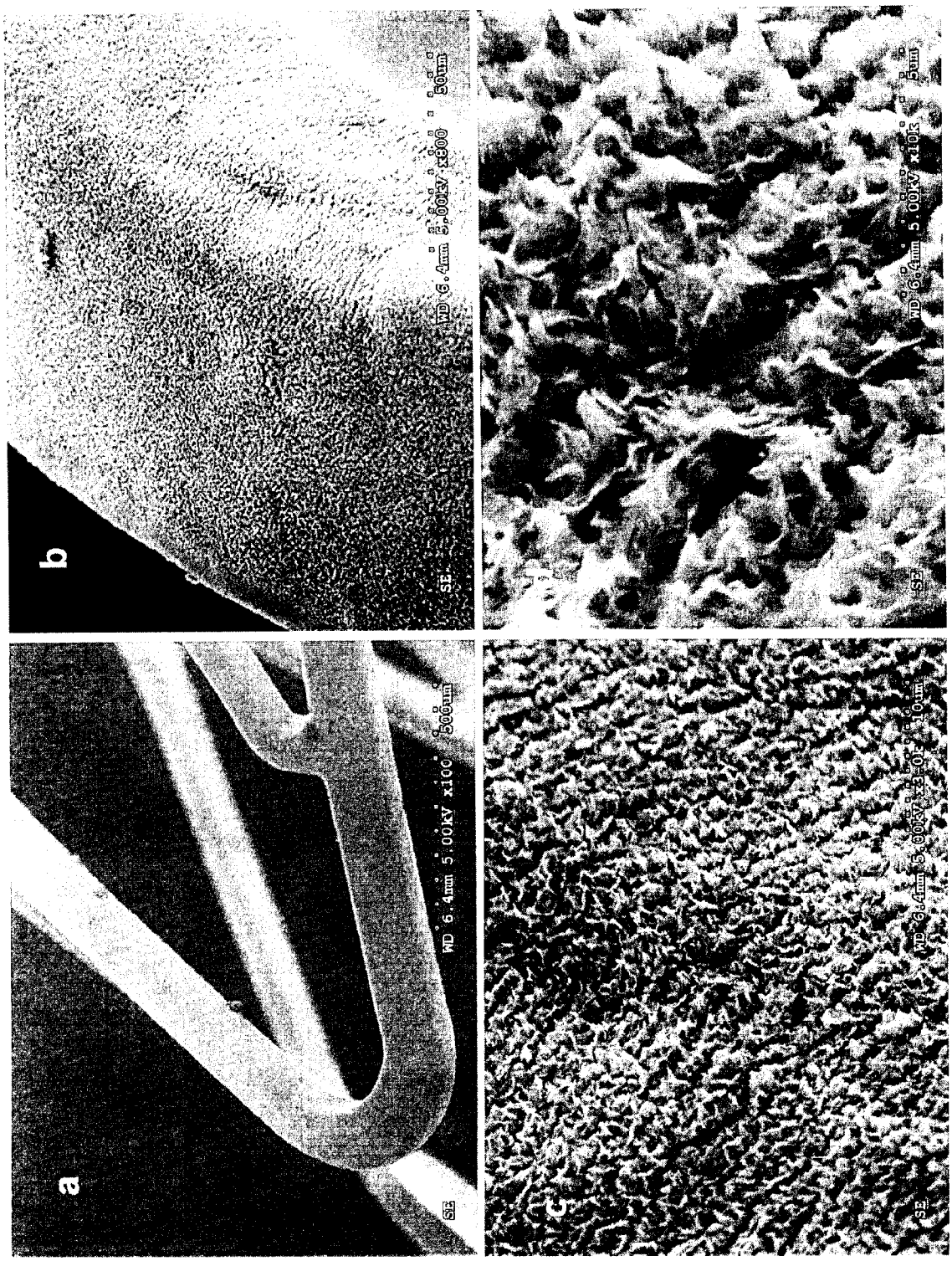
FIGS. 23(a) - (d)


a
WD 5.9mm 5.00kV x100 500um
SE
b
WD 5.9mm 5.00kV x800 50um
SE
c
WD 5.9mm 5.00kV x10k 5um
SE
d
WD 5.9mm 5.00kV x10k 5um
SE

