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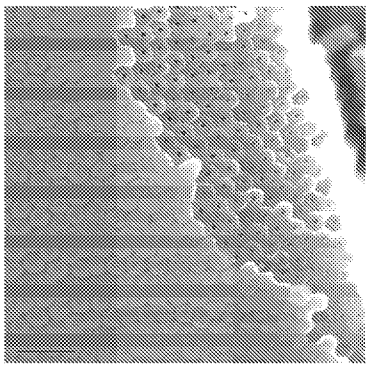
(54) Title: DEVICE HAVING TITANIA NANOTUBE MEMBRANE FOR DRUG DELIVERY

Figure 8



(57) Abstract: The present invention provides a device including a titania nanotube membrane having a plurality of titania nanotubes on a titanium substrate where the titania nanotubes are open at both ends and capable of allowing diffusion of liquids or solids from one side of the membrane to the other through the titania nanotubes. Methods of making the titania nanotube membrane are also provided.

DEVICE HAVING TITANIA NANOTUBE MEMBRANE FOR DRUG DELIVERY

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/566,810, filed December 5, 2011, which is incorporated in its entirety herein for all purposes.

BACKGROUND OF THE INVENTION

[0002] Current injectable drug delivery therapies have debilitating side effects which significantly decrease quality of life for patients. As an example, patients receiving Interferon-alpha (IFN-a) treatment for hepatitis C (HCV) report that the side effects of their treatment are so severe that they are often unable to work. As a result of the debilitating effects of many injected therapies including IFN-a, patients are often not prescribed treatment until damaging effects of the disease have become severe, such as acute liver inflammation for people with HCV. Patients are required to inject themselves with a substance that they know will make them feel very ill for several days. Consequently, patients are disinclined to take their treatments as prescribed, and some cease treatment prematurely, adversely affecting their therapy. Many of the side effects from the interferon therapy are associated with the spike in drag concentration immediately following an injection. Ideally, IFN-a would enter the patient at a constant-rate, thereby reducing side effects. Recent advances in implantable tiiania nanoporous membranes have produced a novel method to control the release of macromolecules, eliminating the concentration spike associated with an injection. Furthermore, subcutaneously implanted devices can increase patient compliance, thereby increasing treatment efficacy while simultaneously reducing side effects. Surprisingly, the present invention meets this and other needs.

BRIEF SUMMARY OF THE INVENTION

[0003] In one embodiment, the present invention provides a device having a capsule suitable for implantation. The device also includes a reservoir encapsulated by the capsule, wherein the reservoir is suitable for containing a therapeutic agent. The device also includes a tiiania nanotube membrane on a titanium substrate, wherein the titanium substrate is

attached to the capsule such that the titanium substrate is in contact with the reservoir, wherein the titania nanotube membrane comprises a plurality of titania nanotubes in fluid contact with the reservoir. The device is such that the plurality of titania nanotubes is the only diffusion pathway out of the reservoir for the therapeutic agent.

[0004] In another embodiment, the present invention provides a method of preparing a titania nanotube membrane, the method including growing a plurality of titania nanotubes on a first side of a titanium substrate under anodization conditions, such that a first end of each nanotube is closed and attached to the titanium substrate and a second end of each nanotube is open. The method also includes etching the titanium substrate on the side opposite the first side, under conditions sufficient to open the first end of a first group of the titania nanotubes, thereby preparing the titania nanotube membrane.

[0005] In another embodiment, the present invention provides a titania nanotube membrane prepared by the process above.

[0006] In another embodiment, the present invention provides a titania nanotube membrane having a plurality of titania nanotubes on a titanium substrate, wherein each nanotube has a first and a second end such that both the first and second ends of a first group of the titania nanotubes are open.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] Figure 1 shows one embodiments of the device of the present invention, with a capsule (100), a reservoir (110) encapsulated by the capsule, a titania nanotube membrane (120) in contact with the reservoir, where the titania nanotube membrane is on a titanium substrate (130), and where the titania nanotube membrane includes a plurality of titania nanotubes (121).

[0008] Figure 2 shows the chamber used for nanotube fabrication on a fixture base.

[0009] Figure 3 shows the chamber with the cathode inserted in the groove in the chamber.

[0010] Figure 4 shows the chamber with anode inserted in the hole in the base of the chamber with the gasket side of the anode remaining in the chamber.

[0011] Figure 5 shows the chamber with the lid placed with the cylinder alignment features inside the chamber.

[0012] Figure 6 shows a schematic for the method of the present invention, including preparation of a titanium substrate (CP grade 1 or 2) from which the titania nanotubes are grown, and then etching the titanium substrate to reveal the titania nanotube membrane.

[0013] Figure 7 shows additional details of the inventive device, including the titania nanotube membranes on the titanium substrate, and the laser welding of the titanium substrate to the reservoir, such that the only avenue for release of the reservoir contents is via the titania nanotube membrane.

[0014] Figure 8 shows titania nanotubes fabricated in the process of the present invention, including the bottoms of the nanotubes (A), side view showing ~60 micron length of the nanotubes (B), and the nanotube tops (C).

DETAILED DESCRIPTION OF THE INVENTION

I. General

[0015] The present invention provides a drug delivery device having a plurality of titania nanotubes forming a titania nanotube membrane on a titanium substrate for delivery of a therapeutic agent. The titania nanotube membrane is prepared by first growing the titania nanotubes on a titanium substrate, and then etching the backside of the titanium substrate, the side without the nanotubes, until the inner portion of the nanotubes is exposed of a first group of the titania nanotubes. The titania nanotube membrane can also include a second group of the titania nanotubes where the first end of the titania nanotubes remains closed. The narrow diameter of the titania nanotubes controls the release of the therapeutic agent in the drug delivery device because the titania nanotubes are the only pathway for diffusion out of the device. The release rate of the therapeutic agent can be zero-order.

II, Definitions

[0016] "Therapeutic agent" refers to any agent capable of providing a therapeutic response, such as a drug or biologic.

[0017] "Titania nanotube membrane" refers to an array of titania nanotubes on a titanium substrate where at least a portion of the titania nanotubes are open at both ends and capable of allowing diffusion of liquids or solids from one side of the membrane to the other through the titania nanotubes.

[0018] "Fluid contact" refers to the contents of the reservoir being able to diffuse from the reservoir to the titania nanotubes. The contents of the reservoir can be in liquid form, but can also be in powder or solid form.

[0019] "Aspect ratio" refers to the ratio of length to diameter of the titania nanotubes, including the internal and external diameter.

[0028] "Zero-order rate of release" refers to the rate of release that is independent of concentration of the therapeutic agent in the reservoir.

[0021] "Contacting" refers to the process of bringing into contact at least two distinct species such that they can react. It should be appreciated, however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0022] "Halogen ion" refers to fluoride, chloride, bromide and iodide ions. The halogen ion can be paired with a suitable counterion, such as ammonium.

[0023] "Water-miscible solvent" refers to a solvent that is at least partially miscible with water, and can be completely miscible with water.

III. Device

[0024] The present invention provides a drug delivery device having a titania nanotube membrane on a titanium substrate providing the only diffusion pathway for any therapeutic agent out of the device.

[0025] In some embodiments, the present invention provides a device having a capsule suitable for implantation. The device also includes a reservoir encapsulated by the capsule, wherein the reservoir is suitable for containing a therapeutic agent. The device also includes a titania nanotube membrane on a titanium substrate, wherein the titanium substrate is attached to the capsule such that the titanium substrate is in contact with the reservoir, wherein the titania nanotube membrane comprises a plurality of titania nanotubes in fluid contact with the reservoir. The device is such that the plurality of titania nanotubes is the only diffusion pathway out of the reservoir for the therapeutic agent.

[0026] The capsule (TOO) of Figure 1 can be any capsule that is biocompatible with the body. The capsule can be prepared from any suitable material such as metals, polymers and

combinations thereof. Useful metals can be pure metals or alloys, and include, but are not limited to, titanium and steel. Polymers useful in the present invention include any natural or synthetic polymer that is biocompatible with the body. In some embodiments, the capsule includes titanium.

[0027] The capsule can have any suitable shape or size. The capsule can be spherical, elliptical, oblong, circular, or cylindrical, among others.

