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(54) Title: METHODS FOR MAKING IMPLANTABLE MEDICAL DEVICES HAVING MICROSTRUCTURES

(57) Abstract: The present invention generally provides methods for fabricating implantable medical devices having microstructures. In one aspect, a method of fabricating an implantable medical device having microstructures for enhancing therapeutic delivery first includes providing a device precursor having an outer surface coated with a photoresist material. The method next includes defining an optical pattern on the photoresist material and electrochemically etching the outer surface to form the microstructures. Then the photoresist material is removed and the device precursor is machined to form the implantable medical device having microstructures. In some embodiments the device precursor comprises a tubular stent precursor and the device comprises a stent.

METHODS FOR MAKING IMPLANTABLE MEDICAL DEVICES HAVING MICROSTRUCTURES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application Serial No. 60/360,298, entitled "A Method of Microstructure Fabrication on Stents for Therapeutic Delivery and the Product Produced Therefrom," filed on February 27, 2002, the entire disclosure of which is hereby incorporated by reference. The present application is related to U.S. Patent No. 6,197,013, entitled "Method and Apparatus for Drug and Gene Delivery," issued to Reed et al. on March 6, 2001, the entire disclosure of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] The present invention relates generally to medical devices and methods. More specifically, the invention relates to methods for fabricating implantable medical device having microstructures and the devices themselves.

[0003] Heart disease is the leading cause of death in the United States. One mechanism of this disease is progressive narrowing of coronary arteries by atherosclerotic plaque, which can lead to acute myocardial infarction and disabling angina. One commonly used technique to change the natural history of coronary atherosclerosis is transcatheter therapy, which includes percutaneous transluminal coronary angioplasty, (or PTCA--commonly referred to as balloon angioplasty), atherectomy, and coronary stenting. During these procedures, an expandable balloon, cutting device, or metal cage mounted on a balloon, respectively, is threaded over a pre-placed wire to the site of coronary blockage. In balloon angioplasty, the balloon is inflated, compressing the atherosclerotic plaque; in atherectomy, the plaque is cut away; and in stenting, the device is expanded and deployed against the plaque. In each case, compression of the plaque and expansion of the coronary artery, or removal of the atherosclerotic plaque, restores lumen patency.

[0004] Despite the overall initial success of these procedures, approximately 20% to 50% of all patients undergoing these therapeutic procedures to clear blocked coronary arteries will suffer restenosis (re-blockage) within six months of the initial procedure. One widely accepted paradigm is that restenosis is a manifestation of the general wound healing response. The injury induced by coronary intervention causes platelet aggregation, inflammatory cell

infiltration and release of growth factors, followed by smooth muscle cell proliferation and matrix formation. In this paradigm, intimal hyperplasia secondary to vascular injury is believed to be the etiology of restenosis. Numerous pharmacological agents and genes have been shown to inhibit restenosis in animal models and some success has been shown in human patients receiving drug eluting stents. Oftentimes, however, restenosis still occurs, perhaps due to the fact that suboptimal doses of agents are often used in order to prevent side effects which will occur from systemic administration of the higher doses required as shown by animal studies.

[0005] The concept of localized intravascular delivery of therapeutics has become an attractive solution to overcome this limitation. One way to enhance local delivery of therapeutics is to implant devices having microstructures on their external surfaces for enhancing therapeutic delivery. Stents and other implantable devices having microstructures on their external surfaces for facilitating delivery of drugs, genes or other therapeutic agents are known. Such devices are described, for example, in U.S. Patent No. 6,197,031, previously incorporated by reference. Direct injection of therapeutic agents through atherosclerotic plaque into a vessel wall via microstructures frequently allows a wider variety of pharmaceuticals to be used when compared to currently available drug eluting stents.

[0006] One method which has been attempted for fabricating stents with microstructures is to fabricate the microstructures from silicon. Typically, however, this has only been attempted on flat surfaces, and at least two issues arise in the fabrication of coronary or other stents with such techniques. First, coronary stents are fabricated from metals, not silicon, and the metals are plastically deformed during deployment. Stainless steel is the most commonly used material for stents, and is a material on which very little microfabrication work has been reported. Second, silicon wafers are flat, while stents are tubular. As a consequence of these two factors, conventional microfabrication techniques used for silicon microfabrication typically cannot be used for fabricating implantable stents with microstructures.