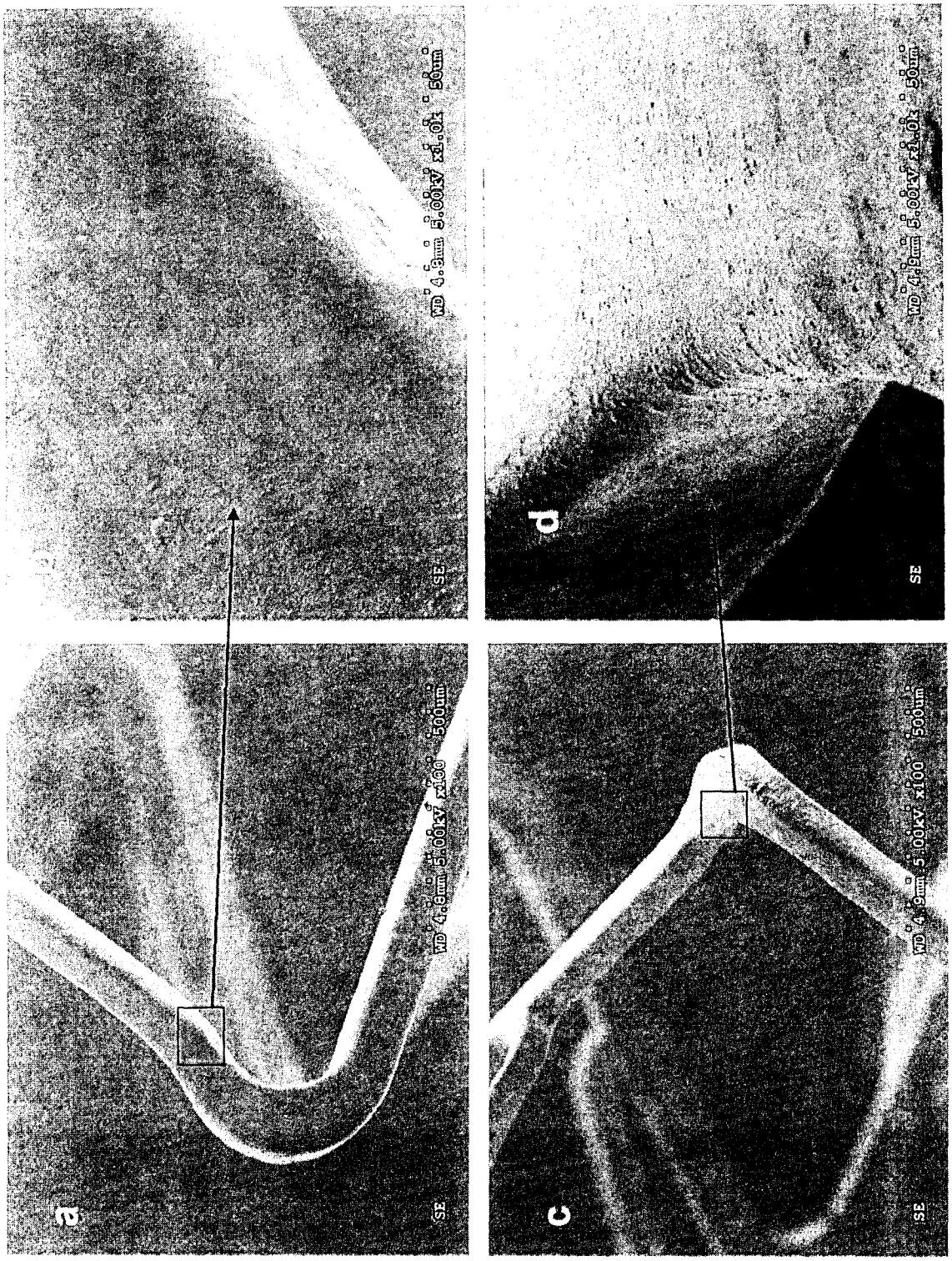
FIGS. 24(a) - (d)


a
SE
WD 5.1mm 5.00kV x100 500um
b
SE
WD 5.1mm 5.00kV x100 50um
c
SE
WD 5.1mm 5.00kV x10k 5um
d
SE
WD 5.1mm 5.00kV x10k 1um