[0028] The device also includes the reservoir (110) of Figure 1 which contains the therapeutic agent. Any therapeutic agent is useful in the device of the present invention. Useful therapeutic agents include drugs and biologies. Suitable therapeutic agents include biologically active macromolecules such as peptides, protein drugs, or polynucleic acids. Suitable peptides or protein biopharmaeeuticais include: hormones, hormone agonists, hormone antagonists, growth factors such as CSF, EPO, and growth hormone, cytokines such as the interleukins, immune modulators such as interferon gamma and interferon beta, anti-infectives such as interferon alpha 2b, anti-inflammatories, immune suppressant/anti-rejection drugs, antibodies, anti-arthritic drugs, and anti-tumor agents. Suitable polynucleic acids include: DNA, RNA, plasmid molecules, antisense DNA, and rihozymes. Small molecular weight molecules are also compatible with the present invention. Suitable small molecular weight molecules include, but are not limited to, pain medications or anti-psychotic agents.

[0029] Preferably, stabilizers co-formulated with the therapeutic agent contained within the reservoir include water miscible solvents, or polymers. Suitable stabilizers include, but are not limited to carbohydrates, sugars, dextrans, polyvinyl pyrrolidone, gum arable, polyethylene glycol, albumin, dendritic polymers, cross-linked polymer matrix, and surfactants. Representative sugars include trehalose, glucose and sucrose.

[0030] In some embodiments, the therapeutic agent can be beta-glueocerobrosidase, interferon alpha, interferon beta, agasidase alpha, agasidase beta, exenatide, nutropin/'somatropin, factor VIII, fondaparinux, aidesleukinand, risperidone, forigerimod, NP fusion proteins, 1L-12, a melanocyte stimulating hormone, or bapineuzumab. Analogues of these therapeutic agents are also contemplated. In some embodiments, the therapeutic agent is interferon alpha.

[0031] The therapeutic agent can be in any suitable form in the reservoir, such as a liquid, a solid or a suspension. Solid forms include, but are not limited to, powders and micronized particles. For example, the powder can be iyophilized.

[0032] The titanium substrate (130) of Figure 1 can be attached to the capsule by any suitable methods in the art. For example, the titanium substrate can be laser welded to the capsule.

[0033] The titania nanotubes (121) of Figure 1 can have any suitable dimensions, including the internal diameter, the length and the aspect ratio. The internal diameter can be from about 1 nm to about 1000 nm, and can be the same or variable along the length of the titania nanotube. When the internal diameter is variable, the internal diameter can increase from one end of the titania nanotube to the other. For example, the internal diameter of the titania nanotube at the end in contact wiih the reservoir can be smaller than at the end opposite the reservoir, where the internal diameter increases gradually along the length of the titania nanotube. The internal diameter can be about I, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 75, 100, 200, 300, 400, 500 or 1000 nm. The internal diameter can be of from about 1 to 1000 nm, or from about 1 to about 100 nm, or from about 1 to about 50 nm, or from about 1 to about 20 nm. Th some embodiments, the internal diameter can be of from about 10 nm to about 1000 nm.

[0034] The titania nanotubes can have any suitable length. For example, the titania nanotubes can be from about 100 nm to about 100 μηι, or about 500 nm, 1 μηι, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 μη. In some embodiments, the titania nanotubes have a length of about 1 μηι to about 100 μni.

[0035] The titania nanotubes can also have any suitable aspect ratio, defined by the length of the titania nanotube divided by the internal or external diameter. The aspect ratio can be from about 10 to about 10,000, or from about 10 to about 1,000. Other aspect ratios include, but are not limited to, about 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, or 10,000.

[0036] The titania nanotubes are in fluid contact with the reservoir such that the therapeutic agent, whether in liquid, solid or suspension form, can diffuse from the reservoir and into the titania nanotubes at the titanium substrate, followed by exiting the titania nanotubes at the opposite end and entering the body. The rate of release of the therapeutic agent can be any suitable rate of release, such as zero-order rate of release. In some embodiments, the release of the therapeutic agent from the reservoir and through the titania nanotube membrane is a zero-order rate of release.

[0037] The titania **nanotube** membrane can be prepared by any suitable method. In some embodiments, the titania nanotube membrane is prepared by the method of the present invention.

IV. Preparation of Tiiania Nanotube Membrane

[0038] The titama nanotube membrane of the device of the present invention can be prepared by any suitable method, namely by growing the titania nanotubes on a titanium substrate, followed by etching the back side of the titanium substrate, the side opposite the titania nanotubes, until the inner portion of a subset of the nanotubes is exposed. In some embodiments, the present invention provides a method of preparing a titania nanotube membrane, the method including growing a plurality of titania nanotubes on a first side of a titanium substrate under anodizatton conditions, such that a first end of each nanotube is closed and attached to the titanium substrate and a second end of each nanotube is open. The method also includes etching the titanium substrate on the side opposite the first side, under conditions sufficient to open the first end of a first group of the titania nanotubes, thereby preparing the titama nanotube membrane.

[0039] The titania nanotube membrane can be a continuous membrane of titania nanotubes, or can be patterned. The patterned titania nanotube membrane has regions of titama nanotubes and regions of titanium. The patterned titania nanotube membrane can have any type of pattern, such as lines, checkerboard, etc.

[0040] The titania nanotube membrane prepared by the method of the present invention can have all the titania nanotubes open at both ends, or have only a portion of the titania nanotubes open at both ends. For example, the titania nanotube membrane can have a first group of titania nanotubes open at the first and second ends of the titania nanotubes. The first group of nanotubes can be all of the nanotubes in the titania nanotube membrane, or a subset of the titania nanotubes in the membrane. When the first group of titania nanotubes is not all of the titania nanotubes in the membrane, the titama nanotube membrane also includes a second group of titania nanotubes where the first end remains closed. In some embodiments, the first end of a second group of the titania nanotubes remains closed. The titania nanotube membrane can include other groups of titania nanotubes.

[0041] The anodization conditions include any conditions capable for growing titania nanotubes. In some embodiments, growing titania nanotubes includes contacting the first side of the titanium substrate with an anodization solution having a halogen ion, water and a water-miscible solvent.

[0042] The titanium substrate can be of any suitable thickness, such as a thickness where an additional substrate or support is not needed to prepare the titania nanotube membrane or support the titania nanotube membrane in the device described above.

[0043] The halogen ion can be fluoride, chloride, bromide or iodide. In some embodiments, the halogen ion can be fluoride. In some embodiments, the anodization solution includes ammonium fluoride.

[0044] The water-miscible solvent can be any solvent miscible in water. In some embodiments, the water-miscible solvent can be ethanol, ethylene glycol, propylene glycol or 1,3-propanediol. In some embodiments, the water-miscible solvent can be ethylene glycol. The water-miscible solvent present in the anodization solution can be present in any suitable amount. For example, the water-miscible solvent can be present in an amount such as 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 wt %. In some embodiments, the water-miscible solvent can be present in an amount of from about 50 to about 99 wt %. In some embodiments, the water-miscible solvent can be present in an amount of from about 95 to about 99 wt %.

[0045] The anodization solution includes any suitable amount of the halogen ion, water and water-miscible solvent. For example, ammonium fluoride as the halogen ion can be present in an amount of from about 0.01 to about 10 wt %, or about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0 or 10.0 wt%. In some embodiments, the ammonium fluoride can be present in an amount of from about 0.01 to about 5 wt %. In some embodiments, the ammonium fluoride can be present in an amount of from about 0.1 to about 1 wt%. In some embodiments, the ammonium fluoride can be present in an amount of about 0.3 wt %.

[0046] The water present in the anodization solution can be present in any suitable amount. For example, water can be present in an amount such as 0.1, 0.5 I, 2, 3, 4, 5, 10, 20, 30, 40 or 50 wt %. In some embodiments, the wafer is present in an amount of from about 0.1 to about 50 wt %. In some embodiments, the water is present in an amount of from about 0.1 to about 5 wt %.

[0047] In some embodiments, the anodization solvent includes ammonium fluoride in an amount from about 0.1 to about I wt %, water in an amount of from about 1 to about 5 wt %, and the water-miscible solvent in an amount of from about 95 to about 99 wt %.

