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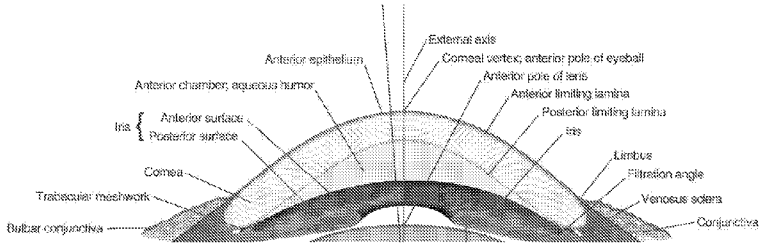
(54) Title: ANTIMICROBIAL TRANSLIMBAL DRAINAGE DEVICE WITH REPLACEABLE FILTER

FIGURE 1



(57) Abstract: This invention is in the field of medical devices and relates to artificial drainage devices and methods of use thereof. In particular, such an artificial drainage device (ADD) may utilize a translimbal and/or transcorneal approach where the device is inserted at the limbus. This device is designed to lower intra-ocular pressure, primarily associated with glaucoma or other eye conditions.

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ANTIMICROBIAL TRANSLIMBAL DRAINAGE DEVICE WITH REPLACEABLE FILTER

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. Provisional Patent Application No. 62/092,549, filed on. December 16, 2014, which is incorporated herein by reference.

STATEMENT OF GOVERNMENTAL SUPPORT

This invention was made with government support under grant number 1350436 awarded by The National Science Foundation. The government has certain rights in the invention.

FIELD OF THE INVENTION

This invention is in the field of medical devices and relates to artificial drainage devices and methods of use thereof. In particular, such an artificial drainage device is inserted at the limbus using a translimbal and/or transcorneal surgical technique. This device is designed to lower intra-ocular pressure, primarily associated with glaucoma or other eye conditions.

BACKGROUND OF THE INVENTION

The standard approach to lowering intraocular pressure (IOP) in patients suffering from glaucoma has not met with an acceptable clinical success. Glaucoma is the second leading cause of blindness worldwide and it is estimated that 70 million patients worldwide suffer from the disease. High IOP damages the optic nerve and results in vision loss. Treatment of glaucoma focuses on lowering IOP; however, a successful long-term solution remains elusive. Topical

medications have limited efficacy and suffer from poor patient adherence, while surgical strategies suffer from high morbidity and limited long-term success. For example, drainage devices lower IOP by shunting aqueous humor from the anterior chamber to another compartment outside of the eye; however, these devices are prone to eventual scarring and closure of the new drainage pathway.

What is needed is a new translimbal and/or transcorneal drainage device that overcomes the existing challenges and barriers in current drainage devices to improve clinical success.

SUMMARY OF THE INVENTION

This invention is in the field of medical devices and relates to artificial drainage devices and methods of use thereof. In particular, such an artificial drainage device (ADD) is inserted at the limbus using a translimbal and/or transcorneal surgical technique. This device is designed to lower IOP, primarily associated with glaucoma or other eye conditions. For example, the present invention relates to an aqueous drainage device and methods of its use for treatment of various medical conditions including, but not limited to, eye diseases, such as glaucoma, using minimally invasive surgical techniques. Specifically, the device may be used in conjunction with a conventional aqueous drainage device or independently as a sole aqueous drainage device.

In one embodiment, the present invention contemplates an ocular translimbal artificial drainage device comprising; i) a housing comprising: a) a cylindrical distal face-plate with a hollow inner diameter; b) a cylindrical body with a middle section and distal and proximal ends, wherein the proximal end comprises a proximal portion with fluid communication with the middle section, wherein the middle section comprises a hollow inner diameter, and wherein said the distal face plate is attached to the distal end of the body of the device; and ii) a filter with a distal and proximal end, wherein said filter at least partially fits within the inner diameter of the

body. In one embodiment, said proximal portion with fluid communication with the middle section mushroom-tipped spinneret further comprises at least two holes in fluidic communication with the inner diameter of the middle section of the cylindrical body to outside the proximal end of the body. In one embodiment, said proximal portion with fluid communication with the middle section comprises a mushroom-tipped spinneret. In one embodiment, said cylindrical body contains features enabling integration with surrounding tissue so as to form a tight seal (including mircpatterns and/or pores to guide corneal stromal cell ingrowth). In one embodiment, said outer cylindrical body may also be polymerized directly to the stromal tissue to form a water tight bond. In one embodiment, the device comprises anti-microbial properties, including anti-microbial particles. In one embodiment, said the inner diameter of the body and said filter comprise interlocking components when at body temperature. In one embodiment, said the inner diameter of the body comprises a receiving feature. In one embodiment, said filter comprises a docking feature. In one embodiment, said proximal portion further comprises at least two holes in fluid communication with the inner diameter of the middle section of the cylindrical body to outside the proximal end of the body. In one embodiment, said antimicrobial properties comprise a coating of antimicrobial particles. In one embodiment, said antimicrobial properties comprise antimicrobial agents. In one embodiment, the device comprises polymers. In one embodiment, polymers serve as a drug carrier. In one embodiment, said antimicrobial agents are on/in the polymer In one embodiment, said coating of antimicrobial particles is on said filter. In one embodiment, said antimicrobial properties comprise titanium dioxide particles embedded in said filter. In one embodiment, said antimicrobial properties comprise copper particles embedded in said filter. In one embodiment, said antimicrobial properties comprise a coating of antimicrobial particles on said housing. In one embodiment, said antimicrobial particles comprises copper particles. In one embodiment, said antimicrobial particles comprises titanium dioxide particles.

In one embodiment, said filter is replaceable. In one embodiment, said housing comprises silicone. In one embodiment, said housing comprises mechanically actuating polymers. In one embodiment, said mechanically actuating polymers comprise liquid-crystalline elastomers. In one embodiment, the housing comprises mechanically actuating polymers, as the housing is intended to be permanent, thus a shape-memory polymer that activates once could make a good candidate. .In one embodiment, said filter comprises mechanically actuating polymers. In one embodiment, said mechanically actuating polymers comprise liquid-crystalline elastomers. In one embodiment, said filter comprises an interconnected porous structure. In one embodiment, said interconnected porous structure comprises an open cellular foam structure (i.e. a bunch of holes that are connected). In one embodiment, said interconnected porous structure comprises a structure of tubular channels (i.e. such as when the fiber mesh dissolves as in Figure 16B from the LCE, fiber/tubular channels will run through the filter). In one embodiment, said interconnected porous structure comprise both an open cellular foam structure (i.e. a bunch of holes that are connected) and a structure of tubular channels (i.e. such as when the fiber mesh dissolves as in Figure 16B from the LCE, fiber/tubular channels will run through the filter). In one embodiment, said interconnected porous structure has an average pore size less than 1 micrometer. In one embodiment, said device is activated after implantation. In one embodiment, said inner diameter of the distal faceplace of the device is less than 200 micrometers. In one embodiment, the outer diameter of the distal faceplace of the device is greater than 250 micrometers. In one embodiment, said inner diameter of the body of the device is between 200-400 micrometers. In one embodiment, said length of the body of the device is at least 800 micrometers. In one embodiment, said middle section of the body of the device is tapered towards the proximal end. In one embodiment, said faceplate of the device is low profile. In one embodiment, said filter has pores with diameters less than 200 nanometers.

In one embodiment, the invention relates to an ocular translimbal and/or transcorneal artificial drainage device. The device and system described herein provides many advantages relative to devices, or implants, for the relief of ocular or glaucomal pressuret currently known in the art. 1. The modular approach with the body of the device providing a base (docking system) first placed within the eye and then the filter goes in to conform with the inner lumen providing a form fit between the filter and the lumen (water tight) and also exerting some force on the docking system to enhance conforming of the docking system to the external corneal tissues. 2. The filter is removable and tailorable. 3. Antimicrobial protection may be provide through two stages a) pores of the filter and b) antimicrobial properties of filter and docking system (coating or particles). 4. Insertion and docking of the the device parts does not require sutures due to form fitting and pushing of the docking system against the wall of the docking system which pushes on the cornea to form fit (see #1). 5. The unique form fitting LCE materials for the filter part of the device are unique developments. 6. The fiter may be made from from electrospun LCE which has antimicrobial properties (such as integration of Cu, TiO_2.etc) within the polymer and/or on its surface. 7. Translimbal implantation is the preferred implantation for this device. Translimbal implantation allows for the device to be near vessels so that scarring of the device into the cornea is possible (this keeps it stable and in place) whereas the transcorneal approach occurs in a place without vessles and thus poor scarring. Also the limbal area superiorly resides entirely under the upper lid and thus provide protection against the environment (faceplate is not exposed to air most of the time). 8. The body of the cylinder may be fused with the surrounding stroma through guided cell ingrowth and/or polymerize the outer shell to the corneal stroma. In one embodiment, the cylindrical body may contain features allowing it to integrate with surrounding tissue to form a tight seal (including surface mircopatterning and/or pores to guide corneal stromal cell ingrowth. The outer cylindrical body may also be polymerized directly to the stromal tissue to

form a water tight bond. . The materials for the device housing/docking system, which are specifically contemplated for devices of the type described herein, would be amenable to micropatterning, particularly for micropatterning on the outer surface. In one embodiment, said micropattern comprises concentric micro-ridges. In one embodiment, said micropattern comprises vertical micro-ridges. In one embodiment, the invention relates to a method comprising; a) providing; i) an ocular translimbal and/or transcorneal artificial drainage device; ii) a subject suffering from a disease state, wherein said disease has at least one symptom, wherein said subject comprises at least one eye; b) implanting said device in at least one eye of said subject; c) treating said subject with said artificial drainage device so as to alleviate said at least one symptom of said disease state. In one embodiment, said disease state comprises glaucoma. In one embodiment, said symptom is elevated intraocular pressure.

In one embodiment, the invention relates to a method of implanting the device described above comprising; a) providing; i) an ocular translimbal and/or transcorneal artificial drainage device; ii) a subject suffering from a disease state, wherein said disease has at least one symptom, wherein said subject comprises at least one eye; b) creation of a cylindrical hole of a diameter smaller than the outer diameter of the middle section of said device in said eye; c) insertion of the housing of said device into the created hole in the eye, wherein said proximal end of the device is oriented to the inside of the eye and the distal end of the device is oriented to the outside of the eye; d) cooling of the surface of the eye near the device to approximately 10°C; e) placement of a chilled filter of said device into the hollow cylindrical center of said housing of said device; and f) allow filter to expand and conform to the center of said housing.

The described features, structures, or characteristics of the invention may be combined in any suitable manner in one or more embodiments. In the following description, numerous specific details are recited to provide a thorough understanding of embodiments of the invention.

One skilled in the relevant art may recognize, however, that the invention may be practiced without one or more of the specific details, or with other methods, components, materials, and so forth. In other instances, well-known structures, materials, or operations are not shown or described in detail to avoid obscuring embodiments of the invention.

Other objects, advantages, and novel features, and further scope of applicability of the present invention will be set forth in part in the detailed description to follow, taken in conjunction with the accompanying drawings, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

DEFINITIONS

To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present invention. Terms such as “a”, “an” and “the” are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not delimit the invention, except as outlined in the claims.

As used herein, the term “patient” or “subject” refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

As used herein, the term "Prevention" or "preventing" is used throughout the specification to include: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject (e.g. patient) is cured and the disease is eradicated. Rather, the present invention also contemplates treatment that merely reduces symptoms, improves (to some degree) and/or delays disease progression. It is not intended that the present invention be limited to instances wherein a disease or affliction is cured. It is sufficient that symptoms are reduced.

As used herein "eye diseases" refers to various conditions of the eye including, but not limited to Glaucoma — optic neuropathy, Glaucoma suspect — ocular hypertension, Primary open-angle glaucoma, Primary angle-closure glaucoma, primary open angle glaucoma, normal or low tension glaucoma, pseudoexfoliation glaucoma, pigment dispersion glaucoma, angle closure glaucoma (acute, subacute, chronic), neovascular or inflammatory glaucoma, ocular hypertension, and other types of glaucoma that are related to dysregulation of intraocular pressure.

As used herein "hypotony" refers to reduced intraocular pressure. The statistical definition of hypotony is IOP less than 6.5 mmHg, which is more than three standard deviations below the mean IOP. The clinical definition of hypotony is IOP low enough to result in pathology (vision loss). The vision loss from low IOP may be caused by corneal edema, astigmatism, cystoid macular edema, maculopathy, or other condition. Hypotony maculopathy is characterized by a low IOP associated with fundus abnormalities, including chorioretinal folds,

optic nerve head edema in the acute setting, and vascular tortuosity.

The term "therapeutically effective amounts" or "pharmaceutically effective amounts", as used herein means that amount which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease or to ameliorate one or more symptoms of a disease or condition (e.g. ameliorate pain).

The term "fascia bulbi" (also known as the capsule of Ténon, the bulbar sheath, or Tenon's capsule) as used herein refers to a thin membrane that envelops the eyeball from the optic nerve to the limbus, separating it from the orbital fat and forming a socket in which it moves.

The term "tubular network", as used herein refers to a series of small tubes connected to a junction or main larger size tube. The tubular network contains egress pathways that change in caliber from large to small as the network moves away from the proximal inlet.

The term "interlocking", as used herein refers to connecting together (such as parts of a mechanism, for example) so that the individual parts affect each other in motion or operation, in particular to create a watertight connection. Examples of interlocking connects include, but are not limited to dovetail joints, tabs, flaps, slots, clips, tongue/groove, ball/receiver and/or self adhesive mechanisms and or agents.

The term "receiving features", as used herein refers to structural features that enable an interlocking watertight connection when interfaced with structural "docking features." Such connections may also be accompanied with chemical aids to enable the watertight embodiment of the connection.

The term "docking features", as used herein refers to structural features that enable an interlocking watertight connection when interfaced with structural "receiving features." Such connections may also be accompanied with chemical aids to enable the watertight embodiment of the connection.

As used herein, the term "micropatterning" preferably refers to millimeter, micrometer, and/or nanometer scale surface modifications including but not limited to laser etching, chemical etching, photo-etching, photolithography, machining, stamping, deposition processes, mechanical drilling, molding, 3D printing, Atomic Layer Deposition or other means of modifying surfaces.

As used herein, the term "antimicrobial properties" refers to an agent or agent that kills microorganisms or inhibits micrbial growth. Such antimicrobial properties include, but are not limited to antimicrobial particles, such as microparticles of copper or titanium dioxide. In other embodiments, antimicrobial properties include the incorporation of antimicrobial drugs into polymeric materials. In some embodiments, antimicrobial drugs may be slowly released from the polymeric material.

DESCRIPTION OF THE FIGURES

The accompanying figures, which are incorporated into and form a part of the specification, illustrate several embodiments of the present invention and, together with the description, serve to explain the principles of the invention. The figures are only for the purpose of illustrating a preferred embodiment of the invention and are not to be construed as limiting the invention.

Figure 1 shows the anatomy of the eye. Key areas of interest are the cornea, limbus, and anterior chamber.

Figure 2A shows an illustration of a conventionally usedEx-Press Shunt® being delivered through a scleral flap.

Figure 2B shows a conventionally used Gold Micro-Shunt®.

Figure 2C shows an illustration of a conventionally used Eyepass® implant.

Figure 2D shows the design of a conventionally used Glaukos iStent® design.

Figure 3A shows a cross-section of one embodiment of an ocular translimbal and/or transcorneal ADD **1** showing the housing section **2**. The measurements are shown in millimeters. The surface of the device is treated with Cu particles. The central porous A-LCE filter may be placed inside the hollow portion of the silicone housing and may be embedded with Cu particles. As the A-LCE filter is heated to body temperature, it expands and locks itself into place due to the shape-switching nature of the material. The housing **2** comprises a cylindrical distal face-plate **3** connected through the cylindrical body middle section **5** ending in a cylindrical body proximal end **7** which, in some embodiments comprises a mushroom-tipped spinneret **8**. The cylindrical body proximal end **7** may comprise tubular channels **12**.

Figure 3B shows a permanent silicone housing **2** with a mushroom-tipped spinneret **8** on an interior (proximal) end **7** and a flanged faceplate at a distal end **3** of an ocular translimbal and/or transcorneal ADD. The measurements are shown in millimeters.

Figure 3C shows another angled transparent view of a permanent silicone housing **2** with a mushroom-tipped spinneret **8** on an interior (proximal) end **7** with multiple holes 12 in fluidic communication with to an interior of the housing and a flanged faceplate at a distal end **3** of the housing.

Figure 3D shows a bottom view of the proximal portion with fluid communication with the middle section **5** in the shape of a mushroom-tipped spinneret **8** with a plurality of holes **12**.

Figure 4A shows a side view of a mushroom-tipped spinneret **8** interfaced with a silicone housing body **2**. The measurements are shown in millimeters.

Figure 4B shows a side view cut out of an ocular translimbal and/or transcorneal ADD indicating dimensional angles and distances. The angles of the holes **12** in the mushroom-tipped spinneret **8** of the proximal end **7** of the housing **2** are shown. The measurements are shown in

millimeters.

Figure 4C shows a bottom view of the proximal portion **7** of the device in the shape of a mushroom-tipped spinneret **8**.

Figure 4D shows another angled transparent view of a permanent silicone housing **2** with a proximal end **7** in the shape of a mushroom-tipped spinneret **8** on an interior end and a flanged faceplate at a distal end **3**.

Figure 5A shows a view of a middle section **5** of the housing **2**.

Figure 5B shows a cross-section of a middle section **5** of the housing **2**. The measurements are shown in millimeters.

Figure 5C shows an overhead view of a middle section **5** of the housing **2**.

Figure 5D shows a side view of a middle section **5** of the housing **2**.

Figure 6A shows an internal shape **9** of the housing section **2** of an ocular translimbal and/or transcorneal ADD may which may be filled with a porous A-LCE filter **10** embedded with Cu particles.

Figure 6B shows the internal dimensions of the housing **2** portion of an ocular translimbal and/or transcorneal ADD in a cross-section, measurements are shown in millimeters maywhich may be filled with a porous A-LCE filter **10** embedded with Cu particles.

Figure 6C shows a top view of an internal section of the housing portion **2** of an ocular translimbal and/or transcorneal ADD.

Figure 6D shows shows an angled view of a porous A-LCE filter **10** embedded with Cu particles.

Figure 7 shows cupping of the optic nerve after loss of neuroretinal rim from elevated IOP.

Figure 8 shows the conventionally used Ex-Press® mini-shunt (ES) implanted under a

scleral flap (SF) and is used to create a new drainage passageway.

Figure 9A-C show schematic illustrations of an ocular translimbal and/or transcorneal ADD **1**.

Figure 9A shows a silicone outer housing **2** prior to insertion into a circular incision in the cornea.

Figure 9B shows a chilled antibacterial liquid-crystalline elastomer (A-LCE) filter **10** inserted into the housing **2**.

Figure 9C shows that the filter **10** expands and locks into place into the housing **2** when heated to body temperature. The filter can recollapse for removal by chilling of the eye.

Figure 10 shows reversible shape change of an LCE material as a function of temperature. The liquid-crystalline elastomer shows reversible shape change as a function of temperature. A strip of programmed LCE is heated above its T_i and then is allowed to cool back to room temperature, exhibiting reversible shape deformation.

Figure 11 shows an illustration of how 3 phases of an LCE transition with respect to stress and temperature. Mesogens are represented as grey ovals.

Figure 12 shows an illustration of a synthesis method to create a permanently stabilized monodomain. A diacrylate mesogen (RM257), a linear spacer (EDDET), and crosslinker (PETMP) is thought to form a polydomain LCE after a Michael addition reaction using dipropyl amine (DPA) as a catalyst. Excess acrylate groups (represented as blue double bonds) can be photo-polymerized using UV light and initiator (2-hydroxyethoxy)-2-methylpropiophenone (HHMP).

Figure 13 shows how a polydomain LCE is stretched and UV cured to form a permanent monodomain. This process enabled shape switching as shown in Figure 10.

Figure 14 shows a confluent monolayer of L-929 cells after 72 hrs using MEM elution of

initial LCE material.

Figure 15 shows an illustration of an electrospinning setup. Polymer solutions are loaded into a syringe, with a metal needle connected to a power supply. A fiber mat is formed as a charged jet of solution accumulates on a grounded connector.

Figure 16A shows a porous LCE scaffold with ~400 μm pores made via salt leaching technique and imaged using micro-CT.

Figure 16B shows an SEM image of poly (vinyl acetate) electrospun mesh.

Figure 17 shows duplicate LCE specimens with electroless deposited copper outerlayer. Top sample under tensile strain of approximately 100% applied by hand. The relatively thin copper layer remains mechanically stable.

Figure 18 shows an SEM image of an LCE coated with a copper outerlayer subsequent to mechanical loading. Imaging reveals no cracking or delamination, which is expected for such a thin coating. Observed surface features are a function of the copper deposition characteristics and with the topography of the polydopamine binding layer. Figure 19 shows an illustration and photo inset of ex vivo perfusion system [1].

Figure 20 shows a SEM image of a representative area containing small-scale acrylate pillars manufactured using a soft-molding technique. Pillars are 10 μm in diameter hexagonally spaced in an extensive array.

Figure 21: (Top) Illustration of phase transition in LCEs as mesogens switch between unaligned and aligned states. (Bottom) A sample is stretched to align the mesogens into a monodomain, resulting in optical transparency.

Figure 22 shows an illustration of the two-stage, thiol-acrylate reaction. (Top) Chemical structures of diacrylate mesogen, flexible di-thiol spacer, and tetra-thiol crosslinking monomer. (Bottom) An unaligned, polydomain sample synthesized via a Michael addition reaction.

Stretching may aligns the mesogens into a monodomain, which may be secured by a photocrosslinking of excess unreacted acrylate groups (represented by red bonds).