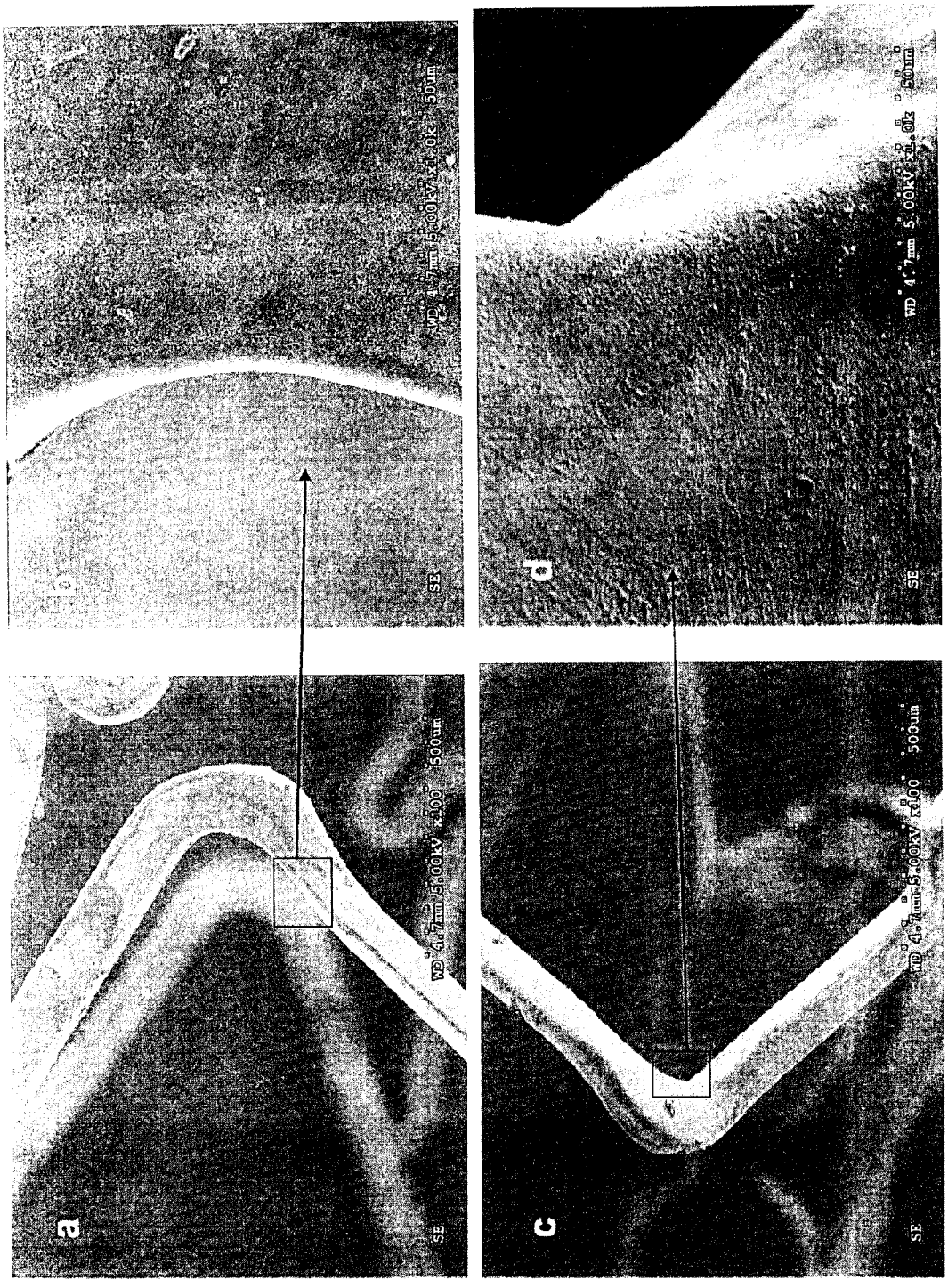
FIGS. 25(a) - (d)


a
WD 6.4mm 5.00kV x100 500um
SE
b
WD 6.4mm 5.00kV x500 50um
SE
WD 6.4mm 5.00kV x10k 5um
SE
WD 6.4mm 5.00kV x10k 1um
SE