[0007] Thus, it would be advantageous to have methods for fabricating stent devices with microstructures for enhancing therapeutic delivery. Such methods would allow microstructures to be fabricated on an external surface of a cylindrical stent or similar device. Ideally, such fabrication methods would be highly reproducible and be capable of producing microstructures fine enough to penetrate atherosclerotic plaque. The methods would allow for production of stent devices that are typically too large for conventional microfabrication techniques and too small for traditional precision machining techniques. At least some of these objectives will be met by the present invention.

BRIEF SUMMARY OF THE INVENTION

[0008] The present invention generally provides methods for fabricating implantable medical devices having microstructures. In one aspect, a method of fabricating an implantable medical device having microstructures for enhancing therapeutic delivery first includes providing a device precursor having an outer surface coated with a photoresist material. The method next includes defining an optical pattern on the photoresist material and electrochemically etching the outer surface to form the microstructures. Then the photoresist material is removed and the device precursor is machined to form the implantable medical device having microstructures. In some embodiments the device precursor comprises a tubular stent precursor and the device comprises a stent. For example, the stent precursor may be fabricated from at least one of stainless steel, titanium, nitinol and tantalum.

[0009] In various embodiments, providing the photoresist coating on the device precursor may include dipping the precursor in the photoresist material, brushing photoresist material on the precursor, spraying the photoresist material on the precursor or electrodeposition of the photoresist material on the precursor. Defining the optical pattern may include one or more steps. In one embodiment, defining the pattern includes positioning a mask over the coated outer surface of the device precursor, exposing the mask and the device precursor to ultraviolet light, and removing the mask from the device precursor. Such a method may additionally include developing the photoresist material. In such methods, the device precursor may often comprise a stent precursor, and the mask may comprise a pattern of equally-sized squares, each square corresponding with a location of a microstructure on the stent. In such a case, the photoresist material may comprise a positive photoresist material. Typically, each of the squares is connected to an adjacent square by at least one strut. In some embodiments, the length of one of the squares is approximately twice the height of one of the microstructures. In another embodiment, the mask comprises a tubular sheath having a pattern of square apertures. In such an embodiment, the photoresist material may comprise a negative photoresist material. Again, the length of one of the squares may be approximately twice the height of one of the microstructures.

[0010] Electrochemical etching may be achieved by any suitable method. In one embodiment, for example, etching includes immersing the device precursor in a bath comprising an etching solution and a cathode material and applying a pulsed wave form across the device precursor. The etching solution, for example, may comprise chloride, glyceride and de-ionized water; an oxalic acid solution; a phosphoric acid solution; or the like. The cathode material may comprise a platinum mesh or any other suitable material.

Pulses of the pulsed wave form may have various frequencies, amplitudes and the like, but in one embodiment have a frequency of about 10 Hz, amplitude of about 20 V and duty cycles of about 10%. In a next step, removing the photoresist may involve exposing the photoresist to a solvent. Finally, machining the device precursor may involve laser cutting the precursor.

[0011] In another aspect, a stent device having microstructures fabricated by photolithography and electrochemical etching comprises a tubular stent having an outer surface and a plurality of microstructures disposed along the outer surface in a pattern formed by a photolithographic technique. For example, the microstructures may comprise at least one of microprobes, microneedles and micropores.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Fig. 1 is a perspective view of a stent device fabricated using methods of an embodiment of the present invention.

[0013] Figs. 2A-2F are side views of a stent device at various, chronological stages of fabrication, showing a method for fabricating a stent device according to an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention provides methods of fabricating an implantable medical device having microstructures on at least one surface for enhancing delivery of a drug, gene or other therapeutic agent. The medical device may comprise any suitable device, but in some embodiments will comprises a vascular stent. A technique similar to methods of the invention is described in M. Datta, "Fabrication of an array of precision nozzles by through-mask electrochemical micromachining," J. Electrochem. So. 142 (11) Nov. 1995, pp. 3801-3805, the contents of which are hereby incorporated by reference. Heretofore, however, techniques such as Datta's have been applied generally to structures having flat surfaces. Methods of the present invention, on the other hand, provide for fabricating microstructures on tubular or cylindrical surfaces, such as the outer surface of a coronary stent. The invention also provides for stent devices fabricated by the inventive methods.