Figure 23 shows an X-ray microtomography image of 75 vol.% porous poly(para-phenylene) with pore sizes ranging from 420-500μm. Foam structure created via particle leaching technique, similar to the material described herein.

Figure 24 shows a schematic of PVA being electrospun onto a grounded wire collector.

Figure 25 shows a 25 micron copper wire coated with PVA nanofibers after about 20 minutes of electrospinning.

Figure 26 shows a SEM image of PVA electrospun on a wire at first magnification.

Figure 27 shows a SEM image of PVA electrospun on a wire at a higher magnification than in Figure 26.

Figure 28 shows an LCE and the PVA nanofiber-coated wire combined in a tip of the pipette.

Figure 29 shows the pipette of Figure 28 shattered and the cylindrical sample of LCE with nanofibers shown.

Figure 30 shows a magnified view of a cross section of a nanoporous LCE.

LIST OF REFERENCE NUMERALS

1 artificial drainage device (ADD)

2 housing

3 cylindrical distal face-plate

4 cylindrical body

5 cylindrical body middle section

6 cylindrical bodydistal end

7 cylindrical body proximal end

8 mushroom-tipped spinneret

9 hollow inner diameter

10 filter

11 interconnected porous structure

12 tubular channels

13 coating of antimicrobial particles

DESCRIPTION OF THE INVENTION

The present invention contemplates an artificial drainage device (ADD) that utilizes a translimbal and/or transcorneal approach where the device is inserted at the limbus. This device is designed to lower IOP, primarily associated with glaucoma. For example, aqueous humor may drain from the anterior chamber of the eye, through the ADD, and to the surface of the eye to lower IOP.

Some features in various embodiments of this invention include, but are not limited to:

Antimicrobial Properties – the device (face-plate, body and filter) may contain anti-microbial properties, including, but not limited to antimicrobial particles, such as copper or titanium dioxide, to serve as an antimicrobial agent designed to kill bacteria and prevent infection of the anterior chamber of the eye.

Replaceable/Tailorable Filter – the device may be designed to have a replaceable filter to physically restrict bacteria from entering the anterior chamber as well as control the outflow of

aqueous humor.

Active Polymer Design (Mechanically Actuating Polymers) – The device body and filter may utilize mechanically actuating polymers (i.e. liquid-crystalline elastomers and/or shape-memory polymers) to aid in the deployment of the device body and/or filter.

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GENERAL DEVICE DESCRIPTION

In one embodiment, the present invention contemplates a translimbal and/or transcorneal drainage device that utilizes a material platform of antimicrobial liquid crystalline elastomers (A-LCEs). Although it is not necessary to understand the mechanism of an invention, it is 10 believed that such elastomers may overcome the existing challenges and barriers in drainage devices. It is further believed that the presently disclosed drainage device reduces IOP by directly draining aqueous humor to the tear film, bypassing the conjunctiva and tissues that commonly scar and prevent outflow. This configuration would promote ease-of-implantation, allowing surgeons to perform the procedure with minimal training. In one embodiment, the drainage 15 device includes an ALCE porous filter that has reversible shape-changing properties, which enables removal and replacement to tailor outflow and ensure long-term efficacy if the filter becomes clogged. Furthermore, the antimicrobial properties may prevent bacteria from entering the eye. This innovation could significantly alter how IOP is treated with drainage devices as well as introduce a novel, unexplored ophthalmic materials platform for future devices.

20 Artificial drainage devices are designed to transport aqueous humor from the anterior chamber of the eye to the external surface of the eye and reduce the amount of increased IOP caused by glaucoma. These devices are used in micro-invasive glaucoma surgeries (MIGS) designed to mitigate damage of the eye tissue during surgery. In one embodiment, the present invention develops a new trans-corneal drainage device designed to be inserted at the limbus and

directly transport aqueous humor to the surface of the eye. Relevant anatomical features of the eye can be seen in Figure 1.

Many ADDs are designed to increase the outflow of aqueous humor by bypassing the trabecular meshwork, which is adversely affected by glaucoma. Many ADD devices follow a similar surgical technique. For example, an incision is made in the conjunctiva to expose the sclera. Next, a scleral flap is created and a device is inserted through the anterior chamber. Once in place, the sclera and conjunctiva are sutured shut. Post-operatively, aqueous humor may drain into a bleb, which is defined by a bulge in the conjunctiva at the outlet of the device.

ADD's have a wide range of materials and designs that are currently in clinical use. The conventionally used Ex-Press® shunt is a stainless steel tube-device inserted in the scleral flap (Figure 2A). The conventionally used Gold Micro-Shunt® is a thin, plate-like device with mini-drainage tubes that is implanted into the suprachoroidal space (Figure 2B). The conventionally used Glaukos iStent® is a titanium device, which allows drainage directly into Schlemm's canal (Figure 2D). The conventionally used Eyepass® implant is made from silicon and has a Y-shaped design to facilitate the flow of aqueous humor from more than one direction (Figure 2C). These conventionally used devices all suffer from long-term complications such as bleb closure due to eventual scar tissue formation and the lack of predictable outflow.

The current invention implant develops a new approach to ADDs that overcomes the limitations of these conventionally used devices. In one embodiment, the current invention implant may be implanted through the cornea, at the edge of the limbus, to reduce any long-term complications associated with bleb formation. In one embodiment, the implant may utilize antimicrobial materials to prevent infection, while utilizing a replaceable liquid-crystalline elastomer filter designed to better tailor outflow and avoid long-term deposition of proteins on the filter.

The following description is intended describe one embodiment of the current invention implant for use as an ADD. The Design Inputs listed in the following sections may provide a guide for verification and validation activities to be conducted in support of development, regulatory approval, and commercialization.

CLINICAL INPUTS

TABLE 1: USER/PATIENT/CLINICAL CONSIDERATIONS	
Design Consideration	**Characteristic**
1. Indications for Use	This device is indicated for use in as an ADD. ADDs are indicated for patients with intraocular pressure that is too high for maintaining a healthy state of the optic nerve such as the case with primary open angle glaucoma and secondary glaucomas.
2. Brief Description of Procedure	• Cut hole with femto-second laser or other precise instrumentation • Insert docking system (ADD base) through incision and secure in place • Cool surface of the eye to 10° C • Place filter component into docking system • Allow to activate and conform to docking system • Remove any instrumentation
3. Patient Population	• Patients suffering from (or at high risk of developing) glaucomatous optic neuropathy
4. Warnings	Prior to use, read all package insert instructions and precautions. Proper implant selection should be made for size and shape limitations.
5. Precautions	User should advise patient of appropriate post-operative precautions applicable to their case
6. Environment of Use	Medical/Surgical facility
7. Medical Specialty of Clinician	Surgeon of Ophthalmology
8. Complaints, Failures, or Other Historical Data for Similar Products	• Infection • Clogging of filter element (biological fouling) • Migration of device

Design Inputs

TABLE 2: PERFORMANCE CHARACTERISTICS	
Design Consideration	**Characteristic**
1. Implantation	• The device must be delivered through a hand-held guide.
2. Activation	• The device may or may not be activated to allow for drainage immediately after implantation.
3. Filter Replacement	• The filter of the device should be collapsible and expandable via an external stimulus (i.e. temperature) to allow for easy removal and replacement as well as secure coupling with the docking unit.
4. Shape (Anterior Chamber)	• The shape of the end of the device must contain fluid outlets that are large and/or numerous, enough to prevent clogging by the iris.
5. Inner Diameter	• The inner diameter of the device should be approximately ~200-400 microns to allow for drainage of the aqueous humor. Egress of aqueous humor may be controlled by the microfilter which may have pores < 200nm in diameter.

TABLE 3: PHYSICAL CHARACTERISTICS	
Design Consideration	**Characteristic**
1. Outer Diameter	• The device must be inserted through approximately a 500 micrometer or smaller hole cut in the cornea/limbus. • Once inserted, the device must securely rest against the corneal wall of the hole without requiring sutures for fixation. • The device may integrate with surrounding stromal tissue through guided cell growth or direct polymerization of the device to the corneal stroma.
2. Length	• The device must span between the ~450 - 650 micron thickness of the cornea.
3. Shape (Corneal Side)	• The shape of the distal end of the device must be of a “low profile” and shape to avoid irritation caused by the eyelid when blinking.
4. Shape (Anterior Chamber)	• The shape of the proximal end of the device must be configured to avoid obstruction by the posterior iris.
5. Inner Diameter	• The inner diameter of the device should be approximately ~200-400 microns to allow for drainage of the aqueous humor.
6. Filter Element Porosity	• The filter element of the device may have a porosity less than 200nm to prevent

	bacteria from entering the anterior chamber along with sufficient anti-bacterial properties to kill any bacteria that invades the device.

TABLE 4: MECHANICAL CHARACTERISTICS	
Design Consideration	**Characteristic**
1. Strength	• The device must provide sufficient strength to remain securely seated in the cornea unassisted by sutures.
2. Flow Rate	• The device must provide a means to tailor flow rate in an effort to control IOP. • This can be achieved via: (a) replacing the filter or (b) adjusting the filter

TABLE 5: BIOLOGICAL CHARACTERISTICS	
Design Consideration	**Characteristic**
1. Biocompatibility	• The materials of the device must be biocompatible with the eye not to cause irritation or an adverse event.
2. Infection Prevention	The device must have safeguards to prevent infection via bacteria entering the anterior chamber via: • The device and corneal interface • The lumen of the device
3. Biofouling Prevention	The device must perform in a way to prevent adverse accumulation of proteins on the following areas of the device: • The corneal end of the device • The inner lumen of the device
4. Sterility	• The device must be capable of being sterilized without adversely affecting its intended use or biological characteristics.
5. Inner Diameter	• The inner diameter of the device should be approximately ~200-400 microns to allow for drainage of the aqueous humor.

DETAILED DESCRIPTON OF THE INVENTION

The design and research that led to the development of embodiments of the present invention challenged the standard approaches to glaucoma surgery by utilizing emerging

multi-functional materials. For example, elevated intraocular pressure (IOP) is a significant risk factor for development of glaucomatous optic neuropathy, and lowering IOP remains the cornerstone for treating patients with glaucoma. Surgical treatments such as trabeculectomy and glaucoma drainage device (GDD) implantation are invasive procedures associated with increased morbidity and high failure rates related to scarring of the artificial outflow tract over time. Therefore, there has been a clinical need to develop less invasive glaucoma surgical devices to lower IOP; however, conventionally used devices have been associated with only marginal long-term efficacy and therefore target only mild glaucomatous disease. There remains a significant need for a minimally invasive surgical procedure that has infrequent adverse events, results in predictable lowering of IOP in patients with mild to severe disease, and does not rely on outflow tracts that inevitably scar and fail over time.

Described herein is an improved approach to surgical intervention for lowing IOP that shunts fluid from the anterior chamber across the cornea and into the tear film in controlled fashion. For example, this improved treatment strategy bypasses the conjunctiva and tissues that commonly scar and prevent outflow post trabeculectomy and GDD surgery, and therefore is expected to be a more effective and longer lasting for lowering IOP. This approach also negates the need for intricate tissue dissection and suturing, allowing surgeons of all skill levels to perform the procedure in various settings around the world. The drainage device includes, but is not limited to, an antimicrobial liquid-crystal elastomer (A-LCE) porous filter that is a material platform with reversible shape-changing properties (e.g., shape memory characteristics), enabling removal and replacement to ensure long-term efficacy. Furthermore, the antimicrobial-properties may prevent pathogens from colonizing the device or surrounding tissues, and prevents breach of microbes into the anterior chamber. These antimicrobial and shape-switching properties are not possible with current materials or devices utilized for treating

ocular diseases. Merging the surgical approach that shunts aqueous into the tear film with the novel polymer platform and device design results in a device that can address glaucoma for the life cycle of the disease with robust efficacy and long-standing performance.

One embodimentof the invention is the development of a biocompatible and tailorable LCEs – This development focused on developing a suitable platform of the LCE material. Based on a two-stage Michael addition and photo-polymerization reaction, the polymer structure may be varied to create LCEs with tailored thermo-mechanical properties. Preliminary results show a cytocompatible response, which is further described in this section.

One embodiment of the invention is the development of a porous LCE filter – Utilizing electrospinning, a LCE porous filter may be created to both tailor aqueous outflow and physically prevent bacteria from crossing through the cornea (endophthalmitis). The spun fiber diameter and distribution (and subsequent porosity) is optimized via careful control of electrospinning conditions and verified using scanning electron microscopy.

One embodiment of the invention is the development of an integration of antimicrobial functionality into materials – In order to actively prevent infection, the LCE is coated with an antibacterial outer layer. Electroless deposition may be used to create a nano-scale surface layer of copper known to be inherently antimicrobial, while still maintaining the flexible shape-switching nature of the material. Ion release rate may be measured by atomic absorption spectroscopy, while wet plate bacteria cultures may assess antibacterial activity.

One embodiment of the invention is the development of a design and ex-vivo validation of a translimbal and/or transcorneal device – The design and functionality of a translimbal and/or transcorneal device is validated using an ex vivo perfusion model. Rabbit globes are pressurized to 30 mm·Hg when the devices are implanted to gauge IOP lowering efficacy. Constant flow rates are ensured via an automated syringe pump with pressure being continuously recorded

using an inline pressure gauge. This development may also correlate filter micro-architecture (porosity) to outflow rates.

One embodiment of the invention is the development of in vivo testing of device – A rabbit model may be used for in vivo testing to prove the feasibility of the translimbal and/or transcorneal drainage device. The rabbit model allows human-sized devices to be tested, and the bacterial flora of the conjunctiva contains similar microorganisms to humans. Post-implantation surveillance with slit lamp exams may be completed. Gross examination and histologic analyses may be performed on enucleated eyes.

Several embodiment of the invention are shown in Figure 3A - Figure 6D. Figure 3A shows a cross-section of one embodiment of an ocular translimbal and/or transcorneal ADD **1** showing the housing section **2**. The measurements are shown in millimeters. The surface of the device is treated with Cu particles. The central porous A-LCE filter may be placed inside the hollow portion of the silicone housing and may be embedded with Cu particles. As the A-LCE filter is heated to body temperature, it expands and locks itself into place due to the shape-switching nature of the material. The housing **2** comprises a cylindrical distal face-plate **3** connected through the cylindrical body middle section **5** ending in a cylindrical body proximal end **7** which, in some embodiments comprises a mushroom-tipped spinneret **8**. The cylindrical body proximal end **7** may comprise tubular channels **12**. Figure 3B shows a permanent silicone housing **2** with a mushroom-tipped spinneret **8** on an interior (proximal) end **7** and a flanged faceplate at a distal end **3** of an ocular translimbal and/or transcorneal ADD. The measurements are shown in millimeters.Figure 3C shows another angled transparent view of a permanent silicone housing **2** with a mushroom-tipped spinneret **8** on an interior (proximal) end **7** with multiple holes 12 in fluidic communication with to an interior of the housing and a flanged faceplate at a distal end **3** of the housing.Figure 3D shows a bottom view of the proximal portion

with fluid communication with the middle section **5** in the shape of a mushroom-tipped spinneret **8** with a plurality of holes **12**.

Figure 4A shows a side view of a mushroom-tipped spinneret **8** interfaced with a silicone housing body **2**. The measurements are shown in millimeters. Figure 4B shows a side view cut out of an ocular translimbal and/or transcorneal ADD indicating dimensional angles and distances. The angles of the holes **12** in the mushroom-tipped spinneret **8** of the proximal end **7** of the housing **2** are shown. The measurements are shown in millimeters. Figure 4C shows a bottom view of the proximal portion **7** of the device in the shape of a mushroom-tipped spinneret **8**. Figure 4D shows another angled transparent view of a permanent silicone housing **2** with a proximal end **7** in the shape of a mushroom-tipped spinneret **8** on an interior end and a flanged faceplate at a distal end **3**. Figure 5A shows a view of a middle section **5** of the housing **2**.

Figure 5B shows a cross-section of a middle section **5** of the housing **2**. The measurements are shown in millimeters. Figure 5C shows an overhead view of a middle section **5** of the housing **2**. Figure 5D shows a side view of a middle section **5** of the housing **2**.

Figure 6A shows an internal shape **9** of the housing section **2** of an ocular translimbal and/or transcorneal ADD may which may be filled with a porous A-LCE filter **10** embedded with Cu particles. Figure 6B shows the internal dimensions of the housing **2** portion of an ocular translimbal and/or transcorneal ADD in a cross-section, measurements are shown in millimeters maywhich may be filled with a porous A-LCE filter **10** embedded with Cu particles. Figure 6C shows a top view of an internal section of the housing portion **2** of an ocular translimbal and/or transcorneal ADD. Figure 6D shows shows an angled view of a porous A-LCE filter **10** embedded with Cu particles.

It is believed that this invention could significantly improve the current standard of care for the surgical treatment of glaucoma, and may also establish a fundamental understanding of an

unexplored multifunctional materials platform that would influence the design and capabilities of future surgical devices.

A. SIGNIFICANCE

Relevance of Problem

Glaucoma is a group of eye diseases that cause pathological changes in the retina and optic nerve with corresponding visual field loss and blindness if left untreated. It is estimated that approximately 2.7 million people in the United States are affected by this chronic illness. Global estimates for patients with primary open angle glaucoma and primary angle-closure glaucoma approached 60.5 million in 2010, with projections to increase to 111.8 million by 2040 [2-4]. Over 120,000 people are blind from glaucoma in the United States alone, representing 9-12% of all cases of blindness [5].

BACKGROUND ON GLAUCOMA

The aqueous humor is a transparent fluid that bathes the anterior chamber of the eye and is constantly secreted by the ciliary processes posterior to the iris. In a healthy eye, the tissue of the trabecular meshwork allows the aqueous humor to pass through and enter Schlemm's canal, which then empties into aqueous collector channels in the anterior wall of Schlemm's canal and finally into aqueous veins. The pressure of the eye is determined by a balance between the production of aqueous humor and its outflow facility through the trabecular meshwork and the inner wall of Schlemm's canal. In most types of glaucoma, the eye's drainage system becomes dysfunctional and outflow facility decreases, resulting in increased IOP. High eye pressure is a major risk factor that leads to retinal ganglion cell death, which results in glaucomatous optic

neuropathy and loss of vision (Figure 7).

Glaucoma Treatment Approaches

The treatment of glaucoma is focused on the reduction of IOP, which has been linked to preventing and slowing the formation and progression of visual field loss in patients suffering from glaucoma or ocular hypertension [6, 7]. High IOP is the only modifiable risk factor for glaucoma. A variety of options are available to lower IOP including topical eye drops, laser procedures, and surgery. While current interventions attempt to stabilize or reduce IOP, a long-term safe and predictable approach for permanently reducing IOP at all stages of glaucoma remains elusive.

Topical ocular medications are the most common initial form of treatment, with US glaucoma pharmaceutical revenues of $1.8 billion in 2008 [8]. However, topical therapy has several challenges: First, various topical drug therapies for glaucoma are associated with significant side effects, such as foreign body sensation, dry eye syndrome, blurred vision, allergic reactions, and even respiratory and/or cardiovascular complications [9-11]. Second, adherence to prescribed therapeutic regimens is poor with a up to 59% of patients failing to take their drops routinely [12-14], especially in elderly patients due to forgetfulness and physical limitations [15, 16]. Unfortunately, medications fail to control glaucoma in a significant number of patients and escalation of therapy to more invasive laser or surgery is required.

Laser trabeculoplasty (LT) induces thermal treatment focused on the trabecular meshwork resulting in remodeling of extracellular matrix and enhancing outflow facility. While LT is a common procedure, it has limited efficacy in more advanced disease and requires retreatment with loss of benefit in subsequent applications.[17, 18] Challenges with this procedure include inflammation, spikes in IOP, high cost of equipment, necessary high degree of skill with some

forms of LT, and the potential for adjacent tissue damage from the laser [19, 20]. Once patients have failed medical therapy and laser, invasive surgical intervention is often recommended which poses unique challenges to both the patient and physician.

Surgical treatments for glaucoma decrease IOP in patients by creating avenues for fluid egress that bypass the diseased trabecular meshwork. Surgery treatments include but are not limited to the following: Trabeculectomy is the gold standard for invasive surgical treatment for glaucoma that involves dissection of the conjunctiva, creation of a scleral flap, and opening a channel into the anterior chamber to bypass the diseased trabecular meshwork. Approximately 24,000 trabeculectomies are performed on Medicare patients every year in the United States [21]. The high morbidity of this procedure limits the number surgical interventions performed. The current morbidity associated with trabeculectomy in the acute postoperative phase includes choroidal effusion in 13%, shallow anterior chambers in 10%, wound leaks in 11%, anterior chamber bleeding in 8%, among other adverse events. With chronic follow up, complications include corneal edema (9%), dysesthesia (ocular discomfort) in 8%, fluid leaks in 6% and endophthalmitis (serious eye infection) in 5% [22]. These procedures are considered amongst the most invasive of ocular surgeries and are also challenged with high degree of failure, up 46.9% failing at five years, resulting in the need for repeated filtration surgery that also has a high rate of failure with associated morbidities[22, 23]. Furthermore, these techniques inherently hinge upon a high degree of skill in microsurgery [24, 25].