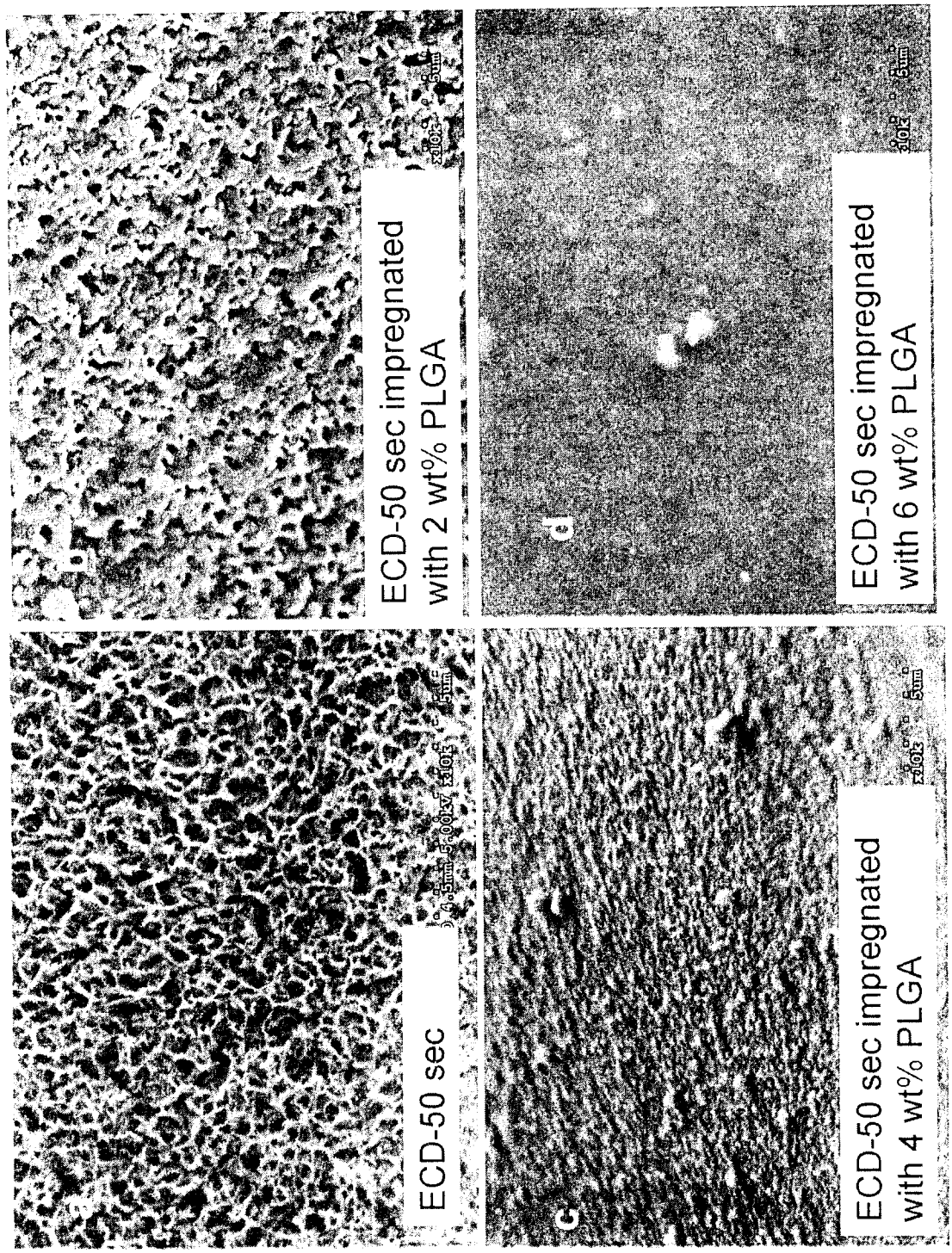
FIGS. 26(a) - (d)


a
WD 4.3mm 5.00kV x1.0k 50um
SE
b
WD 4.8mm 5.00kV x100 500um
SE
c
WD 4.9mm 5.00kV x100 500um
SE
d
WD 4.9mm 5.00kV x1.0k 50um
SE