[0015] Referring now to Figure 1, a stent 1 according to one embodiment includes a plurality of microstructures 5 disposed along the outer surface of stent 1. In some embodiments, stent 1 may also include one or more interstices 2 and/or other features on the inner and/or outer surface of stent 1. Furthermore, stent 1 may comprise any conventional stent or stent-graft device, which are well known in the art. Stent 1 may have any suitable

size, shape, configuration, features and the like and may be fabricated from any suitable material or combination of materials to allow it to be used for any desired purpose. The "outer surface" generally refers to the surface facing away from the lumen of stent 1 and toward a vascular wall when implanted. The "inner surface" generally refers to the surface facing the lumen of stent 1.

[0016] Microstructures 5 may have any size, shape, configuration or the like and any number of microstructures 5 may be disposed on stent 1 to achieve a desired result. For example, microstructures 5 in various embodiments may include but are not limited to microneedles, micropores, microprobes, microbarbs and/or the like. In various embodiments, microstructures 5 may be pyramidal, cylindrical, conical, hollow, arrow-shaped, solid, porous and/or the like. Furthermore, although microstructures 5 are typically disposed on an outer surface of stent, to contact a vessel wall and/or plaque, other microstructures may be placed on an inner surface or other surface of stent 1 in other embodiments. Implantable medical devices other than stents, for example, may utilize microstructures on multiple surfaces. Any configuration or combination of stent 1 and microstructures 5 is contemplated.

[0017] Any spacing between the microstructures 5 may also be used, preferably between about 5 microns and about 10,000 microns. Microstructures 5 have heights which may vary but are typically sufficient to penetrate the lumen wall to a desired depth, such as a depth sufficient for traversal of the thickness of the compressed plaque. Thus, microstructures 5 may have heights which vary from less than 25 μm to over 5000 μm.

[0018] In some embodiments, it is contemplated that one or more microstructures 5 of a stent 1 may be deployable from a non-deployable to a deployable position. Such stents with deployable microstructures are described more fully in U.S. Provisional Patent Application Serial Number 60/421,404, entitled "Expandable Body Having Deployable Microstructures and Related Methods," filed on November 18, 2002, by inventors of the present invention and hereby incorporated fully by reference.

[0019] In some embodiments, microstructures 5 may be used to anchor stent 1 within a lumen and/or to deliver drugs, genes or other therapeutic agents or material to or through the lumen wall. The material may be coupled with microstructures 5 by any suitable means, such as coating the material on one or more surface of microstructures 5. When the material comprises DNA, each microstructure may be coated with an adhesive material to which DNA adheres, such as gold. Preferably, when the material comprises DNA, the material is a gene encoding for nitric oxide synthase or vascular endothelial growth factor. Nitric oxide

synthase inhibits smooth muscle cells from growing and inhibits platelet and white blood cells adherence to denuded surfaces following coronary intervention. Vascular endothelial growth factor stimulates reendothelialization of an injured vessel. To increase the amount of drugs or genes held by the microstructures, the structural material could be made porous. A straightforward way of accomplishing this goal is to anodize the metal forming the apparatus or to coat the metal with a material which is then anodized. Anodization produces a high density of small, vertically oriented pores, of which the size and configuration can be controlled by varying the anodization current, temperature and solution concentration.

[0020] Further, the material may be coated with a biocompatible material which provides a protective coating to prevent the drug or gene from being washed away, and allows for the release of the drug and/or gene over a period of time. Such coatings include biodegradable materials, polymers, hydrogels, and porous ceramics. When the material is a drug which does not include DNA, the material is preferably Sirolimus or Paclitaxel. Sirolimus is a macrocyclic lactone with potent immunosuppressive effects. Sirolimus binds to an intracellular receptor protein and elevated p27 levels, which leads to the inhibition of cyclin/cyclin-dependent kinase complexes and, ultimately, induces cell-cycle arrest in the late G1 phase. It inhibits the proliferation of both rat and human smooth muscle cells in vitro, and reduces intimal thickening in models of vascular injury. Paclitaxel is a taxoid which is used in chemotherapy. Paclitaxel binds to microtubules and inhibits their deploymerization into tubulin. This effectively stops the cells ability to breakdown the mitotic spindle during mitosis, preventing cell division and proliferation. Paclitaxel has also been shown to reduce intimal thickening in models of vascular injury.