Glaucoma Drainage Devices (GDDs) or aqueous shunting implants are devices that are surgically attached to the eye's outer scleral wall and connected to a silicone tube that is inserted into the anterior chamber to shunt fluid to the subconjunctival/ sub-Tenon space. Some devices, like the ExPRESS® glaucoma filtration device, allow fluid drainage after being placed under a scleral flap. This leads to aqueous humor drainage from the eye into a fluid pocket termed a bleb

(Figure 8). Complications from these implants include excessive outflow of fluid (e.g., hypotony), failure to lower IOP, improper implant position causing double vision or pressure on the optic nerve, bleb infection, and sclera tissue erosion with device exposure [26]. In the Trabeculectomy vs. Tube (TVT) 5-year follow up report, 21% of patients implanted with a glaucoma drainage device experienced early postoperative complications. Later stage complications occurred in 34% of patients [22]. The overall failure rate of glaucoma drainage devices was noted to be ~30% in the TVT 5-year follow up study [23]. One major limiting factor for GDDs is that they each take up significant conjunctival space post implantation and surgeons are limited to typically two GDD surgeries (maximum of four). Once GDD surgery fails, patients often undergo laser treatment (known as cyclophotocoagulation) known to cause thermal damage to the ciliary processes, which decreases aqueous humor production leading to significant collateral tissue damage and frequently decline or loss of vision.

Minimally invasive glaucoma surgery (MIGS) implants were introduced to provide IOP lowering surgical interventions while minimizing complications associated with other procedures such as filtration surgery. An example of a MIGS device is the iStent® (Glaukos). iStent lowers the eye pressure by creating a permanent opening in the trabecular meshwork. Limitations of the iStent include only moderate lowering of IOP and unpredictability of the IOP lowering efficacy between patients. Complications for iStent include temporary IOP spike, corneal edema, stent obstruction by blood clot or iris, anterior chamber collapse, and vitreous incarceration [27]. Other MIGS implants not yet widely available include Hydrus™ Microstent (Ivantis), CyPass Micro-Stent® (Transcend Medical), Xen (AqueSys). Similar to iStent, the Hydrus™ Microstent is inserted into Schlemm's canal ab interno, bypassing trabecular meshwork to shunt fluid. The Cypass provides aqueous drainage into suprachoroidal, and the Xen implant is inserted into the subconjuctival space through the trabecular angle to drain the fluid [28]. All of these devices

shunt fluid from one compartment to another; therefore, are susceptible to failure due to scarring from fibroblast invasion. More importantly, all MIGS devices, while possessing enhanced safety profiles, lack the IOP lowering efficacy of filtration surgery and are only used in mild glaucoma.

It should be noted that there are forms of glaucoma that are not amenable to the current surgical treatments available. For example, patients undergoing corneal prosthetic implantation, for example Boston type 1 keratoprosthesis (KPRO) surgery, often develop glaucoma (~30%) due to excessive scarring of the aqueous outflow system [29]. Trabeculectomies and GDDs often fail in these patients due to excessive scarring and poor ability to monitor disease progression (level of IOP and optic nerve status) secondary to the corneal prosthetic hardware interference with examination techniques. The KPRO device is bulky and limits the view to the inside of the eye. Measuring pressure relies on indentation of the natural cornea that is removed at time of KPRO implantation. Such cases would benefit greatly from an intervention that would result in predictable aqueous outflow that can be directly incorporated into the corneal prosthetic hardware.

Previous Attempts at Transcorneal Drainage

Currently, transcorneal drainage devices have not been rigorously explored for glaucoma intervention and as a result no transcorneal drainage devices exist in the market. A past attempt at this approach by Becton Dickenson utilized circular devices inserted into non-circular incisions, that did not allow for watertight closure of the incision [30]. This resulted in poor device performance and the project was abandoned. The main benefit of using a transcorneal device is that it reduces IOP by shunting fluid directly to the tear film bypassing tissues that may scar and prevent the aqueous outflow. Because there are no barriers to outflow, filtration rate can be tailored to the patients needs and, in essence, a programmed and predictable IOP is possible.

There are other advantages with this approach such as avoiding complicated implantation methods, lack of intensive training to acquire implantation skills, fabricating tailorable devices to various fluid flow requirements to "dial in" the desired intraocular pressure as disease state changes over time, and preserving the conjunctiva for more invasive surgery (trabeculectomy and glaucoma drainage device implants) if needed in the future. The approach used in the current invention would apply to all glaucoma disease states from mild to severe and would be uniquely positioned to treat patients who currently have few options such as those with KPRO implants or previously failed surgery in which further conjunctival manipulation is unlikely to succeed due to extensive scar formation.

B. Proposed Solution

Although it is not necessary to understand the mechanism of an invention, it is believed that an improved translimbal and/or transcorneal approach can overcome the existing challenges and limitations of current surgical methods as described above. To achieve this, a unique drainage device has been developed that incorporates a multi-functional materials platform based on antibacterial liquid-crystalline elastomers (A-LCEs) that has not previously been explored. Currently no other GDDs attempt transcorneal drainage. This is in large part because of a perceived increased risk of infection. The approach is unique because the device may incorporate antibacterial properties inherent to the material system. The LCE device may be manufactured to be an interconnected porous construct with pore sizes smaller than most bacteria. Furthermore, the A-LCE device may be coated via electroless deposition by a thin copper layer, which is well established to have a wide range of antimicrobial properties. If successful, this invnetion's outcomes would significantly alter and advance how glaucoma is treated as well as introduce and validate a new functional materials platform for future implant devices.

Description of Approach and Device

In one embodiment, the present invention contemplates a method comprising allowing drainage of aqueous humor directly through the cornea and into the tear film. Some advantages of draining into the tear film are that it allows for a significant and tailorable decrease in IOP (i.e., there is no downstream resistance to limit the IOP lowering floor), while not being influenced by scarring from surrounding tissues. Both pressure differential and scarring hinder the efficacy of procedures such as trabeculectomy and GDDs, which rely on drainage of fluid into subconjunctival fluid pockets (blebs).

The approach and device are designed to reduce both morbidity and technical skill required for implantation. First, a circular tissue punch may be used initially to form a precise cylindrical hole in the cornea, although ultimately femtosecond lasers can be utilized to customize the corneal incisions for implantation. A permanent, silicone implant may then be placed inside this hole (Figure 9a). This permanent silicone housing may held into place by a mushroom-tipped spinneret on the interior (proximal) end and a flanged faceplate at the distal end. This housing may be slightly oversized compared to the corneal hole, which may create a press-fit and watertight seal with the corneal stroma due to the elastomeric nature of the silicone. Next, a chilled, porous A-LCE filter may be placed inside the hollow portion of the silicone housing (Figure 9b). As the A-LCE filter is heated to body temperature, it may expand and lock itself into place due to the shape-switching nature of the material (Figure 9c).

This method of implantation allows for direct access to the site (no other commercially available GDD is accessible) without the need for cutting or suturing. As a result, this may reduce the amount of training needed for surgeons. Furthermore, this approach preserves the conjunctiva for more invasive surgery, such as a trabeculectomy, if needed in the future. Overall,

patients with advanced stage glaucoma and/or patients who are not well suited for medication or laser treatment would most greatly benefit from this approach. It may be particularly beneficial for patients who have conjunctival scarring due to trauma or other causes such as previous surgical glaucoma procedures.

Replaceable and Tailorable LCE Filter

In one embodiment, the present invention contemplates an ocular translimbal and/or transcorneal ADD comprising a liquid-crystalline elastomer (LCE) filter placed inside a permanent silicone housing. LCEs are a class of shape memory materials that can repeatedly and reversibly change shape as a function of temperature. For example, LCEs can apply stresses and/or induce strain-related shape changes up to 400% in response to heat (e.g., for example, direct conduction, electroresistive heating, laser heating) [31, 32] or light (cis-trans photosensitization) [33, 34]. An LCE may lift and lower (e.g., contract and expand) in response to temperature changes. Figure 10.

In one method of using the invention, the LCE filter may be initially removed from chilled saline and placed into position. It may then be flushed with body-temperature saline and allowed to expand into place in several seconds, thus being fixated by a pressure fit. The use of an LCE filter is an innovative solution that allows for ease of removal, in which the filter can recollapse by simply chilling the eye when needed. For example, if the device becomes clogged with organic material, flushing the eye with chilled saline and physically removing and replacing the LCE filter can occur. As the device can be accessed on the corneal surface, the procedure of replacing the filter is noninvasive. Using a replaceable filter design may also help contribute to the long-term efficacy of the device. Although it is not necessary to understand the mechanism of an invention, it is believed that the taper of the distal end in both the filter and the silicone

housing may firmly confine the filter during use.

Currently, there is no accurate method of predicting the rate of drainage of aqueous humor using any GDD; however, by utilizing a filter that can be replaced in a non-invasive procedure, surgeons may have the option to adjust the rate of drainage by selecting different filter designs. Drainage may be accomplished by manufacturing an LCE to be an inter-connected porous structure via electrospinning. The microarchitecture of the porous structure can be controlled during manufacturing to influence the rate of drainage (i.e., a less dense LCE filter with larger pore volume fraction would increase the rate of drainage). This approach overcomes the unknown patient-specific response to a drainage device by allowing the surgeon to adjust the filter and flow-rate throughout treatment, and can be performed at any time, as the filter is readily removable.

Antibacterial Behavior

It is inherently advantageous to have aqueous humor continuously flowing out of a translimbal and/or transcorneal device, implicitly limiting inflow of any foreign bodies; however, in order to actively prevent infection, the LCE may be coated with a small copper layer via electroless deposition. Copper is well established as a naturally antibacterial material. It has been used as a method to purify and store water, and it has demonstrated biocidal properties against a variety of organisms, from bacteria and protozoa to fungi and even malignant aquatic animal species [35]. Coating an LCE can be accomplished via electroless deposition previously described by Lee et al. [36]. Preliminary results show a successfully coated LCE with a copper exterior that remains stable and intact even with the large reversible strains associated with the A-LCE. The active mechanism for copper's antibacterial properties is directly related to ion release rate, which is measured via atomic absorption spectroscopy (AAS) of a 1 cm^2 ALCE

sample to be 100 ppb per hour, which is not expected to cause an adverse reaction in human tissue.

In addition to a copper coating, an LCE filter may be fabricated to be an interconnected porous structure, with average pore size below 1 μm. The inherent advantage is that most bacteria range in size from approximately 1-10 μm. To achieve this porous construct, an electrospinning technique may be employed. Electrospinning is a widely used technique where, under the influence of an electric field, a charged jet of liquid polymer solution forms continuously. Most often the polymer is dissolved in a solvent and is pulled from a syringe. The charged jet is stretched to form continuous fibers on the metal collector as solvent evaporation occurs before the charged jet has reached the collector. The manufacturing method involves casting the LCE over a sacrificial electrospun mesh allowing precise control of flow.

Permanent Silicone Housing

In one embodiment, the present invention contemplates an ocular translimbal and/or transcorneal ADD comprising a permanent silicone housing designed to maximize biocompatibility, stability and functionality. For example, silicone (e.g., Nusil®) may be used due to its long track record of safety and biocompatiblity in and around the eye. The design dimensions, were chosen so that the external wall would bridge the thickness of the peripheral cornea/limbus while allowing for an external faceplate to facilitate positioning and access to the filter for insertion and removal as needed. The external portion of a device as disclosed herein may be located adjacent to the superior limbus to achieve maximum coverage and protection from the upper lid post implantation, and the small footprint may minimize any induced astigmatism post implantation. The inner most portion of the positioning unit is designed to maximize functionality of aqueous outflow through a LCE filter and towards the tear film at the faceplate. An inner aqueous facing surface of the device includes a series of holes to allow for

multiple points of aqueous egress. This may minimize the occurrence of early flow occlusion of inflammatory cells or red blood cells and fibrin that may accumulate on the surface of the device during the acute postoperative phase. Such a design is an improvement over current GDDs, which only have one large opening in the silicone tube that can be clogged under similar circumstances. The invention design may also minimize the possibility of complete occlusion of the outflow pathway if engaged by the iris post device implantation.

C. APPROACH

Section 1:

Develop a tailorable and biocompatible LCE materials platform. One of the main advantages to the current design approach is using an active material that inherently increases device functionality. LCEs are a class a shape memory materials known for their mechanical and optical functionality [37]. For example, Figure 10 demonstrated an LCE built from base constituents that is capable of contracting and expanding over 100% of its original length with respect to a relatively narrow change in temperature. In one embodiment, the present invention takes advantage of a shape-switching effect in LCEs to create a translimbal and/or transcorneal device with a removable filter to tailor the outflow of aqueous humor and prevent clogging of proteins to ensure long-term efficacy. This initial section is designed to tailor the transition temperature of the LCE within body temperature and surgical conditions, as well as establish the necessary biocompatibility data for the material.

BACKGROUND AND PRELIMINARY WORK

LCEs combine aspects of thermoset elastomers (rubber elasticity) with liquid crystals

(self assembly) [38]. As an elastomer, LCEs have many mechanical properties similar to existing ophthalmic materials such as silicone and acrylate hydrogels, with elastic modulus values ranging from 0.5 – 10 megapascals (MPa). The liquid crystal phase of the material enables unique functionality, which is determined by the arrangement of mesogens within the polymer chains. Mesogens typically are defined as a rigid rod-like unit within the polymer that includes at least 3 directly linked benzene rings, which self assemble into a soft crystalline arrangement.

The arrangement of mesogens can determine a liquid crystal phase of the LCE material. Figure 11 illustrates three potential phases and how they relate to mechanical and optical functionality. Most LCEs are synthesized into a polydomain phase, which includes randomly oriented crystal domains [39]. If heated above an isotropic transition temperature (T_i), a polydomain sample may lose its arrangement (isotropic) and become transparent; however, if a polydomain sample is stretched, the crystals may align in the stretched direction to form a transparent single crystal (monodomain). The phenomenon of reversible shape switching occurs when a monodomain sample is heated and cooled around T_i.

Recently, LCEs have been reported with an unprecedented amount of control and scalability [40]. This technique uses a two stage reaction involving an acrylate mesogen, thiol spacer, and thiol crosslinker (Figure 12). Initially, a Michael-addition reaction may form a polydomain LCE, which is resistant to oxygen inhibition and can be simply mixed and poured into a mold. If an excess of acrylate groups exists after the first reaction is completed, a second photo-crosslinking reaction can be used to stabilize a monodomain in stretched samples (Figure 13). Once a stable monodomain is achieved, the LCE is capable of the shape-switching effect. The utility of this reaction is that the thermomechanical properties (modulus and T_i) can be controlled by varying the type and amount of each monomer. One advantage of this process is that the Michael addition reaction allows for facile manipulation of the final shape of the

polymer during manufacturing.

Tailor transition temperature (T_i) to match surgical conditions

In one embodiment, the present invention contemplates a translimbal and/or transcorneal device that takes advantage of the shape-switching nature of LCEs to create an easily replaceable filter. This would involve chilling an LCE device to approximately 10°C to easily place or remove a filter in a contracted state, then allowing the material to reheat to 37°C to expand and lock into place. It is hypothesized that the transition temperature, T_i, of the LCE can be tailored within these surgical conditions by controlling the mesogen and/or polymer structure.

Several methods may be employed to measure the influence of polymer structure on T_i. First, the ratio of thiol crosslinker to thiol spacer may be systematically varied. Based on preliminary evidence, increasing the crosslinker-spacer ratio from 0.2:0.8 to 0.8:0.2 decreased T*i* significantly. The second method is to vary the length of the spacer and functionality of the crosslinker. It should be noted that a wide variety of di-thiol spacers and multi-functional thiol crosslinkers can be purchased from chemical suppliers (e.g., Sigma Aldrich, etc.). Prior work has shown both crosslinker and spacer geometry were able to tailor T_i between 0°C and 100°C in siloxane-based LCE systems [41-43].

The transition temperature, T_i, may be measured using differential scanning calorimetry (DSC). This technique is used to identify thermal transitions, such as phase changes in LCEs [44], by measuring heat flow as a function of temperature. Approximately 10 mg of each material synthesized may be heated from -50°C to 150°C at a rate of 10°C/min to measure the T_i of each network to characterize the influence of polymer chemistry and structure.

Shape switching may be measured using a thermal mechanical analyzer. This technique may record shape change as a function of heating and cooling and may be used to demonstrate

feasibility within surgical conditions. Rectangular strips of monodomain LCEs may be clamped using tensile grips under zero stress and heated and cooled between 10 and 36°C at a rate of 3°C/min for five consecutive cycles. This test may validate and quantify the amount of reversible shape change achievable within surgical conditions.

Verify the potential for biocompatibility of the materials platform

An LCE material platform can undergo a high degree of scrutiny to demonstrate biocompatibility. One common measure of potential risk in any new material's FDA Master File is to undergo leachables/extractables analysis. Materials with tailored transition temperature (T_i) to match surgical conditions previously described may be tested for gel fraction using an organic solvent (i.e. acetone). Samples may be soaked for 1 week and dried. The gel fraction may be calculated as:

$$Gel\ Fraction = M_f/M_i \bullet 100 \qquad \textbf{(Equation 1)}$$

where M_i and M_f are the initial and final weights of the sample, respectively. Gel fractions above 95% generally demonstrate good conversion of the monomers to polymeric material. Next, the solvents may undergo Fourier transform infrared (FTIR) analysis to check for unreacted monomers that were leached from the polymer. Acrylate and thiol monomers may exhibit peaks at 6175 and 2575 cm^{-1}, respectively [45-48].

Next, cytocompatibility testing may be performed on selected material systems with appropriate T_i values. Elution and direct-contact testing may be performed by an independent laboratory, AppTec (St. Paul, MN), to characterize the risk of cytotoxicity of the materials. These materials assess the cytotoxic response of L-929 mouse fibroblast cells in contact with the material or extract of the material over a minimum of 24 hours. These tests are not an absolute measure of biocompatibility; however, are commonly used as an initial measure of risk, and are

required in any set of ISO-10993 tests [49]. Preliminary tests on initial materials have been successful (Figure 14).

Expected Outcomes

Successful completion of the goals of this section may result in a fundamental understanding of how to control the isotropic transition temperature, T_i, and shape switching behavior of cytocompatible LCE materials as a function of polymer structure. Based on previous experience in tailoring a transition temperature of shape-memory polymers [46, 50], it is expected that there may be a range of material chemistries that may be appropriate to work with clinical conditions. Furthermore, this range of polymer chemistries should demonstrate near complete conversion of the monomers and help promote a cytocompatible response. Previous studies on the reaction kinetics of thiol-acrylate systems have shown near 100% conversion of the monomers [48]. Lastly, acrylate-based polymers (PMMA and 2-HEMA) have a relatively good history as ophthalmic materials.

Section 2: Develop a porous LCE Filter

Rationale

A replaceable LCE filter as contemplated herein should have an interconnected porous design such that aqueous humor can drain at an appropriate rate. A reasonable drainage rate appropriate for most patients has been estimated to be approximately 1 μL/min; however, because of patient-specific differences, a single filter design would not be applicable for all patients. A range of patient specific flow rates would be ideal, however, is not possible for any other commercially available GDDs.

Furthermore, due to the nature of translimbal and/or transcorneal drainage, a filter may have a pore size below 1 μm in order to prevent bacteria from entering the anterior chamber of the eye. Approach Electrospinning may be used in order to achieve such small porosities within the filter.

Electrospinning has two inherent advantages: (1) It is a well-established technique often used for creating micron-sized porosity and (2) the size and distribution of the electrospun fibers can be controlled to tailor porosity [51]. Electrospinning is a widely used technique to fabricate nanofibers from thermoplastic polymer solutions [52]. Figure 15 shows a diagram of this process. Under the influence of an electric field, electrostatic charges build up on the surface of the liquid meniscus pumped from the needle tip and a charged jet forms continuously. Then the charged jet is stretched to form continuous fibers on the metal collector, the Rayleigh instability being suppressed by solvent evaporation that occurs before the charged jet has reached the collector. Polymer solutions appropriate for electrospinning can be prepared by dissolving nearly any thermoplastic polymer in its respective solvent and then tuning concentration [53].

Porous LCE filter materials may be designed using an electrospun mesh composite, similar to a technique pioneered by the Mather lab [54, 55]. First, an electrospun fiber mesh may be created from either polyvinyl acetate (PVA) or polycaprolactone (PCL). Next, an LCE monomer solution may be poured around the mesh and allowed to polymerize. What makes this apporach unique is that the electrospun mesh may then be dissolved from the surrounding LCE material, leaving behind a porous architecture in the LCE. The electrospinning conditions (such as syringe pump rate, voltage, and collector distance) may be tuned to create meshes of varying fiber size and distribution. Characterization of the mesh filters may be achieved by scanning electron microscopy (SEM) to link test conditions to mesh properties.

PRELIMINARY WORK

Manufactured and characterized porous polymeric materials (using both SEM and micro-CT) have been previously reported [56, 57]. Figure 16a shows a porous LCE manufactured using the described material system polymerized around salt particles, which were leached similar to approach in this section. The manufacturing may also involve electrospinning (Figure 16b) and polymerizing composites around electrospun meshes.

Expected Outcomes

Successful completion of one embodiment of the invention may link electrospinning conditions with mesh properties to create filters with tailored outflow, which may be a function of fiber size, distribution, and porosity. LCE filters may be combined with shape switching materials..

Section 3: Develop an antibacterial LCE

Rationale and Background

It is hypothesed that coating a porous LCE with a thin layer of copper may result in an antibacterial device. Copper is well-established as a naturally antimicrobial for a wide range of microorganisms [58]. There are three main mechanisms by which copper is suggested to kill bacteria: damage to the cell membrane, DNA degradation, and intracellular damage [35, 59-62]. Experiments have been performed on a wide variety of different species—both micro and macro—to determine the lethality of copper [35]. Copper has been shown to have biocidal effect on a wide variety of bacterial species, including *E. coli*, *Listeria monocytogenes*, and *Staphylococcus aureus*, among others. Humans and other terrestrial animals have a much higher tolerance for copper than other life forms, and copper is considered a vital nutrient for human health. As of March 2008, the EPA has approved registration of copper alloys as antimicrobial

materials, making it the first solid surface material to receive this type of recognition by the EPA.