[0048] In some embodiments, the method of making the titania nanotube membrane also includes annealing the titania nanotubes on the titanium substrate. The annealing can be performed at any suitable temperature for any suitable period of time. In some embodiments, the annealing step includes heating the plurality of titania nanotubes on the titanium substrate at a temperature of from about 200°C to about 1000°C. Other temperatures useful in the annealing step include, but are not limited to, 200, 250°C, 300, 350, 400, 450, 500, 600, 700, 800, 900, or 10QQ°C. In some embodiments, the temperature can be of from about 300°C to about 600°C, or from about 400°C to about 500°C. In some embodiments, the temperature can be about 450°C.

[0049] The etching can be performed by any suitable etching method. For example, the etching can be a plasma etch, or a reactive-ion etch such as a chlorine deep reactive-ion etch.

[0050] In another embodiment, the present invention provides a titania nanotube membrane prepared by the process above.

[0051] In another embodiment, the present invention provides a titania nanotube membrane having a plurality of titania nanotubes on a titanium substrate, wherein each nanotube has a first and a second end such that both the first and second ends of a first group of the titania nanotubes are opens. In some embodiments, the titania nanotube membrane further comprises a second group of the titania nanotubes wherein only the first ends are open. In some embodiments, the titania nanotube membrane can be prepared by the process described above.

V, Examples

Example 1; Nanotube Fabrication on Patterned Disks

General

[0052] Reagents and patterned disks are inspected prior to use. Material safety data sheets (MSDS) for ammonium fluoride (N¾ F) and mild hydrofluoric acid are reviewed, and proper safety equipment is used during handling of fluorine and fluorine-contaminated materials to avoid exposure. The fluoride-containing salt used in the procedures is dissolved in water to become aqueous fluorine, which is toxic by ingestion, inhalation, and skin contact. 18.2 MΩ deionized water (referred to hereafter as "DI water') is used for ail reagent preparation and equipment cleaning. Reagent solutions are neutralized at the end of each fabrication run.

Nanotube Fabrication Assembly Set-Up

[0053] The fixture is placed in an upright position (Figure 2). The cathode is inserted by sliding it into the groove in the chamber of the fixture until seated (Figure 3). The anode is inserted by pushing the wire through the hole in the base of the chamber; the gasket side of the anode should remain in the chamber (Figure 4). If necessary, the fid is placed with the cylinder alignment features inside the chamber (Figure 5). The fixtures are exposed to potentially toxic aqueous fluorine ions during use. Therefore, fixtures should be appropriately cleaned and gloves and safety goggles should be used during assembly and handling.

Anodization Solution Preparation

[0054] A solution of 0.3 wt % ammonium fluoride in aqueous 98% (v/v) ethylene glycol (EG) is prepared by dissolving 3 +/- 0.1 g of NI-I4F in 20 +/- 0.25 mL of FLO in a 1-liter HDPE bottle. After complete dissolution of NH_4F, 980 +/- 5 mL of EG is added to the solution.

Cleaning

[0055] The patterned disks are cleaned via somcation in an aqueous 10% (v/v) Micro-90 solution (Aldrich) for 6 minutes. The disks are removed from the sonication bath, rinsed with FLO followed by eihanol, and dried under a stream of nitrogen. The fabrication fixture and platinum wire may be cleaned in a similar manner if necessary. For convenience, the patterned disks may be left in the sonication bath until set-up of the nanotube fabrication assembly is complete.

Run Set-Up

[0056] The power supplies for the nanotube fabrication assembly are turned on and set to 60 V +/- 0.1 V. Run parameters are set by the user using the software interface:

1. The program is started by pressing the arrow key.

2. Run time (e.g. 18 hours) is entered in the "Hours" text box for each ran.

3. The file name for the first ran is assigned by opening the appropriate folder in the file browser and selecting the most recent ran. The file name is copied and pasted in the file path for the each ran, and the filenames are then edited to reflect the correct ran numbers.

4. Run parameters are entered in the tube table in Excel.

[0057] The nanotube fabrication fixture is placed into the secondary containment, and the patterned disk is firmly pressed into the Viton gasket with the machined windows facing down until it seats. The disks should be level with the work surface. Electrical conductivity is confirmed using an ohmmeter. The anode and cathode are connected to the corresponding quick-disconnect power leads. The fixture chamber is filled with 30 mL of the anodization solution, prepared as described above. The fixtures are covered with lids such that cylinder alignment features are inside the chamber. The thermistors are cleaned with an ethanol-soaked wipe and inserted through the lids into the solution.

Run

[0058] Recording of each run is initiated by pressing the "Begin Run" button on the software interface. The commencement of tube growth is indicated by current spike and decay. After the full duration of the run time as entered during run set-up, the run record should be reviewed to ensure that power did not fail during the ran. Temperature and current fluctuations are recorded; large current fluctuations may indicate a physical disturbance during the run. The program is ended by pressing the "Stop" button, and cleaning of the assembly is conducted immediately.

Cleanup

[0059] The power supply is turned off and the leads to the fabrication fixture are disconnected after the relays have opened and a drop in current is registered. The remaining anodization solution is poured from the assembly into a beaker containing roughly 1-1.5 grams of calcium carbonate. While removing the anodization solution, the fabrication fixture is thoroughly rinsed with ethanol by spraying with an ethanol spray bottle at least 8 times. All ethanol rinses are collected in a waste beaker, and the ethanol rinse is repeated. Additional ethanol is sprayed into the assembly so that the disk and a few millimeters of the chamber are covered, and the fixtures are covered with the lids again. The fixtures may be left in this state for up to a maximum of 24 hours if necessary.

[0068] The time at which the anodization solution was removed from the disks is recorded. The disks and solution are inspected in terms of color, pattern, or other markings. The fixture fids are placed in a stainless steel pan containing ethanol. The fixture itself is placed sideways in the pan, so that the disk stays submerged in ethanol. The Viton gasket/wire assembly is pushed out of the bottom of the fabrication fixture while keeping the disk submerged in ethanol. The disk is carefully removed by pressing the base of the gasket and/or pulling the gasket sides back so that the disk pops out. The disk is cleaned with ethanol, dried in air, placed in a gel pak, and labeled. Both sides of the gel paks are scanned.

Each fabrication fixture and cathode insert are dried separately with nitrogen and placed in a clean screw-top container. Tweezers and secondary containment are rinsed with water and dried with nitrogen or allowed to air dry. The neutralized anodization solution is flushed in a sink with several liters of water (a faucet is left running for ~2-3 minutes).

Example 2: Nanotube Annealing

General

[0061] The annealing procedure involves the use of a high-temperature furnace. The furnace must be cool enough to work with (e.g. room temperature) prior to removing parts or otherwise preparing the instrument. Proper safety equipment includes tweezers or tongs, closed toe shoes, and heat resistant gloves. After annealing, patterned disks with nanotubes are stabilized for use in water and cleaned of tube debris.

Preparing Disk for Annealing

[0062] Patterned disks are inserted into an appropriate furnace (e.g. Ney Vulcan 3-550) with the disks centered. The furnace is programmed by the user with the following parameters.

a. Duration: 1 hour

b. Ramp rate: l()°C/min

c. Temperature: 450°C

d. Ensure that the second and third ramps are to 450°C, and are for 0 minutes.

e. The cycle should be 1 hr and 42 minutes long.

The furnace door is closed and the anneal is started by pressing the start button.

Removing Disks from Annealing Furnace

[0063] Within 15 minutes after the anneal is complete, the furnace door is opened and allowed to cool to 280°C or lower before continuing. The disks are transferred to an aluminum cooling block using tweezers. The disks are removed to aluminum foil to finish cooling. The cooled disks are then placed in labeled gel paks, and the front and back of each gel pak are scanned.

Post-processing

[0064] Each disk is cleaned with ethanol, dried in air, and returned to the gel pak. The front and back of each gel pak are scanned. Nanotube annealing is typically followed by nanotube etching.

Example 3: Nanotube Etching

Titanium Etch Jig Assembly Set-Up

10065] Titanium etch jigs are sonicated in Micro-90 solution. The etch jigs are rinsed with deionized water followed by ethanof and dried under a stream of nitrogen. The etch jigs are debarred if necessary. The jig is squeezed radially to plastically reduce the gap using a pair of clean needle-nose pliers. The jig is spread with a spreader tool, and the patterned disk with naiiostructures is inserted. The bottom of the jig is labeled with the run number and placed in a gel pak.