[0021] Alternatively, the material may be held in one or more internal lumens within the microstructures. Material within the internal lumen(s) of stent 1 may then be expelled into the surrounding body lumen or tissue. In some embodiments, the material may be actively pumped by a delivery microsystem or allowed to diffuse out of the lumen. Various types of delivery microsystems may be used, including electro-osmotic pumps, shape-memory transducers, expansion of polymer gels (such as water-absorbing polyacrylamid gel), osmotic pumps, piezo-electric actuators, electrostatic or electromagnetic pumps, or electro-dissolution of membranes (Santini, J. et al. "A controlled-release microchip", in Nature, Vol 397, January 28, 1999, incorporated herein by reference for all purposes) to release the material followed by diffusion through lumen, to name a few. For further description of various embodiments of such delivery microsystems, reference may again be made to U.S.

Provisional Patent Application Serial Number 60/421,404, previously incorporated by reference.

[0022] Stents 1 of the present invention may be utilized for any sort of treatment which involves delivery of a therapeutic agent and/or anchoring of a device. The devices could be introduced into various body lumens, such as the vascular system, lungs, gastro-intestinal tract, urethra or ureter. The function of the microstructures includes but is not limited to facilitating drug and gene delivery, securing the device in place and providing a mechanical seal to the lumen wall.

[0023] Positioning of stents 1 of the present invention is typically performed via standard catheterization techniques. These methods are well known to cardiac (and other) physicians and are described in detail in many standard references. In brief, percutaneous access of the femoral or brachial arteries is obtained with standard needles, guide wires, sheaths, and catheters. After engagement of the coronary arteries with a hollow guiding catheter, a wire is passed across the coronary stenosis where the apparatus is to be deployed. One or more stents 1 are then passed over this wire, using standard coronary interventional techniques, to the site of atherosclerotic coronary plaque where drug and/or gene therapy is to be delivered. This example is not intended to limit the scope of the invention, and many positioning methods may be used for positioning stents of the invention in any suitable location in a body.

[0024] With reference now to Figures 2A-2F, a method for fabricating stent 1 with microstructures 5 is shown in step-wise fashion. In Figure 2A, a stent precursor 10 with a photoresist coating 12 is provided. Stent precursor 10 may be fabricated with any suitable material(s), such as but not limited to titanium, nitinol, tantalum, cobalt, chromium alloys, and the like. In one embodiment, for example, precursor 10 comprises stainless steel, such as medical grade 316L stainless steel. Photoresist coating 12 may comprise any suitable photoresist material(s) and may be applied via dip coating, brush coating, spray coating, electrodeposition or any other suitable means. Either positive or negative photoresist material may be used. In Figure 2, a positive resist method is shown.

[0025] In Figure 2B, a mask 18 is applied over the outer surface of stent precursor 10. In various embodiments, mask 18 may have any suitable configuration for defining an optical pattern on stent precursor 10. In one embodiment, as in Figure 2B, mask 18 includes multiple squares 14, coupled to adjacent squares 14 by multiple struts 16. Squares 14 generally correspond to locations where microstructures 5 will be formed on the outer surface of stent 1. Dimensions of squares 14 also determine the heights of microstructures 5. For

example, a microstructure 5 in one embodiment will have a height equal to approximately half of a length of one square. In another embodiment, when a negative photoresist is used, mask 18 may comprise a tube with a pattern of square apertures to create the same pattern on stent precursor 10 as in Figure 2B. Once mask 18 is positioned over stent precursor 10, both are exposed to high-intensity ultraviolet light to expose photoresist coating 12. After exposure to ultraviolet light, mask 18 is removed from stent precursor 10. Next, as shown in Figure 2C, photoresist 12 is developed to define areas for electrochemical etching to form microprobes 5. Any conventional means for developing photoresist 12 may be used.

[0026] After the developing step, as shown in Figure 2D, stent precursor 10 is electrochemically etched to form microstructures 5. A method for electrochemical etching is described in M. Datta, "Fabrication of an array of precision nozzles by through-mask electrochemical micromachining," which was previously incorporated by reference. In one embodiment, stent precursor 10 with its photoresist pattern is placed in an electrochemical etch bath comprising sodium chloride, glycerol and de-ionized water. Other etchants, such as an oxalic acid solution, a phosphoric acid solution, or the like may alternatively be used in other embodiments. The solution may be stirred throughout the etching process in some embodiments. Generally, the patterned stent precursor 10 acts as an anode, while a platinum mesh acts as a cathode. A pulsed wave may be used to etch precursor 10. For example, a wave form having a frequency of 10 Hz, an amplitude of 20 V and duty cycles of 10% may be used in one embodiment. Such a process will isotropically etch the unprotected areas of stent precursor 10. Microprobes 5 are formed at the intersection of the etch fronts, propagating from the edges of the masked areas. Calibration experiments may be used to determine the requisite etch times necessary for optimal microstructure formation.