Experimental Approach

A layer of adherent polydopamine may be deposited onto LCE samples as a final step by submerging samples in a dilute aqueous solution of dopamine, buffered to a pH typical of marine environments, for example resulting in a spontaneous deposition of a thin adherent polymer film [34]. Film thickness is expected to be a function of immersion time, with values of approximately 50 nm measured after 24 hours exposure. The polydopamine layer was shown to form on an eclectic group of materials, including wide variety of polymers. Ultimately, the polydopamine may covalently bond with the copper via a catechol group, and may therefore serve as a strong binding agent between the LCE substrate and copper plating. Copper may be deposited onto the polydopamine layer by electroless deposition. Samples suspended in a continuously stirred copper(II) chloride solution may form a copper layer with a thickness directly related to the immersion time.

Preliminary Results

Using test LCE samples described in Section 1 and the electroless deposition outlined by Lee et al.[36], LCEs were fabricated and successfully coated with copper outer-layers of varying thicknesses, ranging from hundreds of nanometers to tens of microns. Briefly described, LCE samples were exposed to a buffer solution for 24 hours to deposit the polydopamine layer. This solution was prepared by dissolving 0.01 M trizma hydrochloride in deionized water, adjusting the pH to 8.8 with sodium hydroxide, and then dissolving in 2 mg/mL polydopamine. Samples were then rinsed with deionized water and air-dried. The copper plating solution was synthesized by dissolving 0.05 M ethylenediaminetetraacetic acid, 0.05 M copper (II) chloride, and 0.10 M

boric acid in deionized water and adjusting the pH to 7.0 with sodium hydroxide. Polydopamine coated LCE samples were suspended in the continuously stirred plating solution for various times ranging from 1 to 4 hours, resulting in the copper-coated LCEs of increasing thicknesses.

Figure 17 demonstrates a rectangular LCE coated with a copper outer-layer under a tensile strain of approximately 100%. With the assistance of the polydopamine adhesive layer, the copper layer remains mechanically stable even at these large strains. Imaging of stretched copper-coated LCEs via scanning electron microscopy (SEM) confirms that no cracking or delamination of the copper occurred, as shown in Figure 18. Interestingly, the solution deposited copper layer forms surface features; similar features in electroplated copper, has been shown to enhance its biocidal effectiveness [63].

Robust methodology for copper layer deposition

Although proof-of-concept copper deposition has been shown, systematic studies may be performed in order to fully understand and optimize the process. Ultimately, one enbodiment of the device of the current invention comprises a semiuniform layer coated over a porous sample. It is expected that variation of submersion time, pH balance, and stirring rate may result in a well-controlled polydopamine and copper layers. Quality and topography of the sample surfaces can be measured directly with a SEM equipped with energy dispersive x-ray spectrometer (EDS) and confocal laser scanning microscopy. Such measurements may be performed prior and subsequent to mechanical testing via tensile loading in order to confirm the coating may not delaminate or fracture.

Demonstrating antimicrobial behavior and safety

The methodology chosen for evaluating antibacterial behavior may be consistent with

that described by Zeiger et al. [63] to facilitate direct comparison with previous studies. Initial characterization can be estimated by copper ion release rate in solution, as ionization is considered the mechanism for its antimicrobial behavior. The copper release rate may be measured by atomic absorption spectroscopy (AAS) of solution in contact with the specimens over systematically increasing times. Preliminary results of the A-LCEs (e.g., Figure 17 & Figure 18) show for a cm^2 area, 100 ppb copper ion release rate per hour; well below what might be considered harmful to the eye. Once ion elution is established, direct antibacterial activity of the copper-coated LCEs may be tested with a wet plating method [64]. This method essentially involves growing bacteria in a culture (specifically *Streptococcal species*, *Staphylococcus aureus* and epidermidis, diptheroids, *Propionibacterium acnes*, and *Escherichia coli* which are typical human conjunctival and skin flora) immediately prior to depositing it on the test coupons and incubating at room temperature [65]. After systematically increasing contact times, 20 μL of the droplets may be removed and assessed via microscopy.

Expected Outcomes, Potential Problems, and Alternate Strategies

Preliminary results strongly indicate that the electroless copper deposition may be successful because copper is known as comprising antimicrobial properties. Results show that the copper ions released from a coating was very effective at killing *E. coli*. Furthermore, if it is decided that copper is not an ideal antimicrobial agent, it is also possible utilize silver, which also demonstrates antibacterial behavior [66-68]. Similar to copper, it is possible to utilize analogous processes to form a silver coating via electroless deposition or embedded silver micro/nano-particles into the LCE.

Section 4: Design and ex-vivo validation of translimbal and/or transcorneal device using

perfusion model

Rationale

This section may focus on developing an ex vivo test model to guide development and validate performance of a translimbal and/or transcorneal device as contemplated herein. Form fit and anatomical positioning in the rabbit eye may be validated prior to in vivo testing (Section 5). Perfusion flow studies may be carried out to demonstrate performance with respect to implantation, stability of the device, flow rate as a function of filter porosity, and replace-ability of the filter.

Preliminary Work

An ex vivo perfusion system has been used to characterize the performance of MIGS devices, such as the iStent (Figure 19) [1]. This system incorporates a standard programmable syringe pump (Pump 11 Plus; Harvard Apparatus). Pressure is monitored via an in-line real-time pressure transducer connected to a single channel chart recorder. Polyethylene tubing with a 1.14 mm inner diameter (PE-160; Warner Instruments, Hamden, CT, USA) is used for all connections. Rabbit globes may be obtained from healthy rabbits with special attention to using specimens that are <1 hrs post collection.

Approach

The rabbit globe, in each case, may be first prepared by injecting Dulbecco's Modified Eagle's Medium (DMEM) (Life Technologies, Carlsbad, CA, USA) through the optic nerve with a 26-gauge needle until the globe had returned to a spherical shape. A fluid line (terminating in another 26-gauge needle) is inserted diagonally through the anterior chamber of the eye, passing through the cornea and pupil and ending with the tip beneath the iris. The globe is then

surrounded by damp gauze, and the perfusion pump (filled with DMEM) set to an initial inflow rate of 7 μL/minute. IOP is allowed to increase until it reaches 30 mmHg to ensure the globe is completely inflated. The infusion rate is then reduced to 2.0-2.5 μL/minute, and a steady-state IOP is maintained for at least 60 minutes prior to insertion of the devices. A circular corneal incision may be created using a standard tissue punch device, a method used successfully by inventor Kahook in previous experiments. Viscoelastic gel may be used to maintain the anterior chamber during this process as needed and may be flushed out of the anterior chamber at the end of the device insertion through a paracentesis incision. The translimbal and/or transcorneal device may then be inserted through a corneal incision and positioned under microscopic view so that the outer wall of the positioning element is flush with the corneal stroma. The faceplate of the positioning unit may be seated flush with the surface epithelium. The low flow filter may then be seated in the positioning device (with expansion occurring after exposure to the 37°C ocular perfusion fluid) and ensured to be in proper position under direct microscopy visualization. A watertight closure of the paracentesis may be ensured achieved with a 10-0 nylon suture. Fluorescein may be used to ensure that there are no aqueous leaks between the cornea and the external positioning element. The flow rate may remain constant, and IOP may be measured until steady state is achieved for at least 1-hour post-insertion of the translimbal and/or transcorneal device in all cases in order to determine that a true steady state is achieved. IOP post device implantation may be compared to the baseline steady state achieved prior to device insertion. Subsequently, a low-flow filter may be extracted using forceps after cooling the filter with 10°C balanced salt solution (BSS) and a high-flow filter may be placed in position. The 37°C fluid flowing into the eye may then lead to expansion of the high flow filter and proper positioning may be ensured using a microscope for visualization. IOP under high flow conditions may be compared to the baseline flow as well as to flow through the low flow translimbal and/or

transcorneal device. This process may be repeated for 8 eyes using the exact methodology outlined before. Flow rates may be calculated and compared across all tests.

Testing performance of permanent outer housing

In one embodiment, the ocular translimbal and/or transcorneal ADD comprises an outer housing component that may be made from a silicon polymer such as Nusil®, which has been used as part of intraocular drug delivery implants, intraocular lenses as well as other devices designed for long-term placement within the eye. Furthermore, silicone is commonly used for intraocular lenses and glaucoma drainage devices and has been shown to be stable in periocular tissues for years [69, 70]. Furthermore, a flow limiting aspect of the device should lie within the LCE filter and not the housing; therefore, the flow rate of the housing may be determined to provide a baseline value. From this value, several standard filtration materials can be inserted into the housing, such as cellulose acetate filters (Millipore), can be tested with a porosity of 0.025 – 10 μm.

Section 5: Implant prototype device in a rabbit model

In one embodiment, the ocular translimbal and/or transcorneal ADD comprises a biocompatibile translimbal and/or transcorneal device as well as both short and long-term functioning of the device under in vivo conditions. Prior to implantation of devices, they may be inspected to ensure they are essentially free from pits, scratches, cracking and crazing (unless present by design) at a minimum of 10x magnification. The edges of the implantable glaucoma device shall appear smooth and free of burrs when inspected at 10x magnification.

For the purposes of the current study, a New Zealand White Rabbit model may provide an adequately size eye for the flow testing that is being performed and may accommodate the

size of the device used. Furthermore, the bacterial flora of the rabbit conjunctiva contains similar microorganisms to humans [65, 71]. In one embodiment, the present invention comprises a glaucoma drainage device that have been evaluated on the following parameters post implantation: (1) inflammatory response of the eye to the material; (2) formation of fibrous tissue and collagen on the implant surface; (3) vascularization around the implant; (4) stability of the implant material(s); (5) Overall performance of the device post implantation.

Surgical Procedure and Follow-Up – All procedures may be performed in accordance with The Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. Twelve New Zealand white rabbits may be divided into two groups: filtration surgery with low flow (LF) translimbal and/or transcorneal device (n=6 rabbits, 6 eyes) and filtration surgery with high flow (HF) translimbal and/or transcorneal device (n=6 rabbits, 6 eyes). The right eye of each animal may receive the translimbal and/or transcorneal device and the left eye may undergo sham surgery (placement of the speculum and drops but no penetration of the eye) and may act as the control for this pilot study. All surgeries may be performed by a single surgeon experienced in animal-based ophthalmic surgery. The glaucoma filtering surgery technique is outlined as follows: The rabbits may be anesthesized using techniques outlined in the Vertebrate Animals document. For the implantation of both the LF and HF translimbal and/or transcorneal device, a lid speculum may be positioned to ensure adequate access to the right eye of each rabbit. Betadine 5% may be used to irrigate the eye prior to any manipulation and allowed to soak in place for 2 minutes. The betadine soaked eye may then be irrigated with BSS. A paracentesis may be created with a 1.0 mm blade followed by injection of a cohesive viscoelastic to maintain the anterior chamber. Next, a 0.12 forceps may be used to secure the eye and a tissue punch may be used to create a precisely sized circular incision in the superior cornea (between 11 and 1 o'clock) placing the incision just anterior to the limbal

tissue. The translimbal and/or transcorneal device positioning device may then be inserted and proper positioning insured. Once the outer positioning device is positioned, either the LF or HF translimbal and/or transcorneal device filter may be placed gently into the central lumen and allowed to expand in place under influence of the body temperature of the rabbit eye. Fluorescein may be used to ensure that there are not leaks between the positioning unit and the corneal stroma. The remaining viscoelastic may then be irrigated out of the eye and the paracentesis may be sutured closed and watertight with 10-0 nylon suture. Topical moxifloxacin 0.5% (Vigamox®; Alcon) and prednisolone acetate 1% (Predforte®, Allergan) may then each be instilled 4 times per day for 7 days following surgery in all eyes.

Post-operative Evaluation – Slit lamp exams may be carried out routinely, including iCare tonometry IOP measurements, along with fundus exams at one week and prior to euthanizing. The "Vertebrate Animals" document contains further details about the follow-up protocol. Prior to euthanizing the animals, each LF and HF translimbal and/or transcorneal device may undergo direct examination under microscopic observation. Fluoresein may be placed over the device face plate to investigate for any leads on the side of the devices (at tissue-positioning device interface) as well as to observe flow through the filter portion of the faceplate (to document functioning devices). Each device filter may then be removed and exchanged for a second filter to evaluate an ability to exchange a filter in vivo. Each device may be observed for 5 minutes with direct visualization for aqueous flow using fluorescein staining. The animals may then be euthanized for enucleation and histologic evaluation. Data analyses may compare all post-operative metrics between groups using one-way ANOVA test may be completed for all data sets. A p-value <0.05 may be considered statistically significant. IOP may be compared between treated and control eyes and between the two surgical groups (HF and LF devices) at each time point. Adverse events, inflammation, neovascularity and histology (see

below) metrics may also be compared between all groups.

Histology – All animals may euthanized at the conclusion of the six months study. All eyes may then be enucleated and immediately immersed in a mixture of 4% paraformaldehyde and 2.5% neutral buffered formalin for 24 h. The globes are then dehydrated, embedded in paraffin and sent for microtome sectioning and staining (Hematoxylin and Eosin and Masson Trichrome; Sigma, St. Louis, MO) in the ophthalmic histology core. Gross macroscopic examination of the entire eye may be completed prior to sectioning. Attention to iris and lens anatomy and retina architecture may be completed. A modified semiquantitative grading system to assess cellularity and collagen deposition of the surrounding corneal stroma may be used to compare findings between the two groups. Corneal endothelium may be evaluated for cell loss and cell morphology, both near the device as well as diffusely. Neovascularity within the corneal stroma and surrounding tissue adjacent to the device may be compared between groups. Presence of inflammatory membranes and induction of cataract may also be noted. Posterior pole tissues may also be examined grossly and representative histologic sections of the retina and choroid examined for pathology (inflammatory tissue or pathogens). Statistical analysis using one-way ANOVA test may be completed for all data sets. A p-value <0.05 may be considered statistically significant.

Description of Animals and How They May Be Used

Twelve New Zealand white rabbits may be divided into two groups: transcorneal drainage device surgery with a low-flow (LF) filter (n=6 rabbits, 6 eyes) and a high-flow (HF) filter (n=6 rabbits, 6 eyes). The right eye of each animal may receive the transcorneal device and the left eye may undergo sham surgery (placement of the speculum and drops but no penetration of the eye) and may act as the control for this pilot study. All procedures may be performed in

accordance with The Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.

The rabbits may be anesthesized using intramuscular injections of ketamine and xylazine (ketamine 40 mg/kg; xylazine 20 mg/kg) as well as topical anesthesia (2% lidocaine gel) before initiation of surgery. For the implantation of both the LF and HF devices, a lid speculum may be positioned to ensure adequate access to the right eye of each rabbit. Betadine 5% may be used to irrigate the eye prior to any manipulation and allowed to soak in place for 2 minutes. The betadine soaked eye may then be irrigated with BSS. A paracentesis may be created with a 1.0mm blade followed by injection of a cohesive viscoelastic to maintain the anterior chamber. Next, a 0.12 forceps may be used to secure the eye and a tissue punch may be used to create a precisely sized circular incision in the superior cornea (between 11 and 1 o'clock) placing the incision just anterior to the limbal tissue. The outer housing of the device may then be inserted and proper positioning insured. Once the outer housing is positioned, either the LF or HF filter may be placed gently into the central lumen and allowed to expand in place under influence of the body temperature of the rabbit eye. Fluorescein may be used to ensure that there are not leaks between the positioning unit and the corneal stroma. The remaining viscoelastic may then be irrigated out of the eye and the paracentesis may be sutured closed and watertight with 10-0 nylon suture. Topical moxifloxacin 0.5% (Vigamox®; Alcon) and prednisolone acetate 1% (Predforte®, Allergan, Irvine, CA) may then each be instilled four times per day for seven days following surgery in all eyes.

Daily handheld slit lamp examinations may be conducted to document any changes at the surgical site. The eyes may be examined one day, three days, one week, two weeks, one month, three months and six months after surgery. Indirect ophthalmoscopy may be performed preoperatively, postoperatively within the first week, and at one month and six months on all

eyes. Observations may include, but may not be limited to, flare, cells, adhesions, neovascularization, corneal edema, intraocular pressure, and location of the components of the device. All animals may be euthanized at the conclusion of the six months study to undergo histological analysis.

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SECTION 6:SHAPE-SWITCHING LIQUID-CRYSTALLINE ELASTOMER FOAMS

LCEs are a class of shape memory and active polymers that can reversibly and repeatedly change their shape in response to a stimulus such as heat (e.g., Figure 10); however, traditional methods to produce LCEs limit the material's manufacturability to small-scale samples (e.g., thin 10 films/fibers).

The described two-stage reaction may advance LCE research in terms of their manufacturability, tailorability, and accessibility. This approach may significantly increase the size scale of which LCEs can be produced, while providing a faster and more repeatable reaction mechanism compared to traditional approaches. The two-stage reaction may allow for precise 15 control over the polymer structure both before and after the alignment of the monodomain. The material is stable after the first stage of synthesis, offering the ability for stretching and photocuring to occur in a separate laboratory.

The use of LCEs has been proposed for several actuator applications; including artificial muscles for potential use in robotic arms, and for manipulation of a lens for optical systems.. 20 Unfortunately, few LCEs have been successfully developed into usable applications. The materials and methods described herein may establish a methodology for fabricating a macro-scale foam elastomer that could be highly compacted for transport (e.g., in a rocket payload), then released and cross-linked to form a more rigid structure, capable of the hallmark reversible shape change.

Basics of Liquid-Crystalline Elastomers (LCEs)

LCEs comprise a class of actively moving polymers that can exhibit large shape changes in response to a stimulus. These polymers combine the properties of amorphous thermoset elastomers (entropy elasticity) with liquid crystals (self-organization) to achieve a wide range of tunable active properties. For example, LCEs can apply stresses or induce strain-related shape changes up to 400% in response to heat (direct conduction, electroresistive heating, inductive heating) [31, 32] or light (cis-trans photosensitization) [33, 34]. Figure 10 demonstrates an LCE lifting and lowering (contracting and expanding) in response to temperature changes.

LCEs are defined by their ability to undergo a reversible phase transition between a polydomain and a monodomain (Figure 21). These domains are determined by the alignment of mesogens, which are aromatic structures built into the polymer network [37]. LCEs can be synthesized as polydomain or monodomain samples, depending on whether or not the mesogens are aligned during network formation. A polydomain sample can be stretched to align the mesogens into a monodomain, which can be seen by a change in optical transparency. If released, the sample may return to its polydomain, opaque configuration with stress being the driver of the phase transition. For monodomain samples, the mesogens are initially ordered in one direction and a high degree of mechanical anisotropy results within the network. When the material is heated above a "clearing" temperature (Tc), the mesogens lose their aligned formation and transition to an isotropic unaligned state. Shape change (contraction) is driven against the direction alignment and temperature is now the driver of the phase transition. If the material is cooled to a temperature below the Tc, the mesogens may regain their monodomain alignment and elongate the sample. One of the most powerful features of LCEs is their ability to undergo a reversible phase transition through alignment switching within the mesogenic domains, which

results in shape-switching behavior.

The use of LCEs has been proposed in sensor and actuator applications, and most notably as potential artificial muscles [31, 72]. Although liquid crystal technology has experienced commercial success within the television and display industry, LCEs have yet to break into the marketplace. One reason LCEs remain under utilized is their limited manufacturability. LCEs typically have complex chemistry, synthesis, and programming conditions, all of which pose significant challenges to investigators without chemistry backgrounds. Furthermore, the current LCE synthesis methods are not practical for large-scale manufacturing and are only used to produce small-scale samples such as thin films [73, 74], or fibers [75-77].

The two-stage reactions to create an open cell porous foam LCE may utilize a thiol-acrylate system in conjunction with Michael addition (Figure 22 - Stage 1) and photopolymerization (Figure 22 - Stage 2) reactions. First, a lightly crosslinked polydomain main-chain LCE may be mixed with sodium chloride and synthesized via a Michael addition reaction. The crosslinking density may be tailored by the amount of crosslinking thiol monomer ($f>2$) in the solution, while the spacing of mesogens along the chain may be tailored by a dithiol flexible spacer. The resulting composite structure may be leached in water, allowing the sodium chloride to dissolve leaving behind an elastomeric foam. Next, the mesogens may be aligned into a monodomain by mechanical stretching. Finally, the aligned monodomain is secured by the Stage 2 photopolymerziation reaction. The final crosslinking density may be determined by the amount of excess acrylate groups unreacted by the Michael addition reaction. The resulting product may represent a robust methodology for creating a highly tailorable LCE foam. Furthermore, the elastomer may remain stable between Stage 1 and Stage 2, allowing for compaction for transport prior to activation. This research would be the first to investigate thiol-acrylate systems for LCE foam synthesis as well as be the first to use them in a novel

two-stage reaction.

Expected Outcomes

Currently advanced cases of glaucoma are treated by implanting a tubular shunt to relieve internal pressure. A LCE foam would have excellent potential as a shunt replacement. Heating to body temperature would allow the LCE to fit snuggly into place, but could be removed if need be using a cold saline bath. Porosity could be tailored to allow appropriate fluid drainage.

Fabrication of Nanoporous Liquid Crystal Elastomer

Step 1: Liquid Crystal Elastomer

Using the 2 stage thiol-acrylate michal addition reaction, main chain liquid crystal elastomers (LCEs) are able to be made for the first time in bulk samples. After a one-time programming, these polymers exhibit reversible shape changing ability by the reorientation of their rigid molecules, called mesogens. Figure 10 shows the shape changing of an LCE which starts at room temperature and is raised above its T_i, or initiating temperature. In the case of an LCE used in the human body, T_i would be just around 97 °F, allowing actuation of a medical device only when it is placed in the body.