Disk Etching

[0066] Disk etching is conducted with a transformer-coupled plasma (TCP) etcher (e.g. Lam Research TCP 9600SE II). The etch jigs are attached to a 6" silicon oxide wafer using 0.005" adhesive-backed Kapton. The bottom of the wafer is cleaned by blowing with a stream of nitrogen before placing the wafer into the entry wafer cassette of the TCP etcher. Argon is used in the inert gas line, and the chiller temperature is set o 15°C. The appropriate etching program is programmed by the user, having the following parameters: 40QW Source Power, 100W Bias, 18.75 mT Chamber Pressure, 120 scem (¾, and 15 seem Ar.

[0067] A total of 60 minutes of etch is performed in 5 minute on-cycle (with 5 minute off-cycle with no RF, chamber pressure of 60 mT, 500 seems Ar). The etch jigs are mounted using Kapton tape on a silicon wafer which had an oxide layer grown in the furnace for extended durations. The etching process is initiated by the user via software controls, and proper wafer feeding into the etcher is confirmed. The etching process is typically conducted over 120 minutes and is automatically controlled by the instrument. The wafer is removed from the exit cassette when the instrument idles after etching, and the jigs with patterned disks are removed from the wafer.

Example 4: Nanotube Fabrication *on* Patterned Disks

General

[0068] Reagents and patterned disks are inspected prior to use. Material safety data sheets (MSDS) for ammonium fluoride (NH_4F) and mild hydrofluoric acid are reviewed, and proper safety equipment is used during handling of fluorine and fluorine-contaminated materials to avoid exposure. The fluoride-containing salt used in the procedures is dissolved in water to become aqueous fluorine, which is toxic by ingestion, inhalation, and skin contact. 18.2 MΩ deionized water (referred to hereafter as "DI water') is used for ail reagent preparation and equipment cleaning. Reagent solutions are neutralized at the end of each fabrication run.

Nanotube Fabrication Assembly Set-Up

[0069] The fixture is placed in an upright position (Figure 2). The cathode is inserted by sliding it into the groove in the chamber of the fixture until seated (Figure 3). The anode is inserted by pushing the wire through the hole in the base of the chamber; the gasket side of the anode should remain in the chamber (Figure 4). If necessary, the fid is placed with the cylinder alignment features inside the chamber (Figure 5). The fixtures are exposed to potentially toxic aqueous fluorine ions during use. Therefore, fixtures should be appropriately cleaned and gloves and safety goggles should be used during assembly and handling.

Anodization Solution Preparation

[0070] A 500 ml, solution of 0.3 wt % ammonium fluoride in 2% DI water / 98% ethylene glycol (EG) (v/v) is prepared by dissolving 1.5 +/- 0.1 g of N¾F in 10 +/- 0.25 mL of DI H_20 in a 1-liter HOPE bottle. After complete dissolution of NH_4F, 490 +/- 5 mL of EG is added to the solution.

Cleaning

[0071] The patterned disks and stainless steel wire are cleaned via sonication in a solution of 10% Micro-90 / 90% water (v/v) for 10 minutes. The disk and wire are removed from the sonication bath and rinsed with DI water. The disk is air dried, while the fabrication fixtures and stainless steel wires are dried with nitrogen. For convenience, the patterned disks may be left in the sonication bath until set-up of the nanotube fabrication assembly is complete.

Run Set-Up

[0072] The power supplies for the nanotube fabrication assembly are turned on and set to 60 V +/- 0.1 V. Run parameters are set by the user using the software interface:

1. The program is started by pressing the arrow key.
2. Rim time (e.g. 18 hours) is entered in the "Hours" text box for each run.
3. The file name for the first run is assigned by opening the appropriate folder in the file browser and selecting the most recent run. The file name is copied and pasted in the file path for the each ran, and the filenames are then edited to reflect the correct ran numbers.
4. Rim parameters are entered in the tube table in Excel.

[0073] The nanotube fabrication fixture is placed into the secondary containment. The anode and cathode are connected to the corresponding quick-disconnect power leads. The

patterned disk is firmly pressed into the Viton gasket with the machined windows facing down until it seats. The disks should be level with the work surface. Electrical conductivity is confirmed using an ohmmeter. The disk is wetted with ethanol (<100.uL). The fabrication fixture chamber is filled with 30 +/- 0.25 mL of the anodization solution, prepared as described above. The fixtures are covered with lids such that cylinder alignment features are inside the chamber.

Run

[0074] Recording of each run is initiated by pressing the "Begin Run" button on the software interface. The commencement of tube growth is indicated by current spike and decay. After the full duration of the ran time as entered during ran set-up, the ran record should be reviewed to ensure that power did not fail during the run. Temperature and current fluctuations are recorded; large current fluctuations may indicate a physical disturbance during the run. The program is ended by pressing the "Stop" button, and cleaning of the assembly is conducted immediately.

Cleanup

[0075] Partially fill 5 mL tubes with ethanol (approximately 2 sprays from the bottle). The power supply is turned off and the leads to the fabrication fixture are disconnected after the relays have opened and a drop in current is registered. The remaining ethylene glycol solution is poured from the assembly into a beaker containing roughly 1-1.5 grams of calcium carbonate. While removing the ethylene glycol solution, the fabrication fixture is thoroughly rinsed with ethanol by spraying with an ethanol spray bottle at least 8 times. All ethanol rinses are collected in a waste beaker, and the ethanol rinse is repeated. Additional ethanol is sprayed into the assembly so that the disk and a few millimeters of the chamber are covered, and the fixtures are covered with the fids again. The fixtures may be left in this state for up to a maximum of 24 hours if necessary.

[0076] The time at which the anodization solution was removed from the disks is recorded. The disks and solution are inspected in terms of color, pattern, or other markings. The fixture lids are placed in a tube containing ethanol. The fixture itself is placed sideways in the pan, so that the disk stays submerged in ethanol. The Viton gasket/wire assembly is pushed out of the bottom of the fabrication fixture while keeping the disk submerged in ethanol. The disk is carefully removed by pressing the base of the gasket and/or pulling the gasket sides back so that the disk pops out. The disk is placed nanotube side down into a 5-ml tube partially filled with ethanol and sonicated for 15 minutes. The disk is removed from the tube and sprayed several times with ethanol. The disk is transferred directly to a hotplate at 100°C to dry. The

disk is removed when dry (usually after 30-60 s on the hotplate). The disk is allowed to cool, placed in a gel pak, and labeled. Both sides of the gel paks are scanned. Each fabrication fixture and cathode insert are dried separately with nitrogen and placed in a clean screw-top container. Tweezers and secondary containment are rinsed with water and dried with nitrogen or allowed to air dry. The neutralized anodization solution is flushed in a sink with several liters of water (a faucet is left running for ~2-3 minutes).

Example 5: Nanotube Fabrication on Patterned Disks

General

[0077] Reagents and patterned disks are inspected prior to use. Material safety data sheets (MSDS) for ammonium fluoride (NH_4F) and mild hydrofluoric acid are reviewed, and proper safety equipment is used during handling of fluorine and fluorine-contaminated materials to avoid exposure. The fluoride-containing salt used in the procedures is dissolved in water to become aqueous fluorine, which is toxic by ingestion, inhalation, and skin contact. 18.2 MΩ deionized water (referred to hereafter as "DI water') is used for all reagent preparation and equipment cleaning. Reagent solutions are neutralized at the end of each fabrication run.

Nanotube Fabrication Assembly Set-Up

[0078] The fixture is placed in an upright position (Figure *2).* The cathode is inserted by sliding it into the groove in the chamber of the fixture until seated (Figure 3). The anode is inserted by pushing the wire through the hole in the base of the chamber; the gasket side of the anode should remain in the chamber (Figure 4). If necessary, the lid is placed with the cylinder alignment features inside the chamber (Figure 5). The fixtures are exposed to potentially toxic aqueous fluorine ions during use. Therefore, fixtures should be appropriately cleaned and gloves and safety goggles should be used during assembly and handling.

Anodization Solution Preparation

[0079] A solution of 1.0 wt % ammonium fluoride in aqueous 98% (v/v) ethylene glycol (EG) is prepared by dissolving 7.5 +/- 0.005 g ofNH_4F in 15 +/- 0.1 mL ofH_2O in a 1-liter HOPE bottle. After complete dissolution of NH_4F, 980 +/- 5 mL of EG is added to the solution.