[0027] Referring now to Figure 2E, after microstructures 5 are formed, photoresist 12 is removed by exposing photoresist-coated precursor 10 to a solvent, such as by rinsing photoresist 12 with acetone. This process leaves precursor 10 and microstructures. Once photoresist 12 is removed, precursor 10 is laser cut to form stent 1 with microstructures, as shown in Figure 2F.

[0028] While the invention has been fully described above in terms of exemplary embodiments, variations to the invention may be made without departing from the scope of the present invention. For example, steps of a method for fabricating implantable medical devices may be added, subtracted or substituted and/or the order of steps may be altered, without significantly effecting the result. Therefore, the description above is provided for

exemplary purposes only and should not be interpreted to limit the scope of the claims as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A method of fabricating an implantable medical device having microstructures for enhancing therapeutic delivery, the method comprising:

providing a device precursor having an outer surface coated with a photoresist material;

defining an optical pattern on the photoresist material;

electrochemically etching the outer surface to form the microstructures;

removing the photoresist material; and

machining the device precursor to form the implantable medical device having microstructures.

2. A method as in claim 1, wherein providing the device precursor comprises providing a tubular stent precursor.

3. A method as in claim 2, wherein providing the precursor comprises providing a precursor fabricated from at least one of stainless steel, titanium, nitinol, cobalt, chromium alloy, and tantalum.

4. A method as in claim 1, wherein providing the device precursor comprises at least one of dipping the precursor in the photoresist material, brushing photoresist material on the precursor, spraying the photoresist material on the precursor or electrodeposition of the photoresist material on the precursor.

5. A method as in claim 1, wherein defining the optical pattern comprises:

positioning a mask over the coated outer surface of the device precursor;

exposing the mask and the device precursor to ultraviolet light; and

removing the mask from the device precursor.

6. A method as in claim 5, further comprising developing the photoresist material.

7. A method as in claim 5, wherein the device precursor comprises a stent precursor, and wherein the mask comprises a pattern of equally-sized geometric shapes, each geometric shape corresponding with a location of a microstructure on the stent.

8. A method as in claim 7, wherein the geometric shapes comprise squares.

9. A method as in claim 7, wherein the geometric shapes comprise circles.

10. A method as in claim 9, wherein a radius of each of the circles is approximately equal to a height of each microstructure on the stent.

11. A method as in claim 7, wherein the photoresist material comprises a positive photoresist material.

12. A method as in claim 7, wherein each of the geometric shapes is connected to an adjacent geometric shape by at least one strut.

13. A method as in claim 7, wherein the length of each of the geometric shapes is approximately twice the height of each of the microstructures.

14. A method as in claim 5, wherein the mask comprises a tubular sheath having a pattern of apertures corresponding to the geometric shapes.

15. A method as in claim 14, wherein the photoresist material comprises a negative photoresist material.

16. A method as in claim 14, wherein the length of each of the geometric shapes is approximately twice the height of each of the microstructures.

17. A method as in claim 1, wherein defining the optical pattern comprises:

projecting an image onto at least a first portion of an outer surface of the device precursor; and

exposing at least the first portion of the outer surface to ultraviolet light.

18. A method as in claim 17, further comprising:

rotating the device precursor;

projecting an image onto a second portion of the outer surface; and

exposing at least the second portion of the outer surface to ultraviolet light.

19. A method as in claim 1, wherein defining the optical pattern comprises applying a laser beam on an outer surface of the device precursor.

20. A method as in claim 1, wherein electrochemically etching comprises:

immersing the device precursor in a bath comprising an etching solution and a cathode material; and

applying a pulsed wave form across the device precursor.

21. A method as in claim 20, wherein the etching solution is selected from the group consisting of a solution of sodium chloride, glyceride and de-ionized water; an oxalic acid solution; and a phosphoric acid solution.

22. A method as in claim 20, wherein the cathode material comprises a platinum mesh.

23. A method as in claim 22, wherein pulses of the pulsed wave form have a frequency of about 10 Hz, amplitude of about 20 V and duty cycles of about 10%.