Step 2: Creating Nanopore Template via Electrospinning

In order to create nano-scale features in the bulk LCE, a sacrificial template of water soluble nanofibers is set in, then dissolved out of the LCE. To create the nanofibers, a process called electrospinning is used. In this process, a solution of poly-Vinyl Alcohol (PVA) and water is placed in a syringe/pump set up. The tip of the syringe is charged with a 10 kV DC voltage, and the solution is slowly ejected. Facing the tip of the syringe is a grounded collector. As the

solution is pulled towards the collector by the electric field, it splays into hundreds of individual fibers. The water is able to evaporate and the PVA forms nanofibers on the grounded collector. Figure 24 shows a schematic of the PVA solution being electrospun onto a thin wire collector. In our setup, a 25 micron copper wire was used. Figure 25 shows a section of wire after the electrospinning process and Figure 26 and Figure 27 shows SEM images of the wire after electrospinning and a close up surface view of the nanofiber-coated wire.

Step 3: Creating a Porous LCE

Once the wire was covered in nanofibers, the LCE was cast around it. To do this, LCE monomers were prepared without a catalyst. The catalyst was added to the monomers and the mixture was poured over the nanofibers, effectively infiltrating the fibers before the LCE polymerized. This was done in the tip of a capillary tube in order to create a porous LCE that was small enough to be used for a trans corneal glaucoma drainage device. Figure 28 and Figure 29 shows LCE which has been combined with the PVA nanofiber-coated wire, before and after removing it from the tip of a pipette. This shows the same results as a capillary tube with on a slightly larger scale for viewing ease.

After infiltrating the nanofibers with LCE and polymerizing, the nanofibers were dissolved out in 55 °C water for 48 hours. Figure 30 shows an SEM image of the surface of a cross-section of a cylindrical porous LCE. The fibers which were dissolved out to create these pores were randomly oriented. This explains the oval shape of some of the pores seen in the image.

Thus, specific compositions and methods of antimicrobial translimbal drainage device with replaceable filter have been disclosed. It should be apparent, however, to those skilled in the

art that many more modifications besides those already described are possible without departing from the inventive concepts herein. Moreover, in interpreting the disclosure, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

Although the invention has been described with reference to these preferred embodiments, other embodiments can achieve the same results. Variations and modifications of the present invention will be obvious to those skilled in the art and it is intended to cover in the appended claims all such modifications and equivalents. The entire disclosures of all applications, patents, and publications cited above, and of the corresponding application are hereby incorporated by reference.

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CLAIMS:

We claim:

1. An ocular artificial drainage device comprising;

i) a housing comprising:

a) a cylindrical distal face-plate with a hollow inner diameter;

b) a cylindrical body with a middle section and distal and proximal ends, wherein the proximal end comprises a proximal portion with fluid communication with the middle section , wherein the middle section comprises a hollow inner diameter, and wherein said the distal face plate is attached to the distal end of the body of the device; and

ii) a filter with a distal and proximal end, wherein said filter at least partially fits within the inner diameter of the body and contains anti-microbial properties.

2. The device of Claim 1, wherein said proximal portion with fluid communication with the middle section further comprises at least two holes in fluidic communication with the inner diameter of the middle section of the cylindrical body to outside the proximal end of the body.

3. The device of Claim 1, wherein said proximal portion with fluid communication with the middle section comprises a mushroom-tipped spinneret.

4. The device of Claim 1, wherein said cylindrical body contains features enabling integration with surrounding tissue.

5. The device of Claim 1, wherein said outer cylindrical body is polymerized directly to the stromal tissue to form a water tight bond.

6. The device of Claim 1, wherein said antimicrobial properties comprises a coating of antimicrobial particles.

7. The device of Claim 1, wherein said antimicrobial properties comprises a coating of antimicrobial particles on said filter.

8. The device of Claim 1, wherein said antimicrobial properties comprises a coating of antimicrobial particles on said housing.

9. The device of Claim 1, wherein said antimicrobial properties comprises copper particles.

10. The device of Claim 1, wherein said antimicrobial properties comprises titanium dioxide particles.

11. The device of Claim 1, wherein said filter is replaceable.

12. The device of Claim 1, wherein said housing comprises silicone.

13. The device of Claim 1, wherein said housing comprises mechanically actuating polymers.

14. The device of Claim 13, wherein said mechanically actuating polymers comprise liquid-crystalline elastomers.

15. The device of Claim 1, wherein said filter comprises mechanically actuating polymers.

16. The device of Claim 15, wherein said mechanically actuating polymers comprise liquid-crystalline elastomers.

17. The device of Claim 1, wherein said filter comprises an interconnected porous structure.

18. The device of Claim 17, wherein said interconnected porous structure comprises an open cellular foam structure.

19. The device of Claim 17, wherein said interconnected porous structure comprises a structure of tubular channels.

20. The device of Claim 17, wherein said interconnected porous structure comprise both an open cellular foam structure and a structure of tubular channels.

21. The device of Claim 17, wherein said interconnected porous structure has an average pore size less than 1 micrometer.

22. The device of Claim 1, wherein said device is activated after implantation.

23. The device of Claim 1, wherein said inner diameter of the distal faceplace of the device is less than 200 micrometers.

24. The device of Claim 1, wherein the outer diameter of the distal faceplace of the device is greater than 250 micrometers.

25. The device of Claim 1, wherein said inner diameter of the body of the device is between 200-400 micrometers.

26. The device of Claim 1, wherein said length of the body of the device is at least 800 micrometers.

27. The device of Claim 1, wherein said middle section of the body of the device is tapered towards the proximal end.

28. The device of Claim 1, wherein said faceplate of the device is low profile.

29. The device of Claim 1, wherein said filter has pores with diameters less than 200 nanometers.

30. A method comprising;

a) providing;

i) the device of Claim 1;

ii) a subject suffering from a disease state, wherein said disease has at least

one symptom, wherein said subject comprises at least one eye;

b) implanting said device in at least one eye of said subject;

c) treating said subject with said artificial drainage device so as to alleviate said at least one symptom of said disease state.

31. The method of Claim 30, wherein said disease state comprises glaucoma.

32. The method of Claim 30, wherein said symptom is elevated intraocular pressure.

33. A method of implanting the device of Claim 1 comprising;

a) providing;

i) the device of Claim 1;

ii) a subject suffering from a disease state, wherein said disease has at least one symptom, wherein said subject comprises at least one eye;

b) creation of a cylindrical hole of a diameter smaller than the outer diameter of the middle section of the device in Claim 1 in said eye;

c) insertion of the housing of the device of Claim 1 into the created hole in the eye, wherein said proximal end of the device is oriented to the inside of the eye and the distal end of the device is oriented to the outside of the eye;

d) cooling of the surface of the eye near the device to approximately 10°C;

e) placement of a chilled filter of the device in Claim 1 into the hollow cylindrical center of said housing of the device of Claim 1; and

f) allow filter to expand and conform to the center of said housing.

FIGURE 1

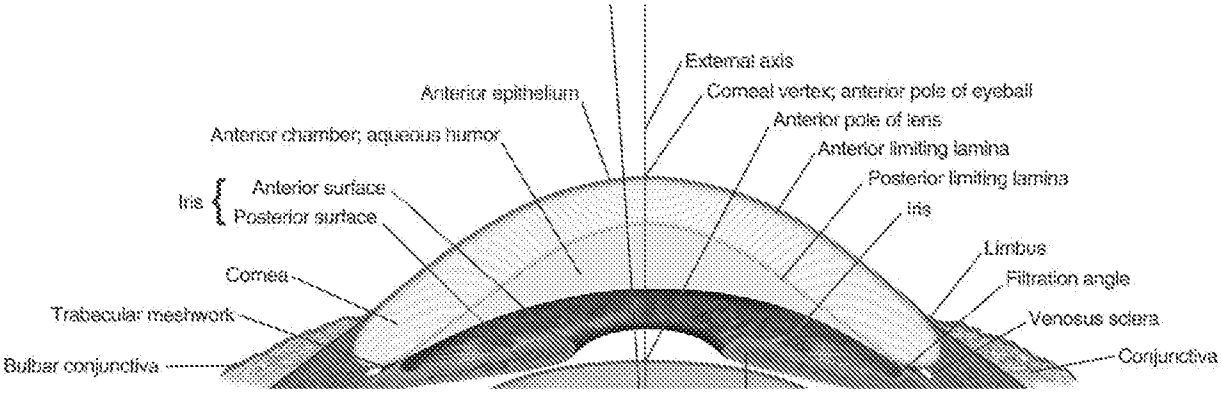

External axis
Anterior epithelium
Corneal vertex; anterior pole of eyeball
Anterior pole of lens
Anterior chamber; aqueous humor
Anterior limiting lamina
Posterior limiting lamina
Iris
Anterior surface
Posterior surface
Iris
Limbus
Cornea
Filtration angle
Trabecular meshwork
Venosus sclera
Bulbar conjunctiva
Conjunctiva

FIGURE 2

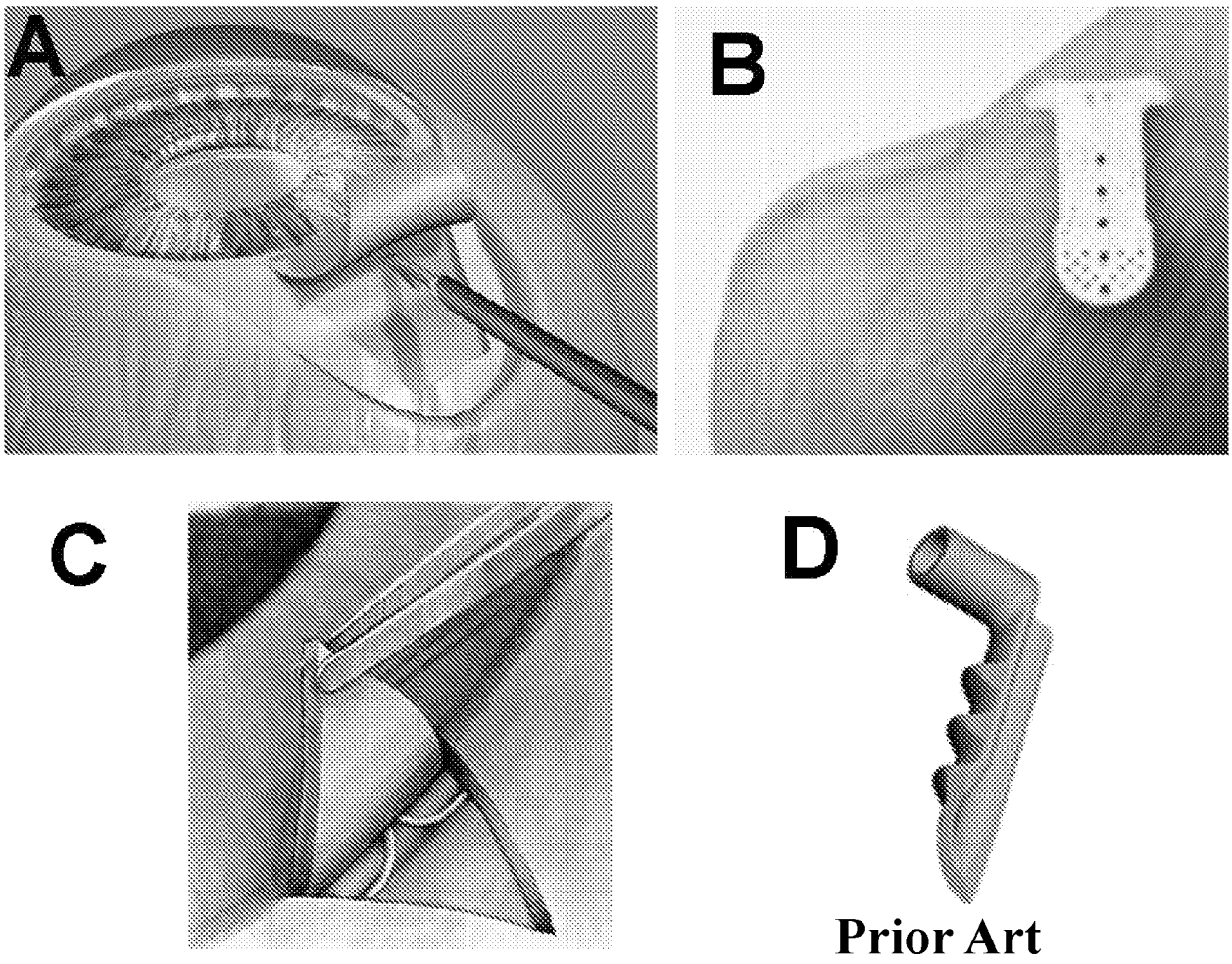


FIGURE 3A

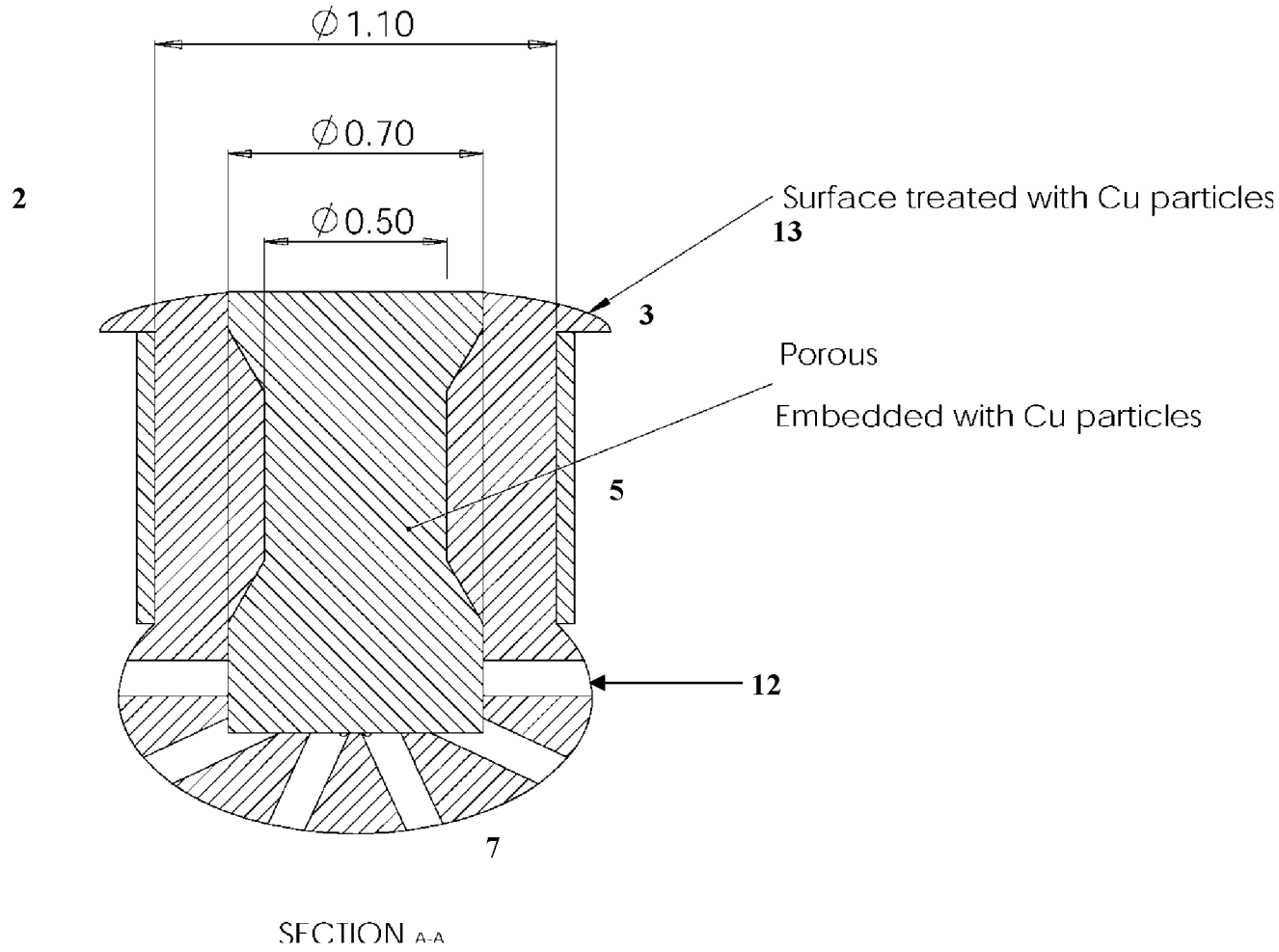

∅1.10
∅0.70
∅0.50
2
Surface treated with Cu particles
13
3
Porous
Embedded with Cu particles
5
12
7
SECTION A-A