Cleaning

[0088] The patterned disks are cleaned via sonication in an aqueous 10% (v/v) Micro-90 solution (Aldrich) for 6 minutes. The disks are removed from the sonication bath, rinsed with H_2O followed by ethanol, and dried under a stream of nitrogen. The fabrication fixture and

platinum wire may be cleaned in a similar manner if necessary. For convenience, the patterned disks may be left in the sonication bath until set-up of the nanotube fabrication assembly is complete.

Run Set-Up

[0081] The power supplies for the nanotube fabrication assembly are toned on and set to 50 V +/- 0.1 V. Run parameters are set by the user using the software interface:

1. The program is started by pressing the arrow key.
2. Run time (e.g. 18 hours) is entered in the "Hours" text box for each run.
3. The file name for the first run is assigned by opening the appropriate folder in the file browser and selecting the most recent ran. The file name is copied and pasted in the file path for the each run, and the filenames are then edited to reflect the correct run numbers.
4. Run parameters are entered in the tube table in Excel.

[0082] The nanotube fabrication fixture is placed into the secondary containment, and the patterned disk is firmly pressed into the Viton gasket with the machined windows facing down until it seats. The disks should be level with the work surface. Electrical conductivity is confirmed using an ohmmeter. The anode and cathode are connected to the corresponding quick-disconnect power leads. The fixture chamber is filled with 30 mL, of the anodization solution, prepared as described above. The fixtures are covered with lids such that cylinder alignment features are inside the chamber. The thermistors are cleaned with an ethanol-soaked wipe and inserted through the lids into the solution.

Run

[0083] Recording of each run is initiated by pressing the "Begin Run" button on the software interface. The commencement of tube growth is indicated by current spike and decay. After the full duration of the run time as entered during run set-up, the run record should be reviewed to ensure that power did not fail during the run. Temperature and current fluctuations are recorded; large current fluctuations may indicate a physical disturbance during the run. The program is ended by pressing the "Stop" button, and cleaning of the assembly is conducted immediately.

Cleanup

[0084] The power supply is turned off and the leads to the fabrication fixture are disconnected after the relays have opened and a drop in current is registered. The remaining

anodization solution is poured from the assembly into a beaker containing roughly 1-1.5 grams of calcium carbonate. While removing the anodization solution, the fabrication fixture is thoroughly rinsed with isopropanol by spraying with a spray bottle at least 8 times. All isopropanol rinses are collected in a waste beaker, and the isopropanol rinse is repeated. Additional isopropanol is sprayed into the assembly so that the disk and a few millimeters of the chamber are covered, and the fixtures are covered with the lids again. The fixtures may be left in this state for up to a maximum of 2.4 hours if necessary.

[0085] The time at which the anodization solution was removed from the disks is recorded. The disks and solution are inspected in terms of color, pattern, or other markings. The Viton gasket/wire assembly is pushed out of the bottom of the fabrication fixture while keeping the disk wet with isopropanol. The disk is carefully removed by pressing the base of the gasket and'or pulling the gasket sides back so that the disk pops out. The disk is cleaned with isopropanol, sonicated in isopropanol (10 minutes, followed by another 5 minutes in fresh isopropanol), dried in air, placed in a gel pak, and labeled. Both sides of the gel paks are scanned. Each fabrication fixture and cathode insert are dried separately with nitrogen and placed in a clean screw-top container. Tweezers and secondary containment are rinsed with water and dried with nitrogen or allowed to air dry. The neutralized anodization solution is flushed in a sink with several liters of water (a faucet is left running for ~2-3 minutes).

Example 6: Nanotube Etching

[0086] Using the same titanium etch jig assembly described in example 3, disk etching is conducted with a transformer-coupled plasma (TCP) etcher (e.g. Lam Research TCP 9600SE 11). The etch jigs are attached to a 6" silicon wafer using a thermal coupling fluid. The bottom of the wafer is cleaned by blowing with a stream of nitrogen before placing the wafer into the entry wafer cassette of the TCP etcher. The chiller temperature is set to 15°C.

[0087] Prior to etching the titanium, any titanium oxide on the unanodized side of the substrate is removed via CF_4 etch. A total of 75 minutes of etch is perfoiined to remove the titanium and expose the titania nanotubes using the following parameters: 400W Source Power, 100W Bias, 18.75 ml ' Chamber Pressure, 100 seem C¾. Any residual chlorine is then removed by oxygen plasma.

[0088] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the

appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A method of preparing a titama nanotube membrane, the method comprising:

growing a plurality of titama nanoiubes on a first side of a titanium substrate under anodization conditions, such that a first end of each nanotube is closed and attached to the titanium substrate and a second end of each nanotube is open; and

etching the titanium substrate on the side opposite the first side, under conditions sufficient to open the first end of a fsrst group of the titama nanotubes, thereby preparing the titama nanotube membrane.

2. The method of claim 1, wherein the first end of a second group of the titama nanotubes remains closed.

3. The method of claim 1, wherein the growing step comprises:

contacting the first side of the titanium substrate with an anodization solution comprising a halogen ion, water and a water-miseible solvent.

4. The method of claim 3, wherein the anodization solution comprises ammonium fluoride.

5. The method of claim 3, wherein the water-miscible solvent is selected from the group consisting of ethanol, ethylene glycol, propylene glycol, and 1,3-propanediol.

6. The method of claim 3, wherein the anodization solvent comprises ammonium fluoride in an amount of from about 0.01 to about 5 wt %.

7. The method of claim 3, wherein the anodization solvent comprises water in an amount of from about 0.1 to about 50 wt %.

8. The method of claim 3, wherein the anodization solvent comprises water-miscible solvent in an amount of from about 50 to about 99 wt ¾.

9. The method of claim 3, wherein the anodization solvent comprises

ammonium fluoride in an amount from about 0.1 to about I wt %;

water in an amount of from about 1 to about 5 wt %; and

the water-miscible solvent in an amount of from about 95 to about 99 wt %.

10. The method of claim 1, wherein the method further comprises annealing the plurality of titama nanotubes on the titanium substrate.

11. The method of claim 10, wherein the annealing step comprises:

heating the plurality of titania nanotubes on the titanium substrate at a temperature of from about 200 to about 1000°C.

12. The method of claim 11, wherem the heating is at a temperature of about 450°C.

13. The method of claim 1, wherein the etching is performed using a deep reactive-ion etch.

14. A titania nanotube membrane prepared by the process of claim 1.

15. A titania nanotube membrane comprising a plurality of titania nanotubes on a titanium substrate, wherem each nanotube has a first and a second end such that both the first and second ends of a fsrst group of the titama nanotubes are open.

16. The titama nanotube membrane of claim 15, wherein the titania nanotube membrane further comprises a second group of the titama nanotubes wherein only the first ends are open.

17. The titania nanotube membrane of claim 15, prepared by the process of claim 1.

18. A device comprising:

a capsule suitable for implantation;

a reservoir encapsulated by the capsule, wherein the reservoir is suitable for containing a therapeutic agent; and

a titania nanotube membrane on a titanium substrate, wherein the titanium substrate is attached to the capsule such that the titanium substrate is in contact with the reservoir, wherein the titania nanotube membrane comprises a plurality of titania nanotubes in fluid contact with the reservoir,

such that the plurality of titania nanotubes is the only diffusion pathway out of the reservoir for the therapeutic agent.

19. The device of claim 18, wherein the capsule comprises titanium.

20. The device of claim 18, wherein the titania nanotubes have an internal diameter of from about 10 ran to 1000 nm.

21. The device of claim 18, wherein the titania nanotubes have a length of about 1 μm to about 100 μm.

22. The device of claim 18, wherein the titania nanotubes have an aspect ratio of about 10 to about 10,000.

23. The device of claim 18, wherein the therapeutic agent is selected from the group consisting of beta-glucocerobrosidase, interferon alpha, interferon beta, agasidase alpha, agasidase beta, exenatide, nutropinfeomatropin, factor VIII, fondaparinux, aldesJeukinand, risperidone, forigerimod, NP fusion proteins, IL-12, a melanocyte stimulating hormone, and bapineuzumab.

2.4. The device of claim 18, wherein the therapeutic agent is interferon alpha.

25. The device of claim 18, wherein the release of the therapeutic agent from the reservoir and through the titania nanotube membrane is a zero-order rate of release.