24. A method as in claim 1, wherein removing the photoresist comprises exposing the photoresist to a solvent.

25. A method as in claim 1, wherein machining the device precursor comprises laser cutting the precursor.

26. A method as in claim 1, further comprising releasably coupling at least one material with one or more of the microstructures, wherein the at least one material is released to provide a therapy in a lumen in which the implantable medical device is implanted.

27. A method as in claim 26, wherein the at least one material comprises at least one of a gene and a drug.

28. A method as in claim 26, wherein releasably coupling the at least one material comprises coating the material on at least one surface of one or more of the microstructures.

29. A method as in claim 26, wherein releasably coupling the at least one material comprises disposing the material in a microstructure lumen within of one or more of the microstructures.

30. A stent device having microstructures fabricated by photolithography and electrochemical etching, the stent device comprising:

a tubular stent having an outer surface; and

a plurality of microstructures disposed along the outer surface in a pattern formed by a photolithographic technique.

31. A stent device as in claim 30, wherein the microstructures comprise at least one of microprobes, microneedles, micropores, and microbarbs.

32. A stent device as in claim 30, further comprising at least one material coupled with one or more of the microstructures, wherein the at least one material is released to provide a therapy in a lumen in which the implantable medical device is implanted.

33. A stent device as in claim 32, wherein the at least one material comprises at least one of a drug and a gene.

34. A stent device as in claim 30, wherein the stent device comprises at least one of a shape-memory alloy, stainless steel, titanium, tantalum, vanadium, cobalt chromium alloy and a polymer.

35. A stent as in claim 30, wherein the microstructures extend radially a distance of between about 25 microns and about 5000 microns from the outer surface of the tubular stent.