FIGURE 3B

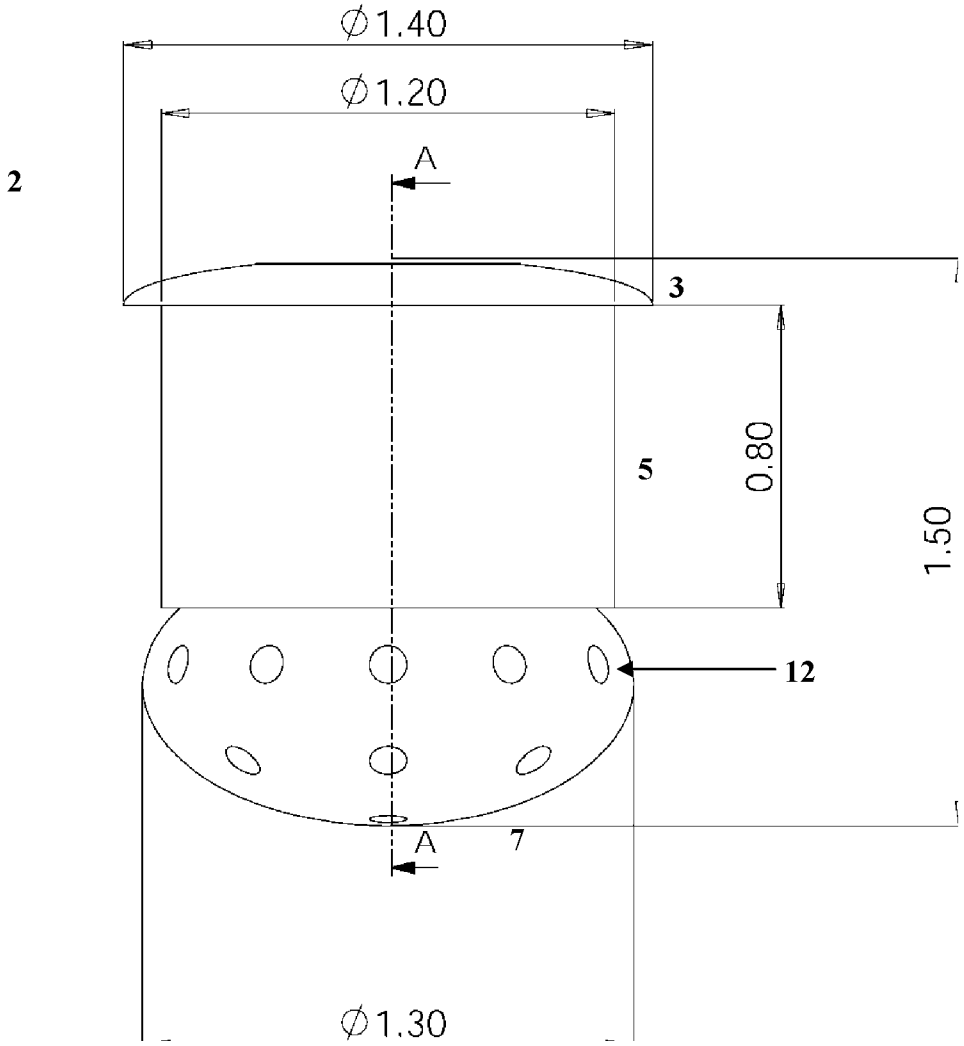


FIGURE 3C

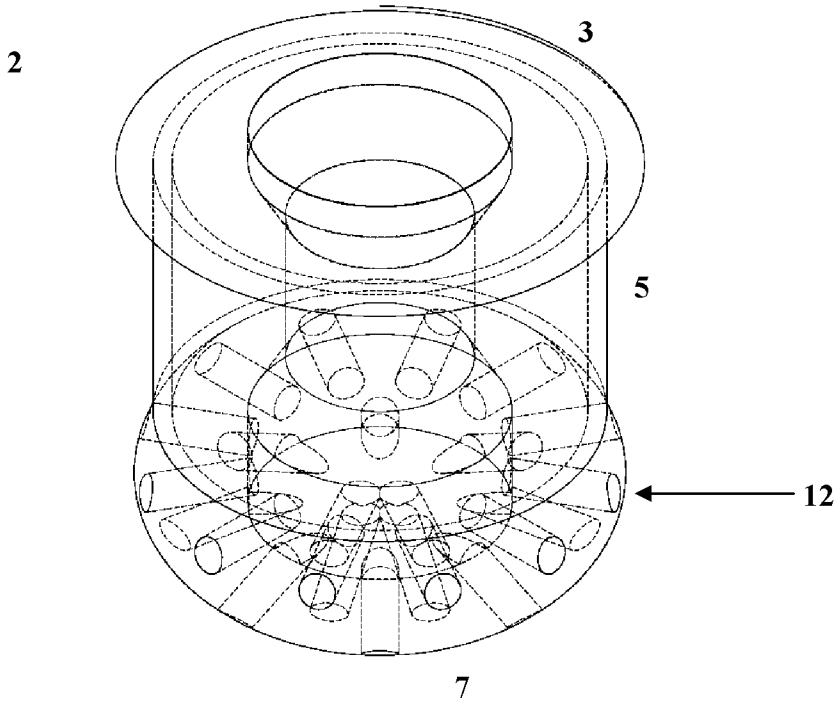


FIGURE 3D

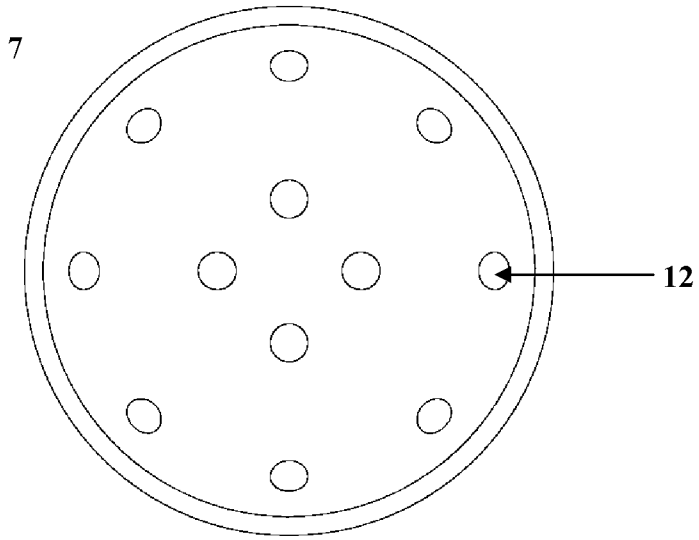


FIGURE 4A

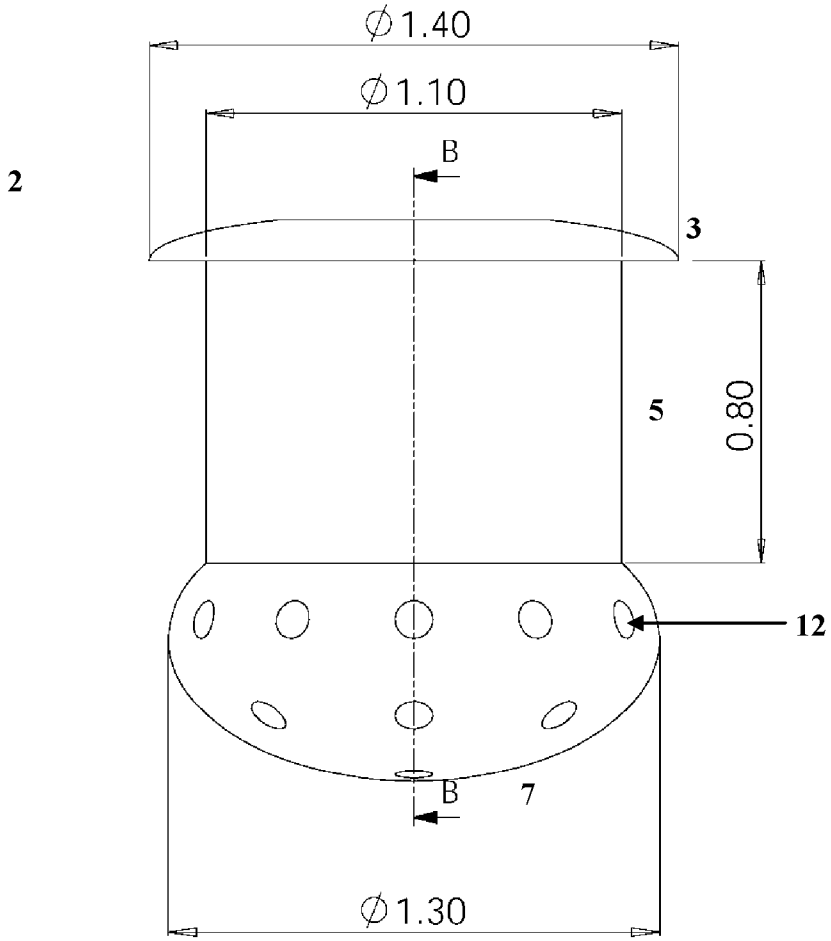


FIGURE 4B

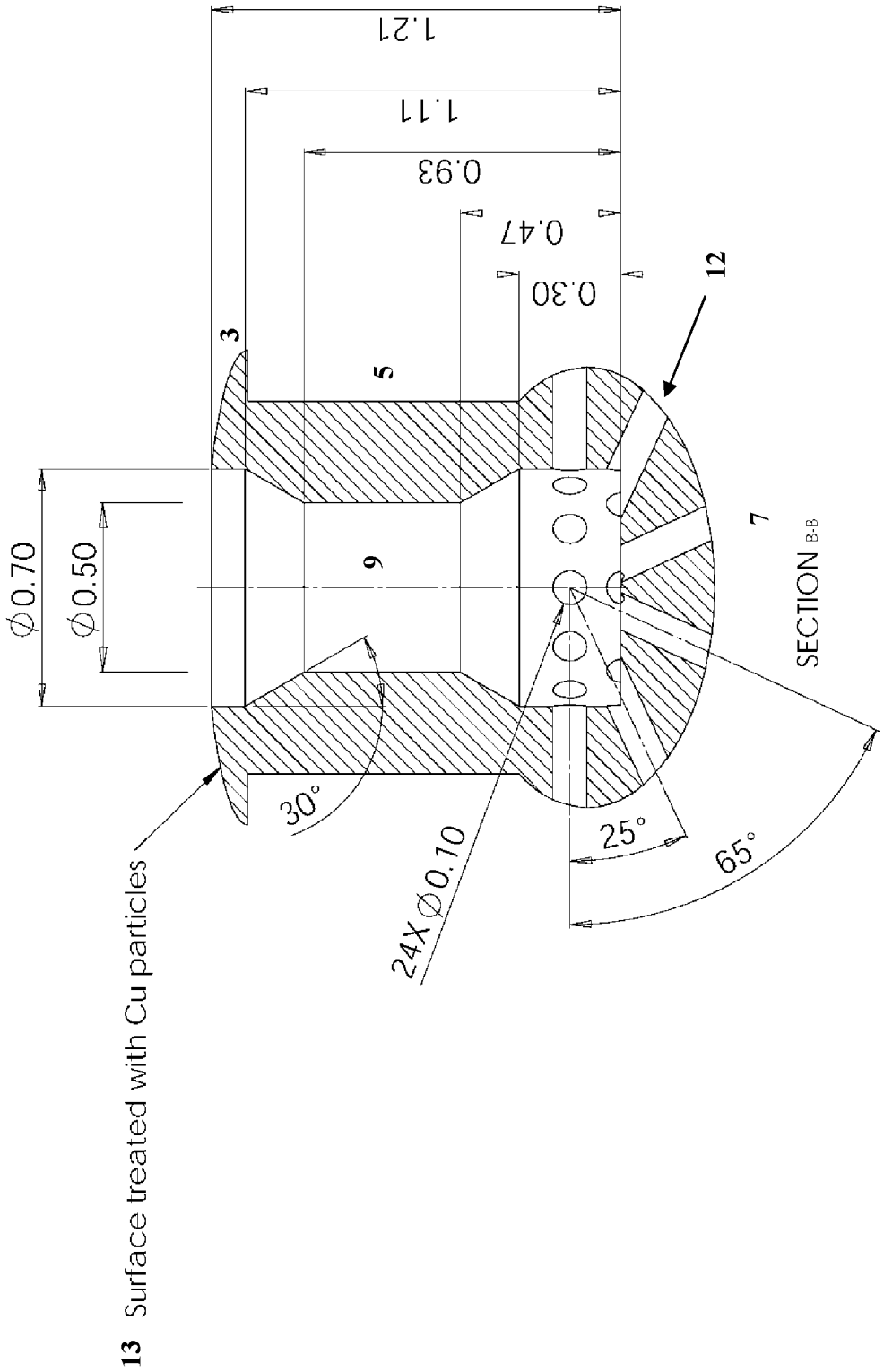

1.21
1.11
0.93
0.47
0.30
12
3
5
9
7
SECTION B-B
Ø0.70
Ø0.50
30°
25°
65°
24X Ø0.10
13 Surface treated with Cu particles

FIGURE 4C

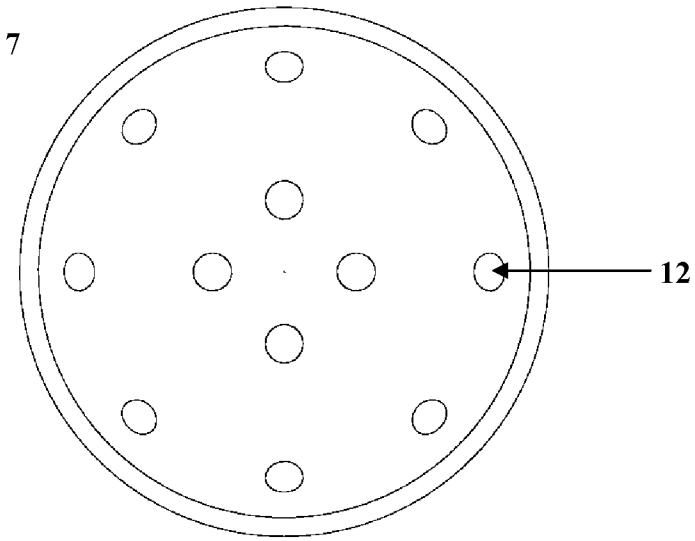


FIGURE 4D

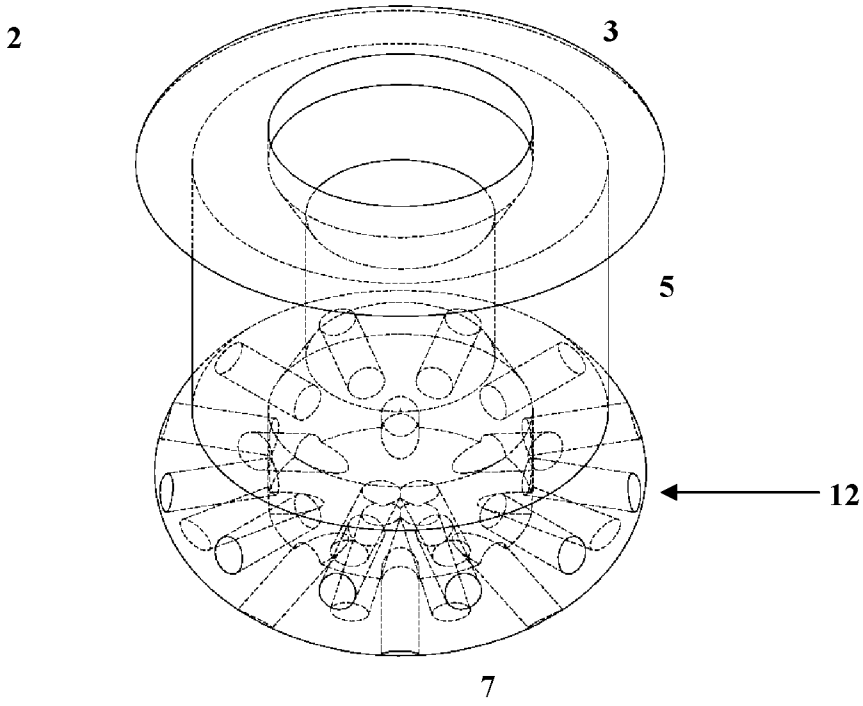


FIGURE 5A

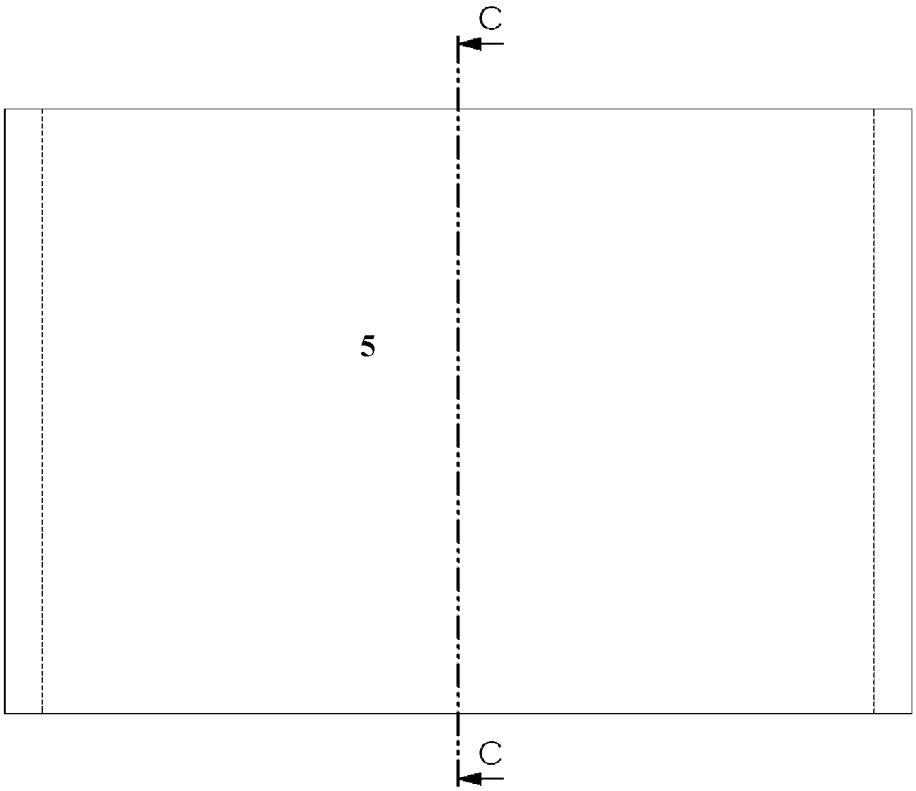
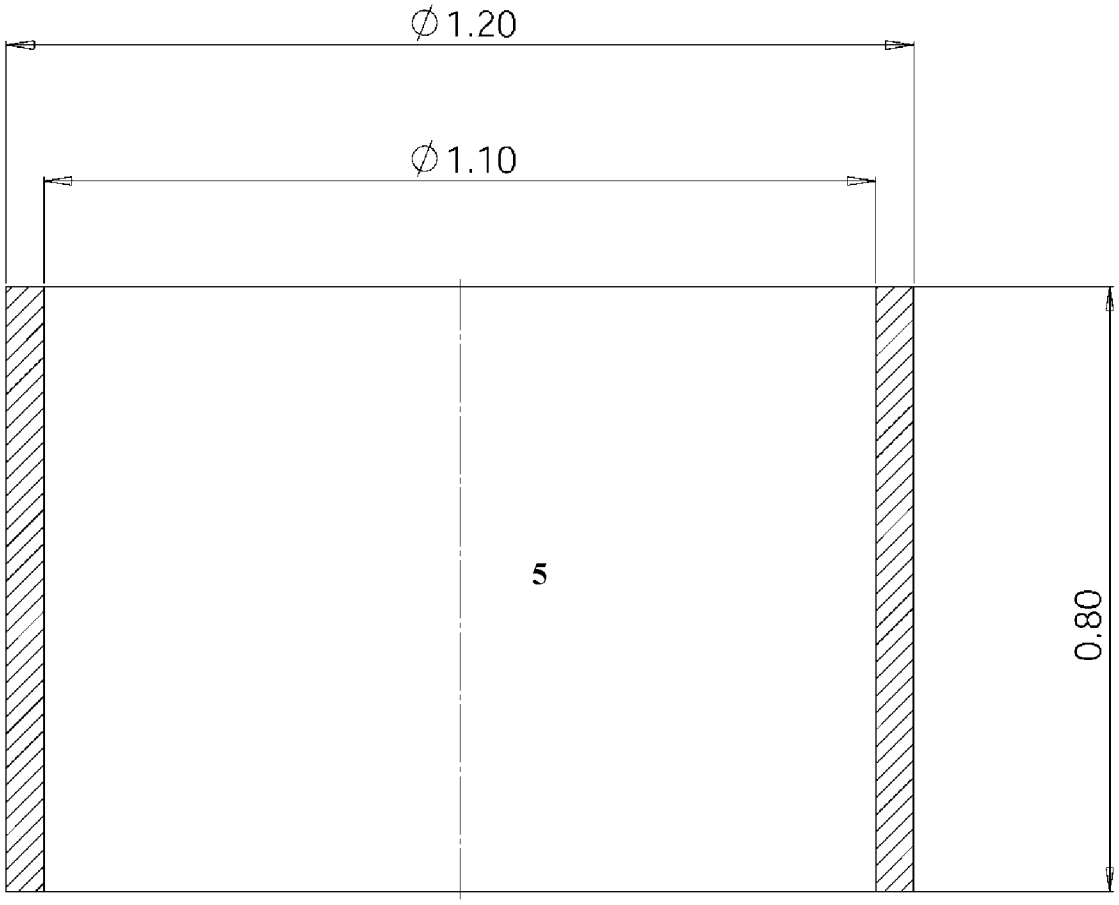