26. The device of claim 18, wherein the titania nanotube membrane is prepared by the process of claim 1.

AMENDED CLAIMS
RECEIVED BY THE INTERNATIONAL BUREAU ON 19 APRIL 2013
(19.04.2013)

1. A method of preparing a titania nanotube membrane, the method comprising:
growing a plurality of titania nanotubes on a first side of a titanium substrate under anodization conditions, such that a first end of each nanotube is closed and attached to the titanium substrate and a second end of each nanotube is open; and
etching the titanium substrate on the side opposite the first side, under conditions sufficient to open the first end of a first group of the titania nanotubes, thereby preparing the titania nanotube membrane.

2. The method of claim 1, wherein the first end of a second group of the titania nanotubes remains closed.

3. The method of claim 1, wherein the growing step comprises:
contacting the first side of the titanium substrate with an anodization solution comprising a halogen ion, water and a water-miscible solvent.

4. The method of claim 3, wherein the anodization solution comprises ammonium fluoride.

5. The method of claim 3, wherein the water-miscible solvent is selected from the group consisting of ethanol, ethylene glycol, propylene glycol, and 1,3-propanediol.

6. The method of claim 3, wherein the anodization solvent comprises ammonium fluoride in an amount of from about 0.01 to about 5 wt %.

7. The method of claim 3, wherein the anodization solvent comprises water in an amount of from about 0.1 to about 50 wt %.

8. The method of claim 3, wherein the anodization solvent comprises water-miscible solvent in an amount of from about 50 to about 99 wt %.

9. The method of claim 3, wherein the anodization solvent comprises
ammonium fluoride in an amount from about 0.1 to about 1 wt %;
water in an amount of from about 1 to about 5 wt %; and

AMENDED SHEET (ARTICLE 19)

the water-mi scible solvent in an amount of from about 95 to about 99 wt %.

10. The method of claim 1, wherein the method further comprises annealing the plurality of titania nanotubes on the titanium substrate.

11. The method of claim 10, wherein the annealing step comprises:

heating the plurality of titania nanotubes on the titanium substrate at a temperature of from about 200 to about 1000°C.

12. The method of claim 11, wherein the heating is at a temperature of about 450°C.

13. The method of claim 1, wherein the etching is performed using a deep reactive-ion etch.

14. A titania nanotube membrane prepared by the process of claim 1.

15. A titania nanotube membrane comprising a plurality of titania nanotubes on a titanium substrate, wherein each nanotube has a first and a second end such that both the first and second ends of a first group of the titania nanotubes are open, wherein the titania nanotube membrane is prepared by the method of claim 1.

16. The titania nanotube membrane of claim 15, wherein the titania nanotube membrane further comprises a second group of the titania nanotubes wherein only the first ends are open.

18. A device comprising:

a capsule sui [able for implantation;

a reservoir encapsulated by the capsule, wherein the reservoir is suitable for containing a therapeutic agent; and

a titania nanotube membrane on a titanium substrate, wherein the titanium substrate is attached to the capsule such that the titanium substrate is in contact with the reservoir, wherein the titania nanotube membrane comprises a plurality of titania nanotubes in fluid :ontact with the reservoir, and wherein the titania nanotube membrane is prepared by the method of claim 1,

such that the plurality of titania nanotubes is the only diffusion pathway out of the reservoir for the therapeutic agent.

19. The device of claim 18, wherein the capsule comprises titanium.

20. The device of claim 18, wherein the titania nanotubes have an internal diameter of from about 10 nm to 1000 nm.

21. The device of claim 18, wherein the titania nanotubes have a length of about 1 μm to about 100 μm.

22. The device of claim 18, wherein the titania nanotubes have an aspect ratio of about 10 to about 1C,000.

23. The device of claim 18, wherein the therapeutic agent is selected from the group consisting of beta-glucocerobrosidase, interferon alpha, interferon beta, agasidase alpha, agasidase beta, exenatide, nutropin/somatropin, factor VIII, fondaparinux, aldesleukinand, risperidone, forigeri nod, NP fusion proteins, IL-12, a melanocyte stimulating hormone, and bapineuzumab.

24. The device of claim 18, wherein the therapeutic agent is interferon alpha.

25. The device of claim 18, wherein the release of the therapeutic ageni from the reservoir and through the titania nanotube membrane is a zero-order rate of release.