FIGS. 27(a) - (d)


a
WD 4.7mm 5.00kV x100 500um
SE
b
WD 4.7mm 5.00kV x100 50um
SE
c
WD 4.7mm 5.00kV x100 500um
SE
d
WD 4.7mm 5.00kV x1.0k 20um
SE

FIGS. 28(a) - (d)


ECD-50 sec
ECD-50 sec impregnated with 2 wt% PLGA
ECD-50 sec impregnated with 4 wt% PLGA
ECD-50 sec impregnated with 6 wt% PLGA

FIGS. 29(a) - (d)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/001100

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61L 31/08*** (2006.01) , ***A61L 31/10*** (2006.01) , ***A61L 31/12*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[8]: A61L

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Scopus, Delphion, PubMed, Canadian Patent Database (electrolyte, electrochem* deposition, etch, calcium phosphate, surface, pretreat*, adhesion, medical device, oxid*)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/024201 A2 (TROCZYNSKI ET AL.) 25 March 2004 • abstract • page 7, line 4 to page 9, line 7 • Examples 3 and 9-11	1, 9-16, 20-25, 28, 29 and 49-69
X	US 5 759 376 A (TELLER ET AL.) 02 June 1998 • abstract • column 1, lines 45-50 • column 2, lines 15-38 • Examples 1 and 2	1, 9-16, 23-25 and 49-58
X	US 6 974 532 (LEGEROS ET AL.) 13 December 2005 • abstract	1, 5-7, 11-16, 23-25 and 30-38

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2007 (23-08-2007	11 October 2007 (11-10-2007)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Ryan Jaecques 819- 953-6570

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/001100

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

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

1. [ ] Claim Nos. :
because they relate to subject matter not required to be searched by this Authority, namely :

2. [X] Claim Nos. : 1, 26, 28, 59 and 69
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

See Extra Sheet

3. [ ] Claim Nos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

See Extra Sheet

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

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

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

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

Remark on Protest

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

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

[ ] No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	• column 2, lines 20-41 and 55-56 • column 4, lines 1-16	
X	CA 2 571 853 A1 (RAJA ET AL.) 12 January 2006 • paragraphs [0028], [0031] and the examples	1-3, 11-17, 23-25 and 39-48
X	Calcium Phosphate Crystal Growth Under Controlled Atmosphere in Electrochemical Deposition", *Journal of Crystal Growth*, vol. 284, (**2005**), pp. 506-516 (LU ET AL.) • pages 506-508	1, 11-16 and 23-25
X	CA 2 574 115 A1 (WANG ET AL.) 26 January 2006 • abstract • paragraphs [0041] and [0058] • Example 2	1, 4-8, 11-38 and 59-69
X	WO 92/13984 A1 (SHIRKHANZADEH) 20 August 1992 • abstract • page 4 • page 6 • Example 1 --	1, 4-6, 11-19, 23, 24, 26, 27, 30-38 and 59-69

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2004024201	25-03-2004	AU2003266882 A1	30-04-2004
		BR0314265 A	26-07-2005
		CA2498743 A1	25-03-2004
		EP1551470 A2	13-07-2005
		JP2006501887T T	19-01-2006
		US2006134160 A1	22-06-2006
US5759376	02-06-1998	AT164085T T	15-04-1998
		DE4431862 A1	14-03-1996
		EP0774982 A1	28-05-1997
		WO9607438 A1	14-03-1996
US6974532	13-12-2005	WO2004098436 A2	18-11-2004
CA2571853	12-01-2006	EP1776227 A2	25-04-2007
		WO2006004686 A2	12-01-2006
CA2574115	26-01-2006	WO2006007730 A1	26-01-2006
WO9213984	20-08-1992	AU1181092 A	07-09-1992
		CA2096850 A1	05-08-1992
		EP0570417 A1	24-11-1993
		JP6505052T T	09-06-1994
		US5205921 A	27-04-1993

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Continuation of Box II:

Each claims 1, 26 and 28 refers to 'calcium and phosphate species', but nowhere in the description is it defined what is meant by 'species'. Since no proper definition has been provided, it can only be concluded based on claims 15, 27, 29 and the examples, that what was intended was for the term to refer to calcium phosphate precursors; i.e. species which provide the calcium and phosphate components to the electrolyte such that calcium phosphate is deposited during the electrochemical process, but excluding calcium phosphate itself. This meaning of 'species' was what was used when the prior art was considered.