FIGURE 5B



SECTION C-C
SCALE 200 : 1

FIGURE 5C

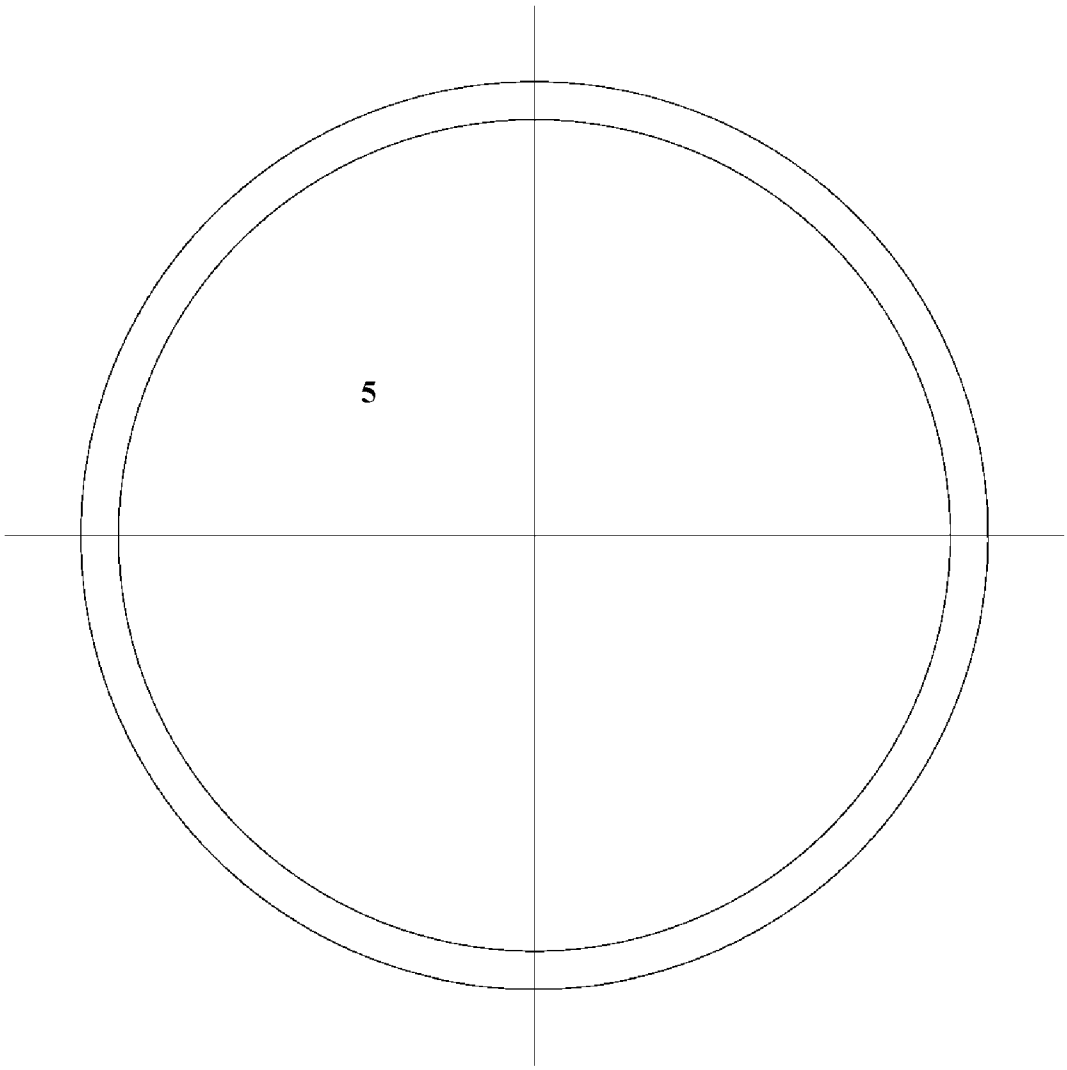


FIGURE 5D

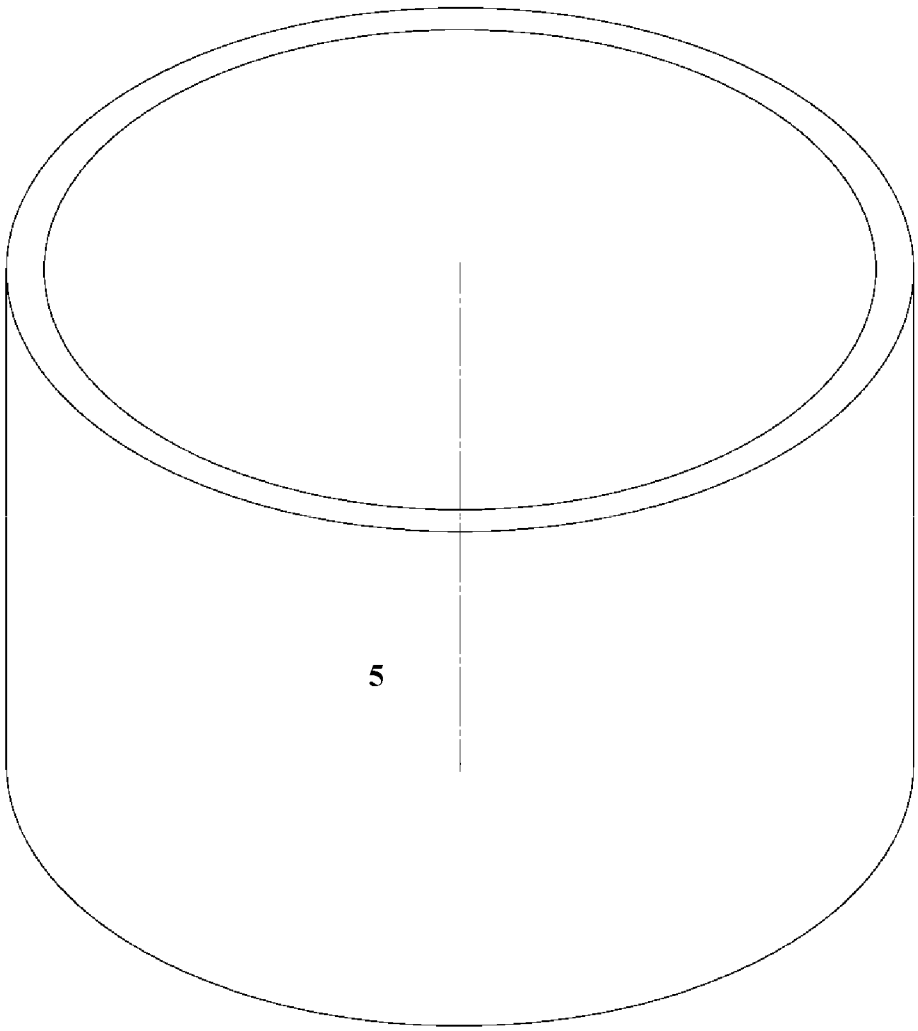


FIGURE 6A

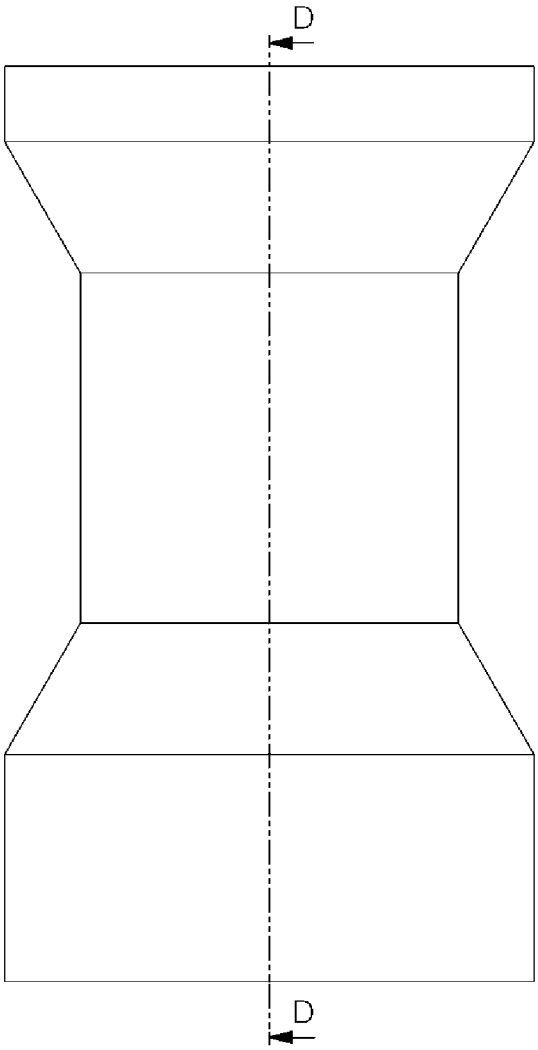
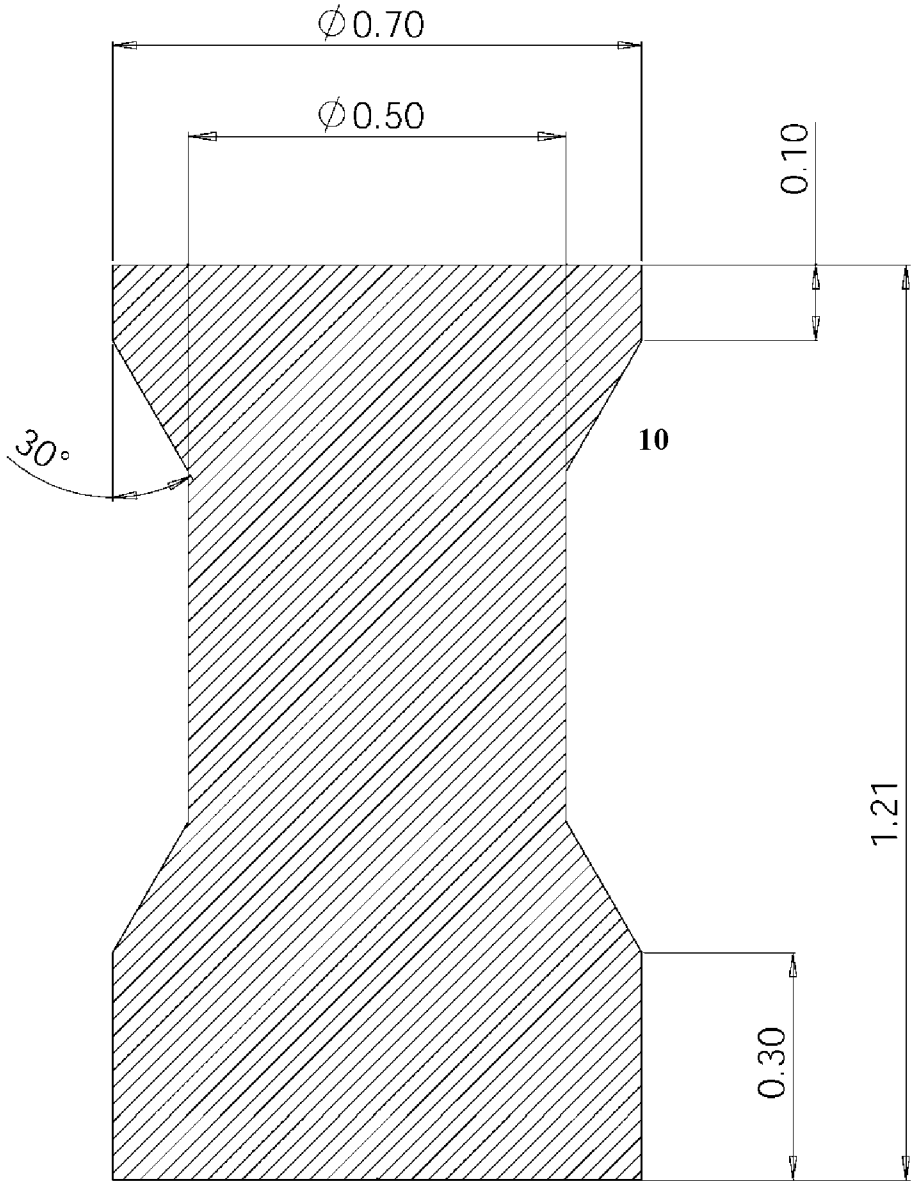