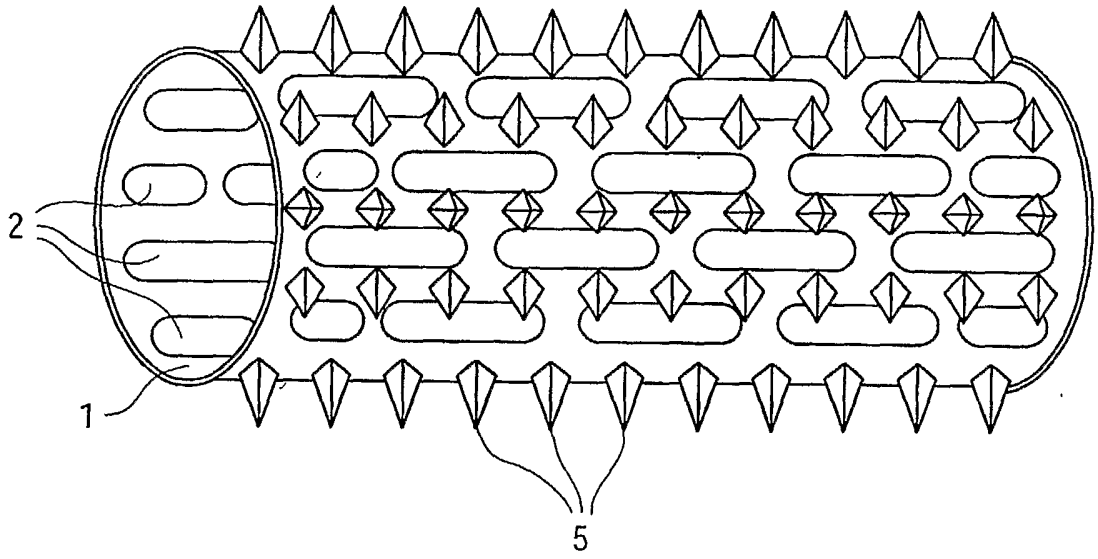

FIG. 1

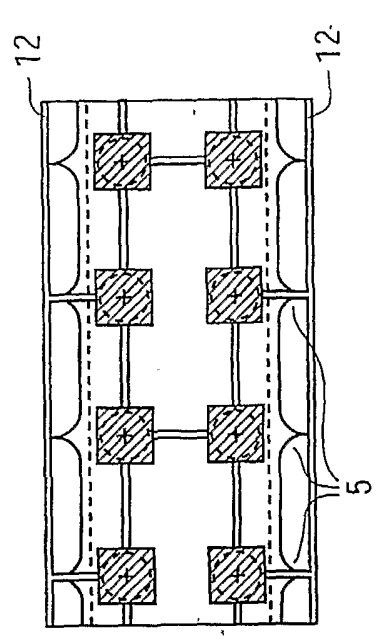

FIG. 2D

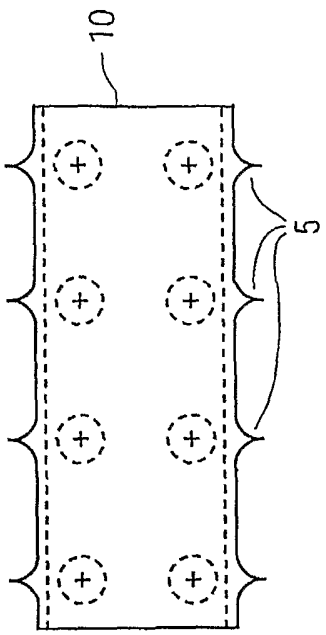

FIG. 2E

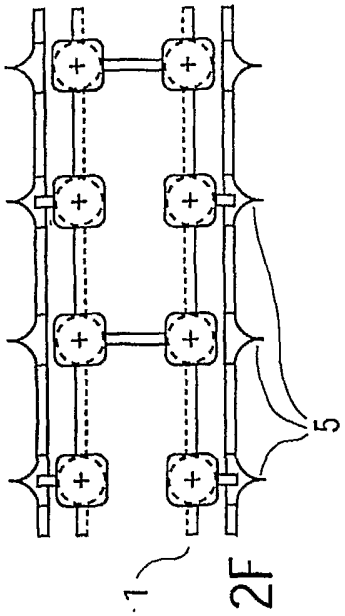

FIG. 2F

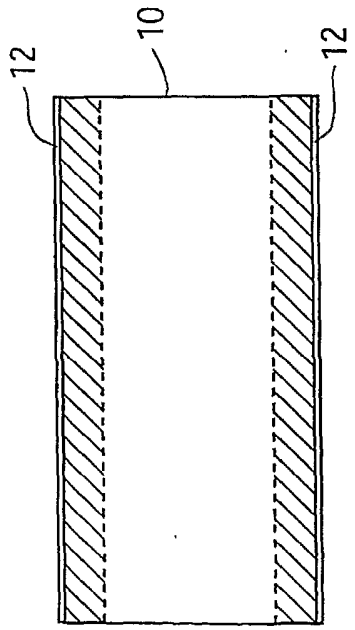

FIG. 2A

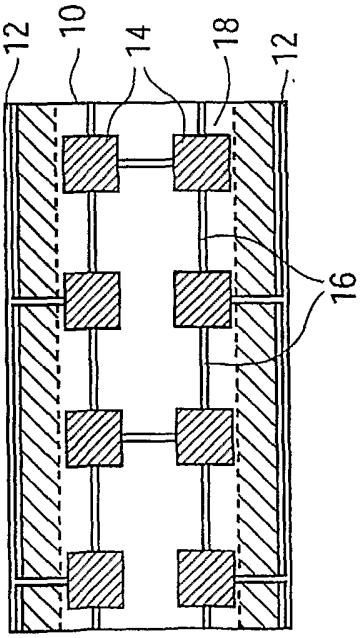

FIG. 2B

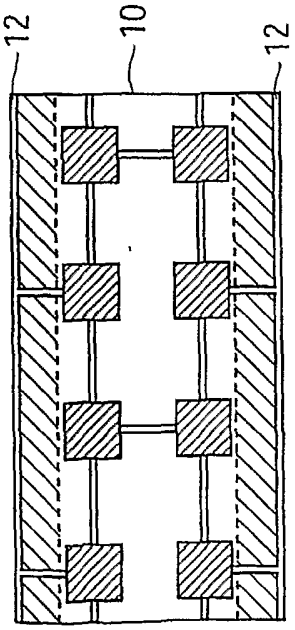

FIG. 2C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/06237

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : B23H 11/00, 3/00, 5/00, 7/00; C25F 3/00
US CL : 205/640, 655, 666, 667

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)
U.S. : 205/640, 655, 666, 667

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,902,475 A (TROZERA et al) 11 May 1999 (11.05.1999), Abstract, Figs. 1-5, and cols. 4-9.	1-35
Y	US 6,197,013 B1 (REED et al) 6 March 2001 (06.03.2001), Abstract, Figs. 1-8, and cols. 4-13.	1-35
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☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 July 2003 (16.07.2003)	30 JUL 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Wesley A. Nicolas Telephone No. (703) 308-1193

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