Figure 1

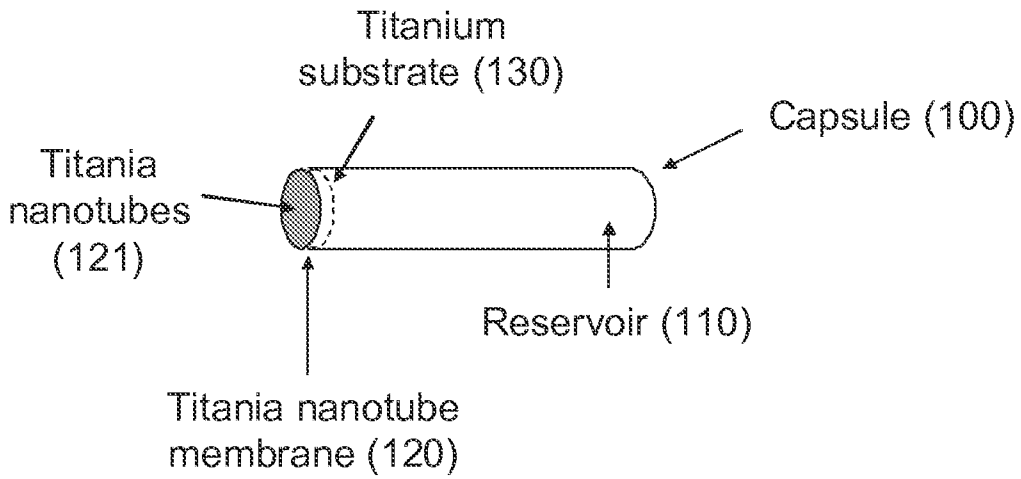


Figure 2

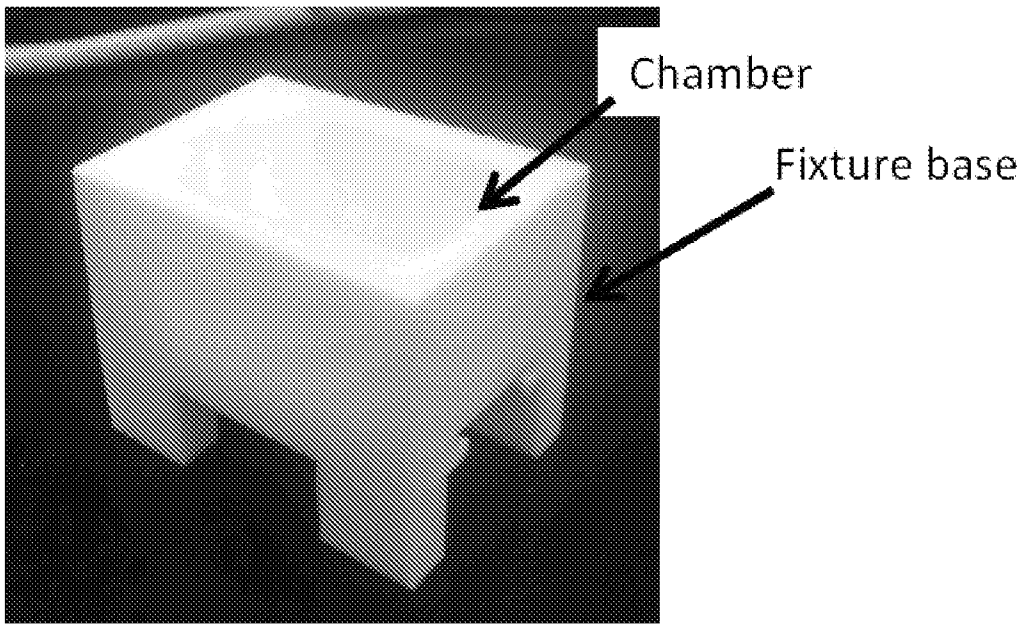


Figure 3

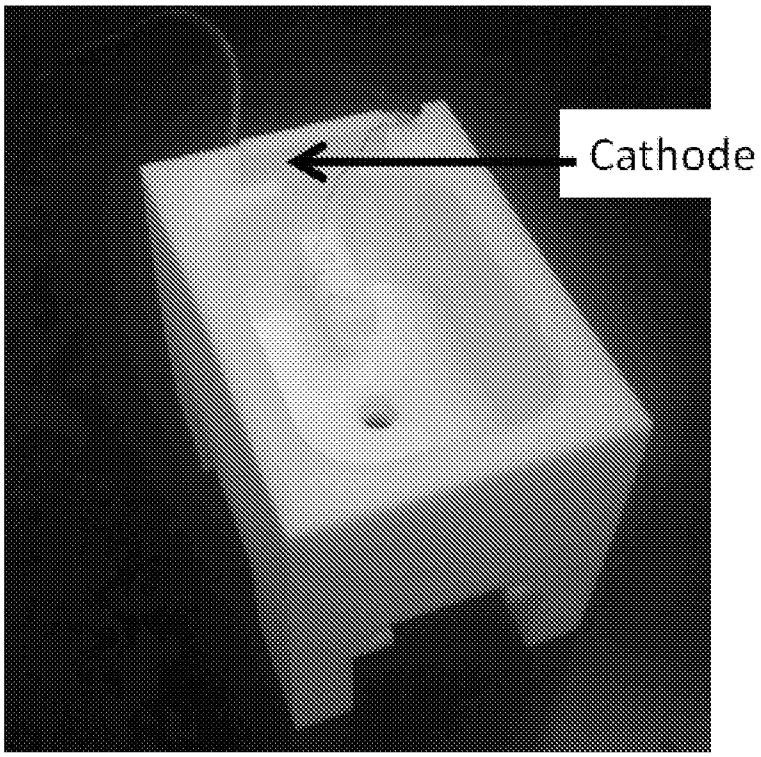


Figure 4

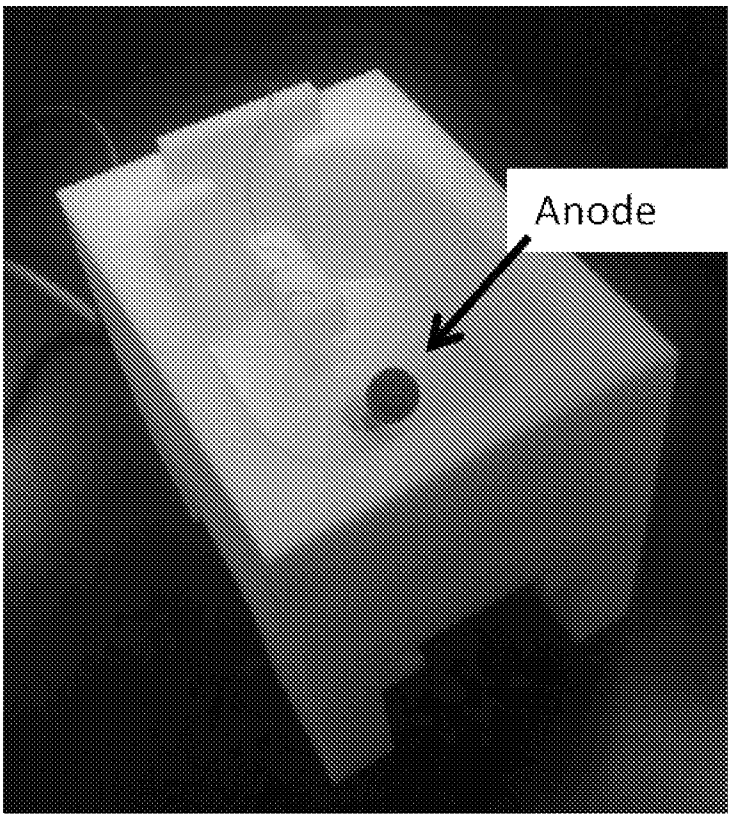


Figure 5

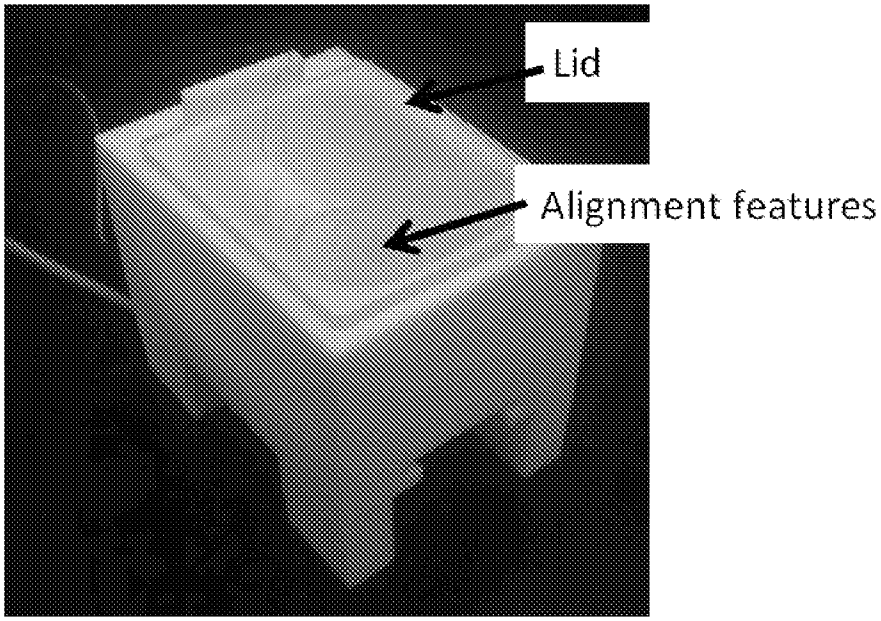


Figure 6

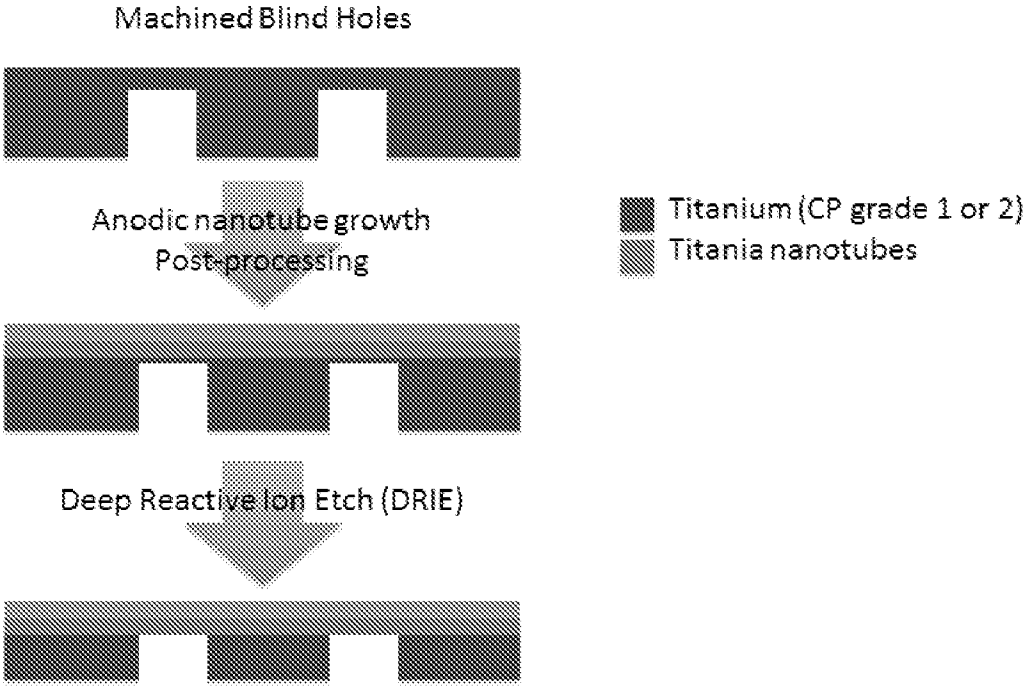


Figure 7

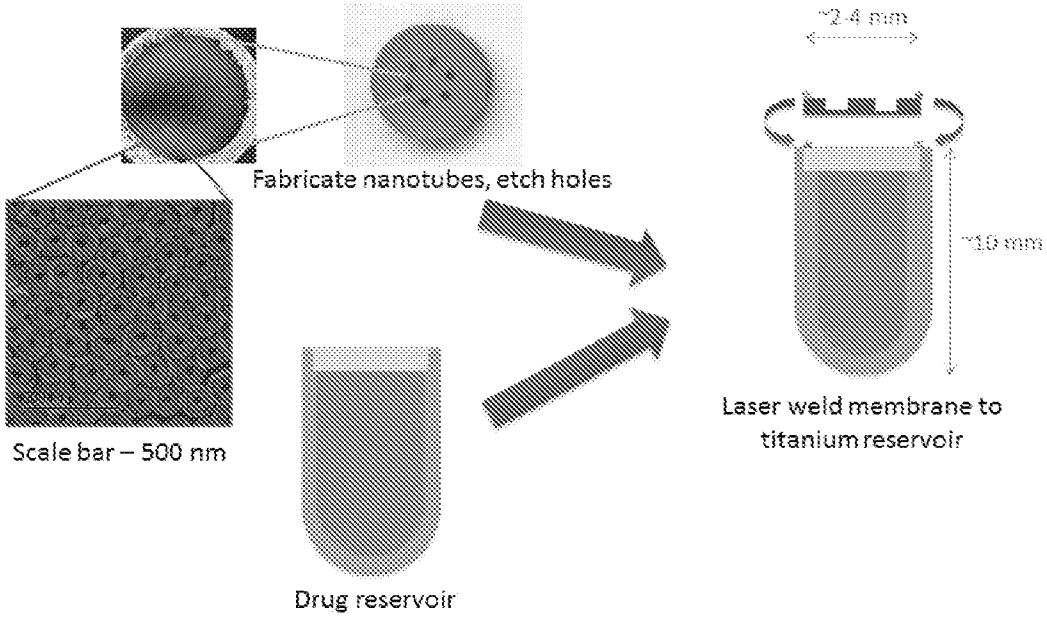
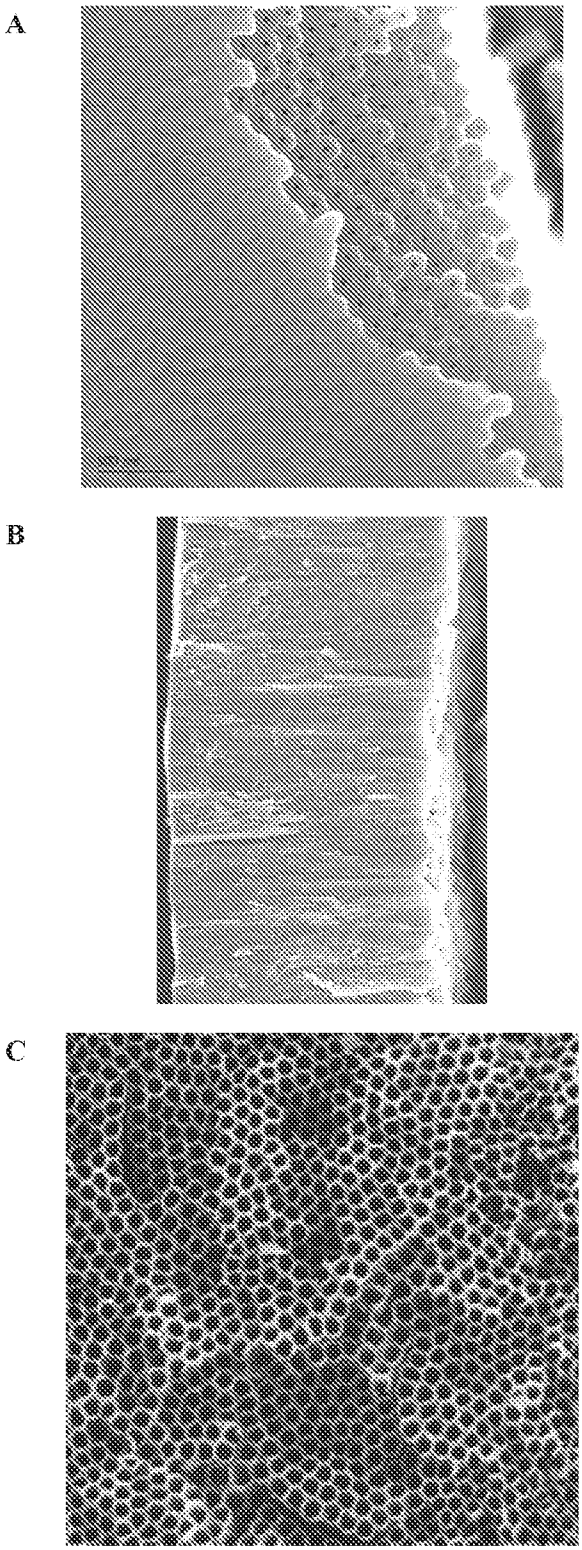


Figure 8



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/67868

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C09D 5/44 (2013.01)
USPC - 204/450; 204/492; 977/773
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)
USPC - 204/450; 204/492; 977/773

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - all classes; NPL (key word limited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; Google Scholar/Patents
Search Terms - "deep reactive ion etch", removal, substrate, titania, nanotube, Mendelsohn, Fischer, Peng, remov* w2 substrat*, titani* w2 nanotube*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X – Y	US 2010/0213046 A1 (Grimes et al.) 26 August 2010 (26.08.2010); para [0019], [0020], [0031]-[0038]; Fig. 3	15, 16 --------- 1-14, 17
Y	US 2010/0187172 A1 (Paulose et al.) 29 July 2010 (29.07.2010); para [0036], [0037], [0040], [0055], [0062]; Fig. 7b	1-14, 17

☐ Further documents are listed in the continuation of Box C.

* 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 dale
"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
18 March 2013 (18.03.2013)	**05 APR 2013**

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. **571-273-3201**	Lee W. Young **PCT Helpdesk: 571-272-4300** **PCT OSP: 571-272-7774**

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/67868

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
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:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. Ill 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:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-17, directed to a method of preparing a titania nanotube membrane, the method comprising:
growing a plurality of titania nanotubes on a first side of a titanium substrate under anodization conditions, such that a first end of each nanotube is closed and attached to the titanium substrate and a second end of each nanotube is open; and
etching the titanium substrate on the side opposite the first side, under conditions sufficient to open the first end of a first group of the titania nanotubes, thereby preparing the titania nanotube membrane.

----------See Supplemental Sheet Below----------

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