Claims 59 and 69 are so broad that the entire scope of the claims could not be meaningfully searched. These claims refer to a continuous ceramic phase and a continuous polymer phase being on a medical device substrate. The claims encompass any ceramic material (the definition of 'ceramic' may encompass clay and other materials not provided for by the description), and 'phase' can mean that the two are discrete layers, separated by others, or that one or more of them is continuous, but localised (e.g. in a striped pattern). The claims also include devices where no pretreatment was done to the substrate, which was a key aspect of the invention, and no electrochemical deposition need have taken place. Because of the breadth and lack of clarity in the scope of these claims, for the purposes of the search, they have been restricted to that which was taught. In other words, the substrate must have been pretreated to increase the adhesion of an electrochemically deposited calcium phosphate coating, and wherein the polymer phase was either formed by being present in the electrolyte, or via impregnation. Although an ISA 206 could have been drafted for the alternative subject-matter, the teaching of the description is such that it is clear that no other ceramics were intended, there must have been a pretreatment step prior to electrochemical deposition of calcium phosphate, and the polymer must be applied in one of the two stated ways. No other invention was apparent from the description that could account for the rest of the matter of these claims and that would require a separate search fee.

Continuation of Box III:

The claim set-contains 8 independent claims, three processes, four devices and one use.

The three process claims are related to pretreating the surface of the substrate to enhance calcium phosphate adhesion, followed by electrochemical deposition of calcium phosphate from an electrolyte comprising calcium and phosphate species. The processes are summarised below:

Process claim 1 contains only these features;

Process claim 26 involves the inclusion of a polymer into the electrolyte that is concomitantly deposited with the calcium phosphate during electrochemical deposition; and

Process claim 28 introduces a polymer in addition to the calcium phosphate coating, but it is impregnated into said coating after the electrochemical deposition step.

Among these process claims, the common technical features are the pretreatment of the substrate, and electrochemical deposition of calcium phosphate from an electrolyte comprising calcium and phosphate 'species'. None of these technical features define a contribution over the art, since each of **D1-D5** specifically teach such processes.

The claims are thus considered to encompass three alternative processes for coating calcium phosphate onto implantable medical devices as defined in these claims.

Three of the device claims (claims 30, 39 and 49) relate to products that would be made by the process according to claim 1. They can thus be considered to belong to the same alleged inventive concept as that claim; however, the common technical features shared between these claims also do not define a contribution over the art, since the pretreatment of substrates to enhance adhesion of an electrochemically deposited calcium phosphate layer by a sol-gel process is known from **D1** and **D2,** the micro-etching thereof is an analogous means to the acid etching of **D3** and **D5**, and **D4** teaches the use of an anodised layer, giving rise to a further lack of unity amongst these claims. Any one of the devices defined in claims 30, 39 and 49 could be considered unified with process claim 1.

(Continued on Extra Sheet)

Claim 69 is related to the use of a device that falls within the scope of claim 59. As such, this claim shares an inventive concept with this claim, but not with any of the others.

Claim 59 is very general and is clearly encompassed by the prior art, and so it too does not have any special technical feature in common with any of the other device claims.

Because the scope of these claims was restricted based on what was actually disclosed (see Box II), claims 59 and 69 fall within the scope of products formed by either the process of claim 26 or 28.

Therefore, to summarise the above, the independent claims can be grouped according to alleged invention as follows:

Group A- process claim 1;

Group A_1 - device claim 30
Group A_2 - device claim 39
Group A_3 - device claim 49

Group B - process claim 26, device claim 59, and use claim 69; and

Group C - process claim 28, device claim 59, and use claim 69.

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