2. ☐ 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 claims 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 claims Nos.:
1-17

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/67868

Continuation of Box III- Observations where Unity is lacking

Group II: Claims 18-26, directed to a device comprising:
a capsule suitable for implantation;
a reservoir encapsulated by the capsule, wherein the reservoir is suitable for containing a therapeutic agent; and
a titania nanotube membrane on a titanium substrate, wherein the titanium substrate is attached to the capsule such that the titanium substrate is in contact with the reservoir, wherein the titania nanotube membrane comprises a plurality of titania nanotubes in fluid contact with the reservoir,
such that the plurality of titania nanotubes is the only diffusion pathway out of the reservoir for the therapeutic agent.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group II does not include the inventive concept of growing a plurality of titania nanotubes on a first side of a titanium substrate under anodization conditions, such that a first end of each nanotube is closed and attached to the titanium substrate and a second end of each nanotube is open; and
etching the titanium substrate on the side opposite the first side, under conditions sufficient to open the first end of a first group of the titania nanotubes, thereby preparing the titania nanotube membrane, as required by Group I.

Group I does not require a device comprising
a capsule suitable for implantation;
a reservoir encapsulated by the capsule, wherein the reservoir is suitable for containing a therapeutic agent; and
a titania nanotube membrane on a titanium substrate, wherein the titanium substrate is attached to the capsule such that the titanium substrate is in contact with the reservoir, wherein the titania nanotube membrane comprises a plurality of titania nanotubes in fluid contact with the reservoir,
such that the plurality of titania nanotubes is the only diffusion pathway out of the reservoir for the therapeutic agent, as required by Group II.

Groups I and II share the technical features of a titania nanotube membrane and a titanium substrate, but this is not a contribution over US 2010/0213046 A1 to Grimes et al. (26 August 2010) ('titanium substrate,' para [0046]; "membrane 30,' para [0054]; 30 Fig. 3; abstract). As these features were known at the time, as evidenced by the teaching of Grimes, they cannot be considered special technical features that would otherwise unify the groups.

Groups I and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.