FIGURE 6B



SECTION D-D

FIGURE 6C

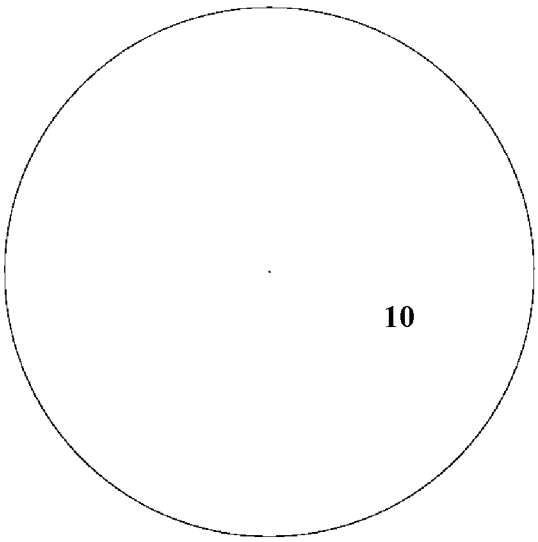


FIGURE 6D

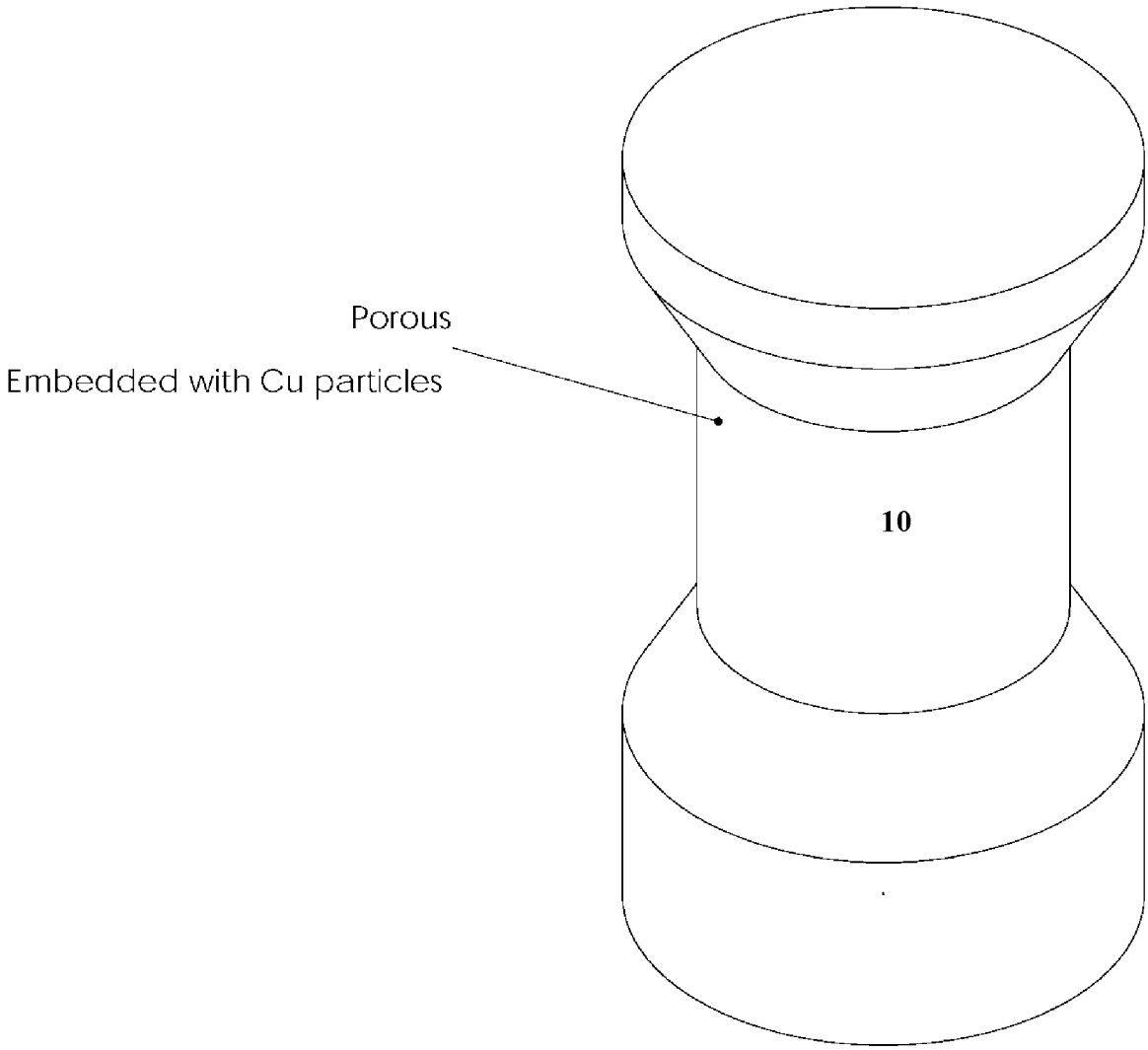


FIGURE 7

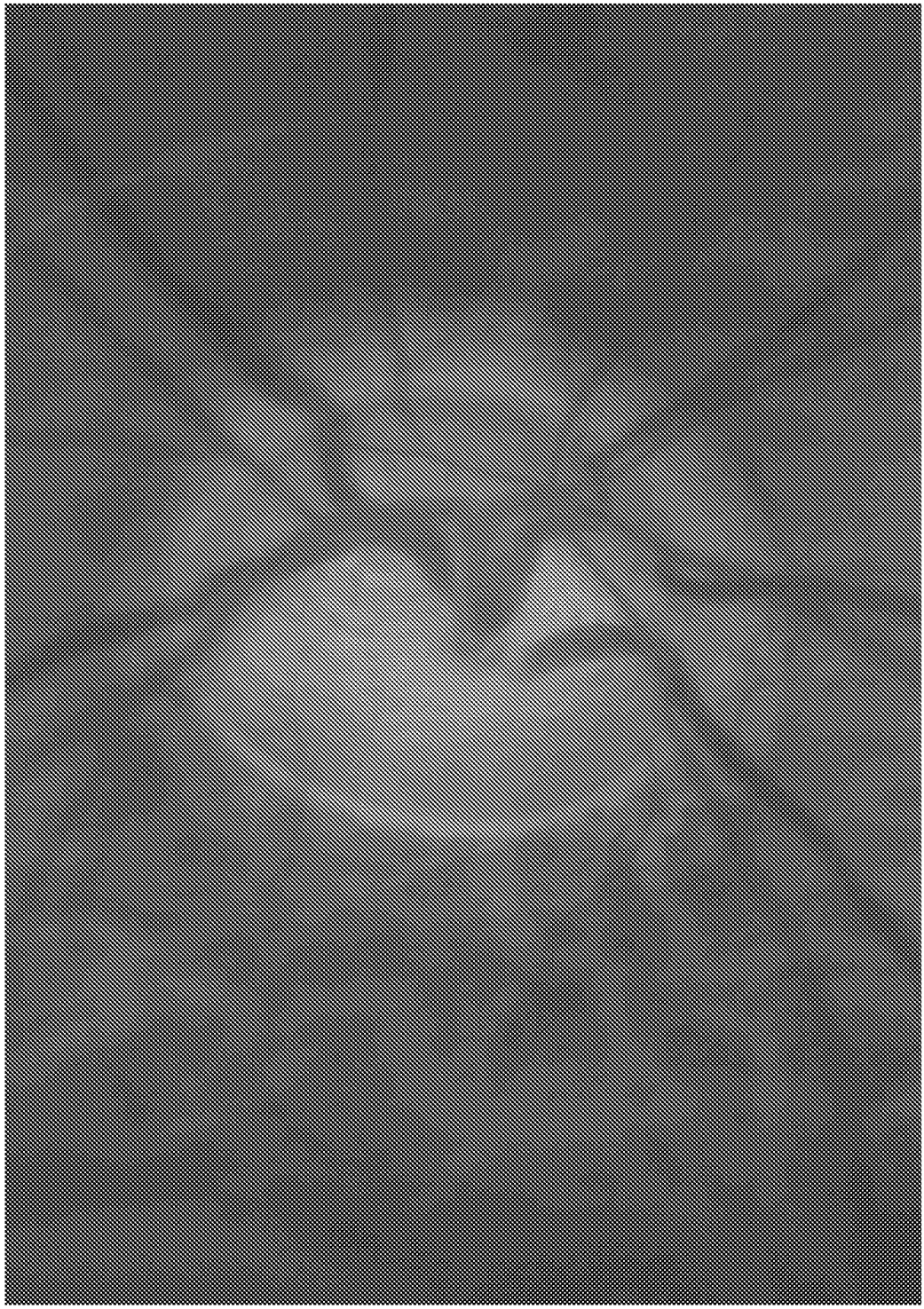


FIGURE 8

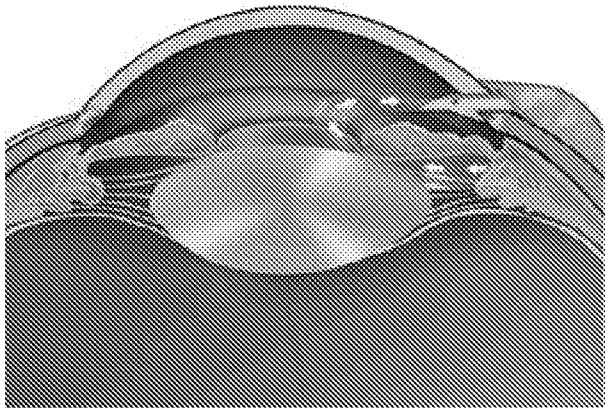


FIGURE 9

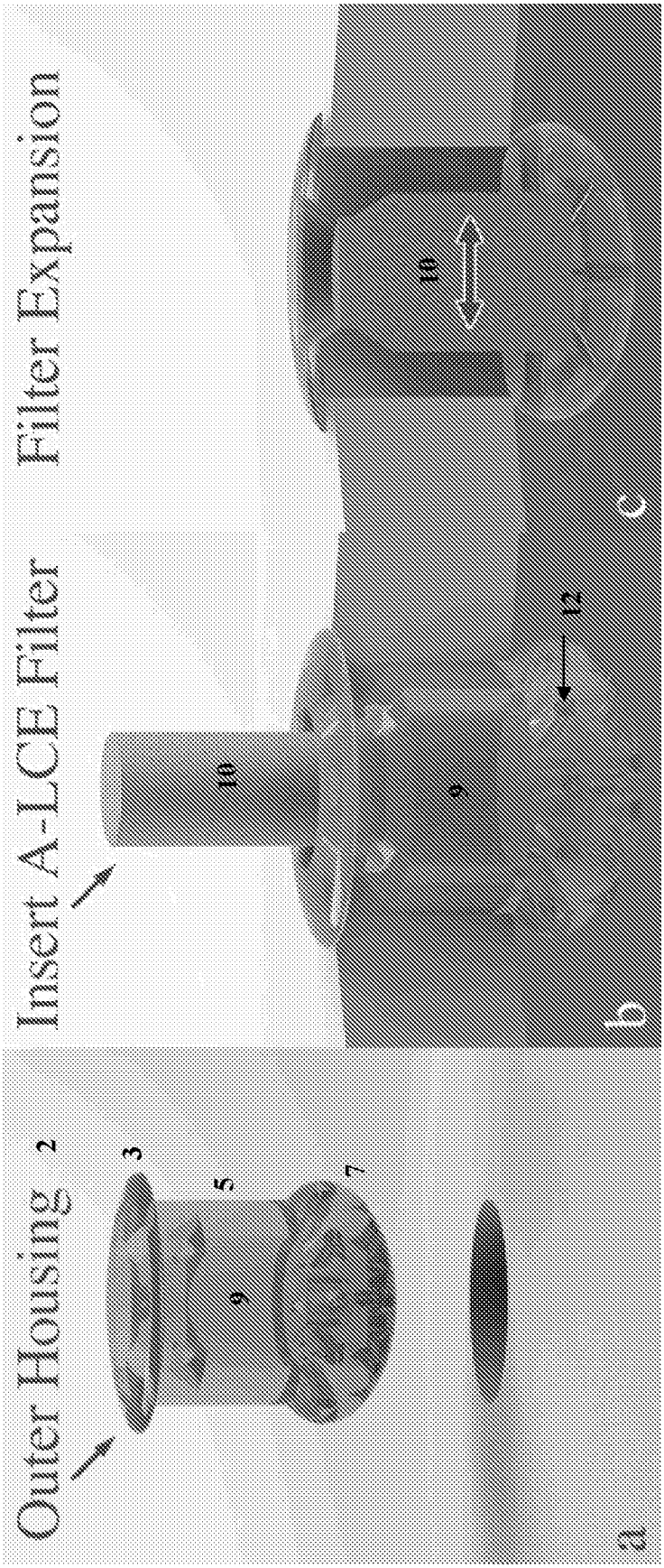

Outer Housing 2
Insert A-LCE Filter
Filter Expansion
3
5
7
9
10
12
a
b
c

FIGURE 10

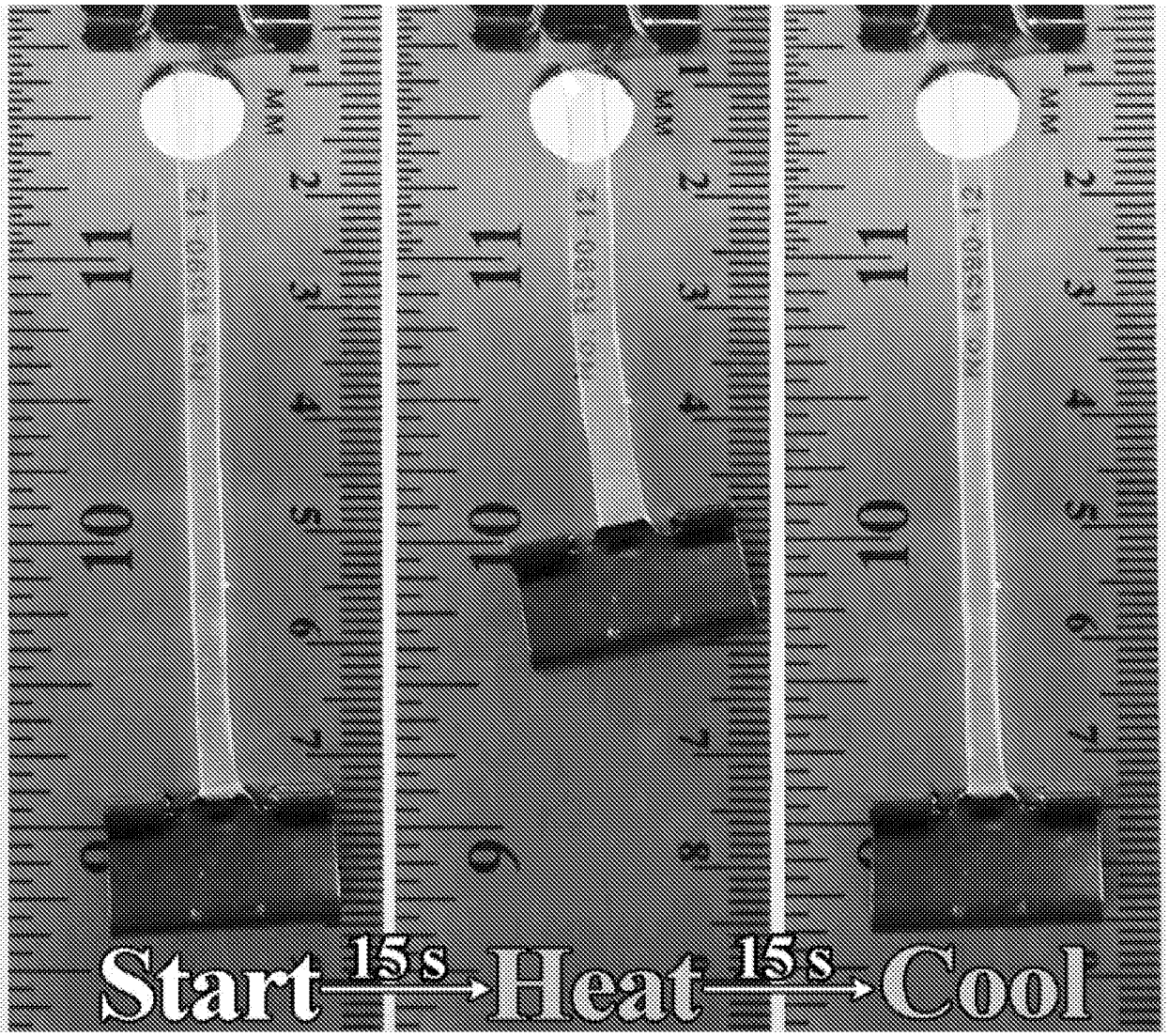


FIGURE 11

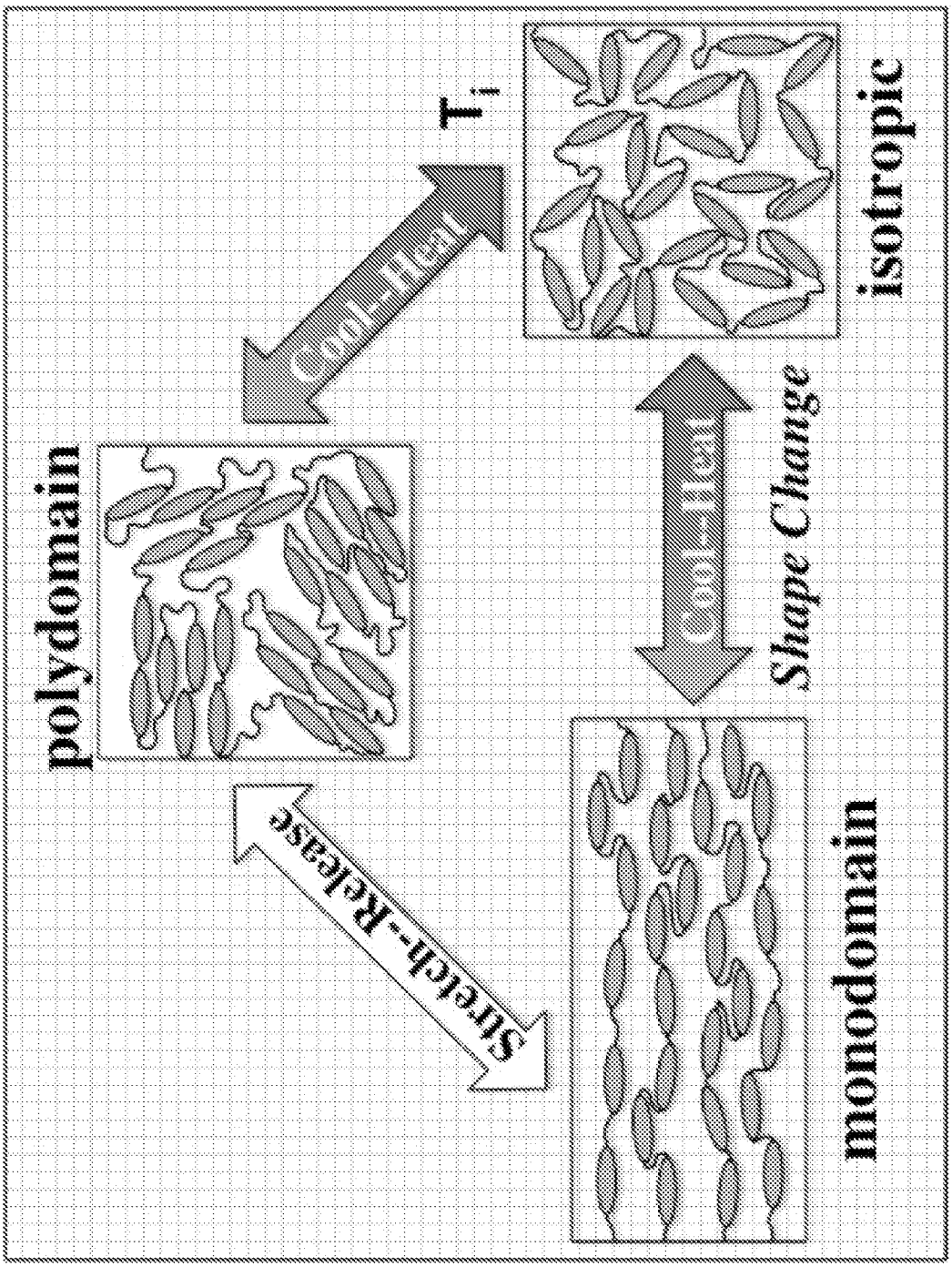

polydomain
Stretch-Release
monodomain
Cool-Heat
T_i
isotropic
Cool-Heat
Shape Change

FIGURE 12

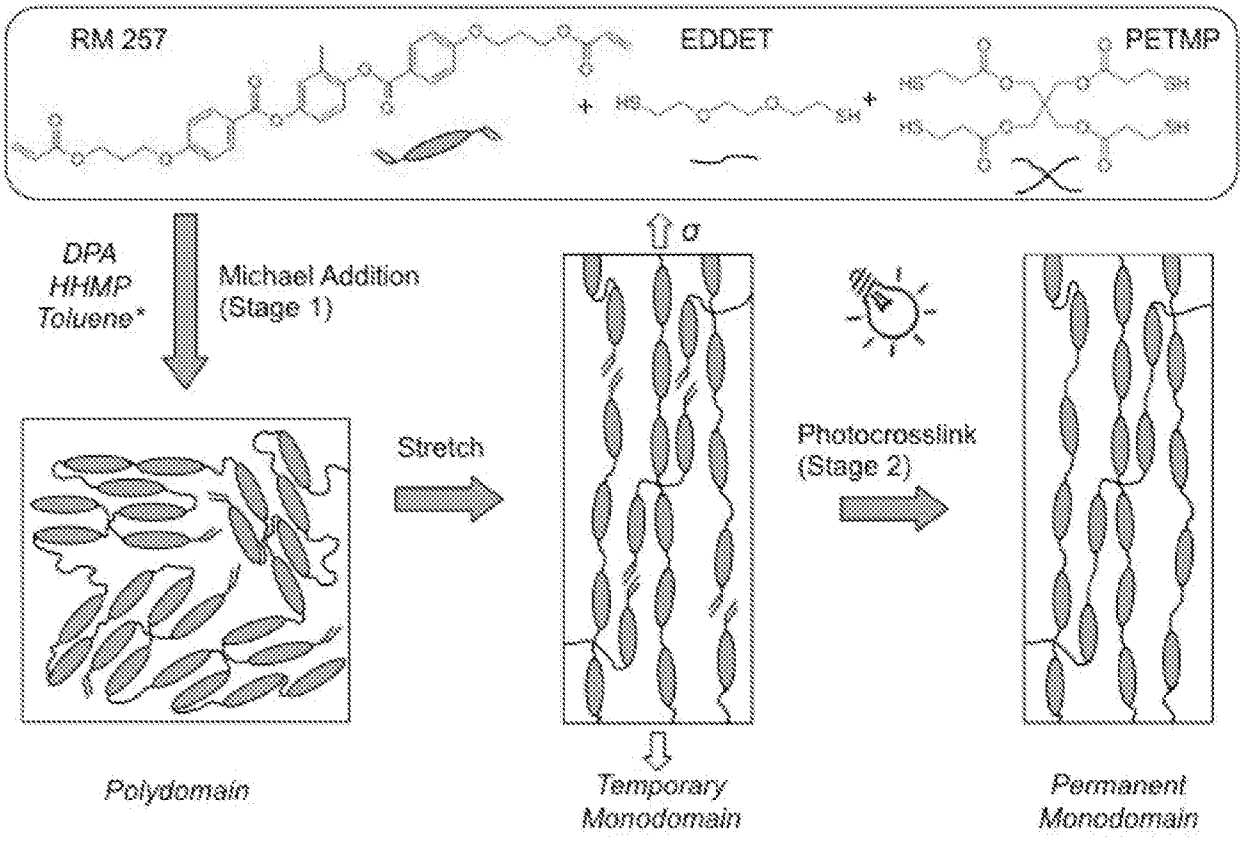

RM 257
EDDET
PETMP
DPA
HHMP
Toluene*
Michael Addition
(Stage 1)
Stretch
σ
Photocrosslink
(Stage 2)
Polydomain
Temporary
Monodomain
Permanent
Monodomain

FIGURE 13

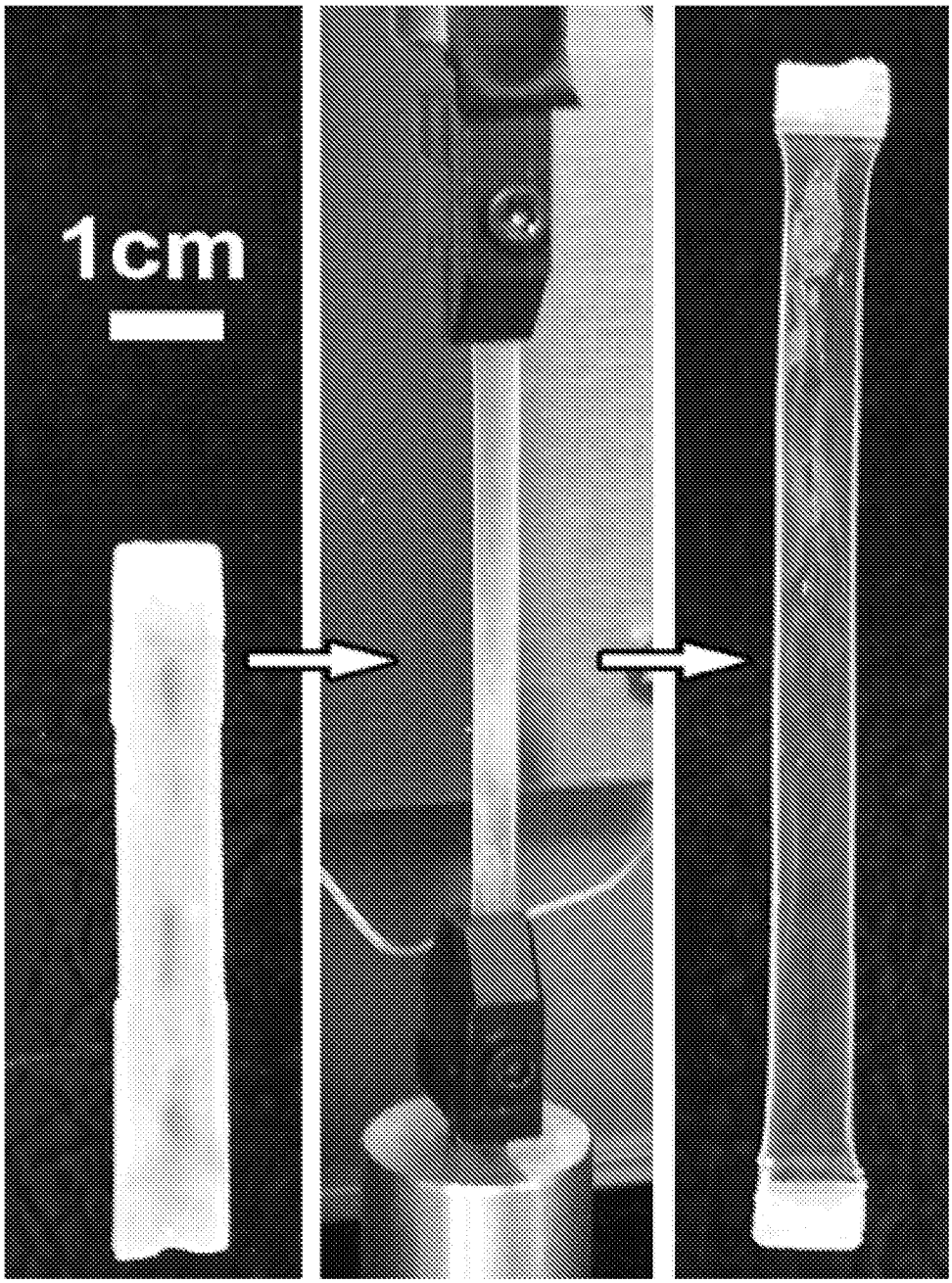


FIGURE 14

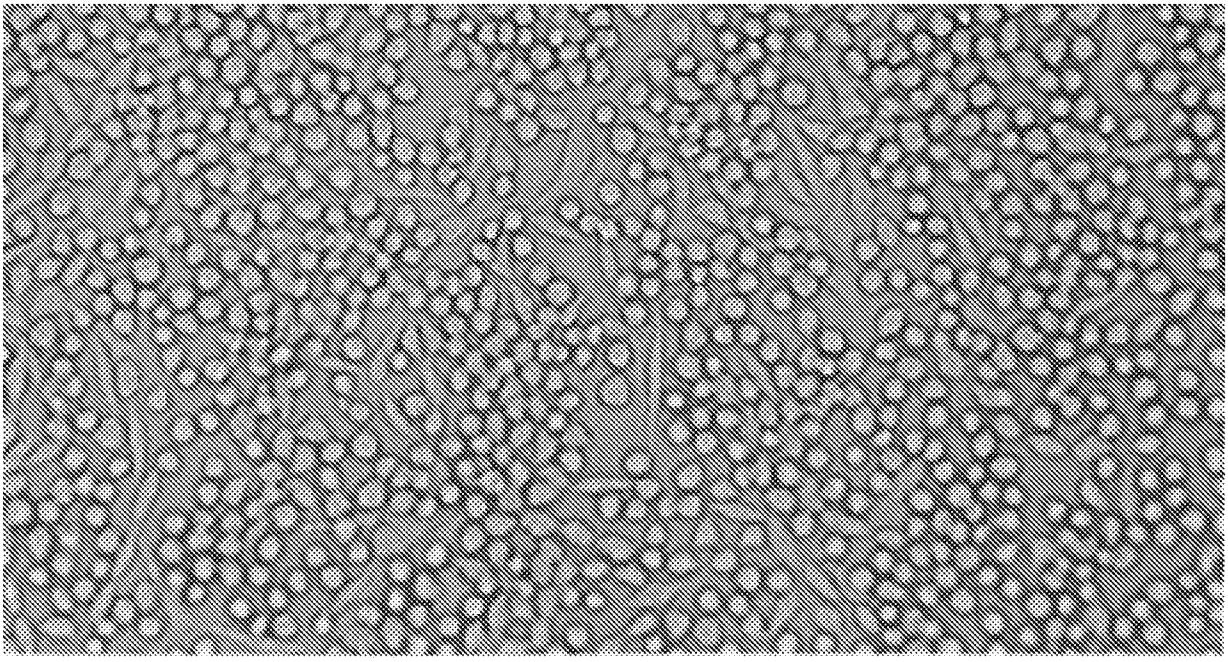


FIGURE 15

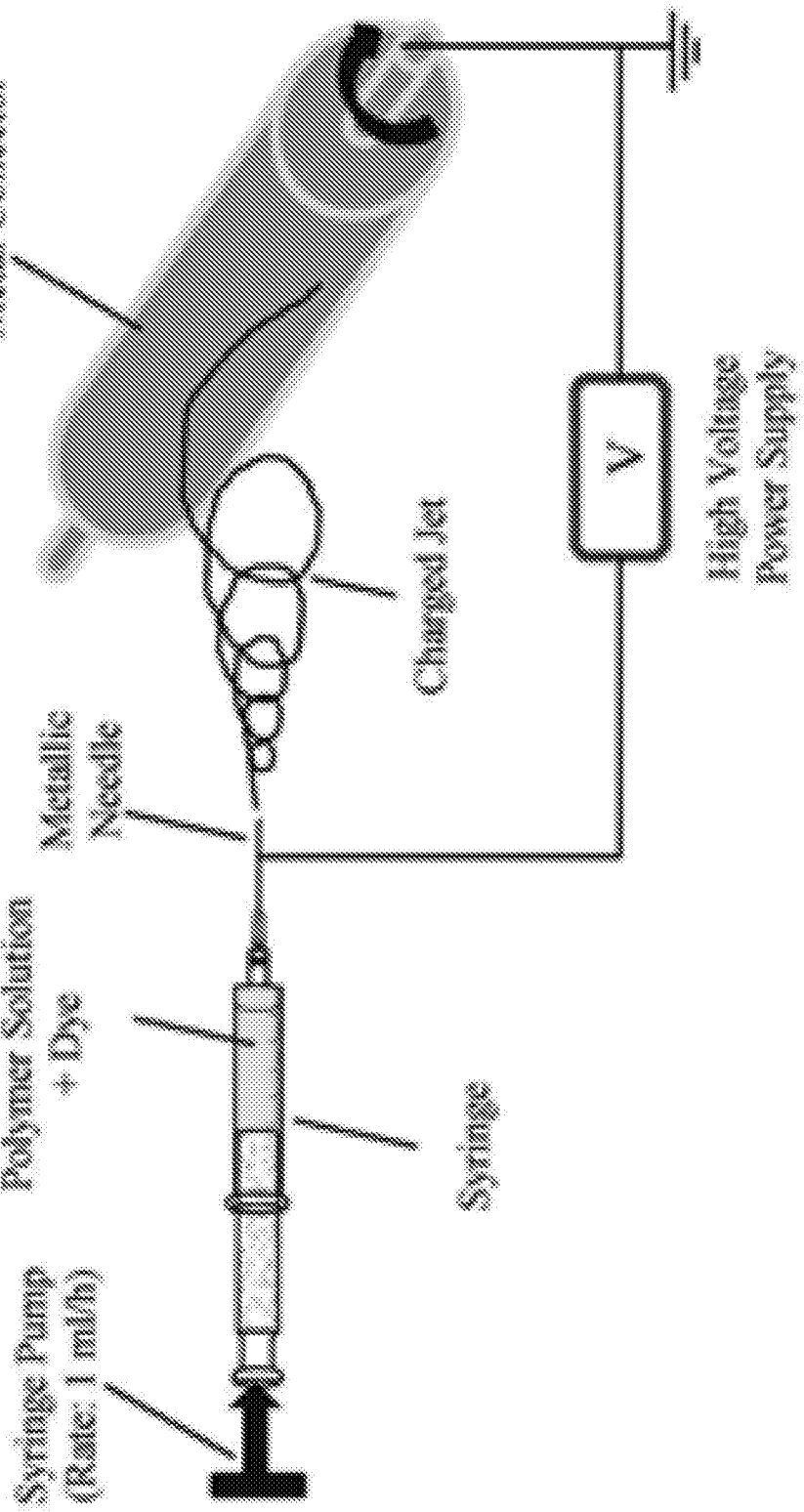
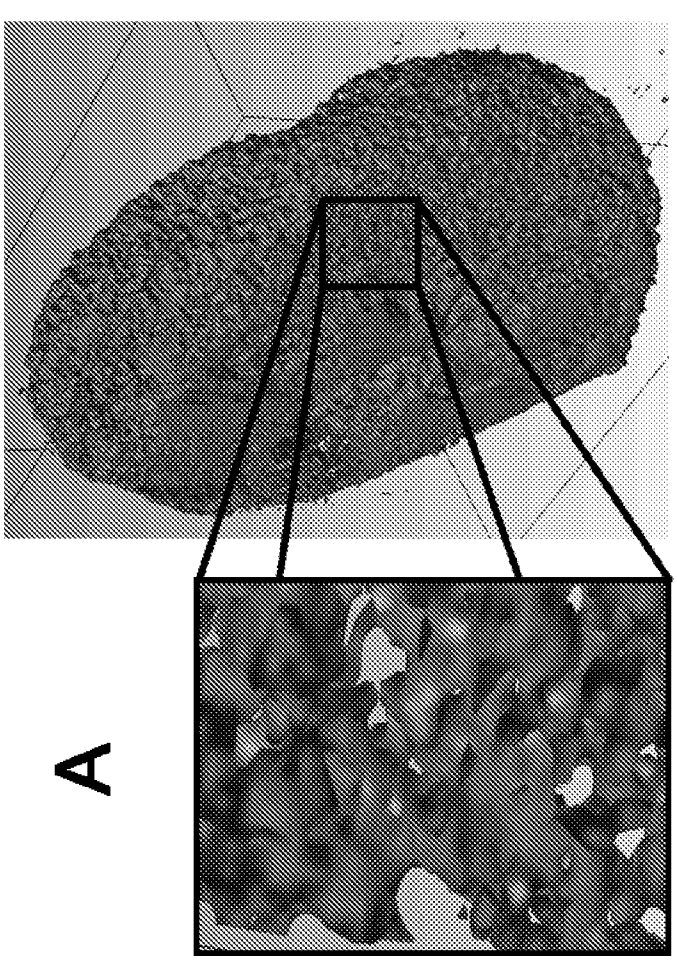

Metal Collector
Charged Jet
V
High Voltage
Power Supply
Metallic
Needle
Polymer Solution
+ Dye
Syringe
Syringe Pump
(Rate: 1 ml/h)

FIGURE 16



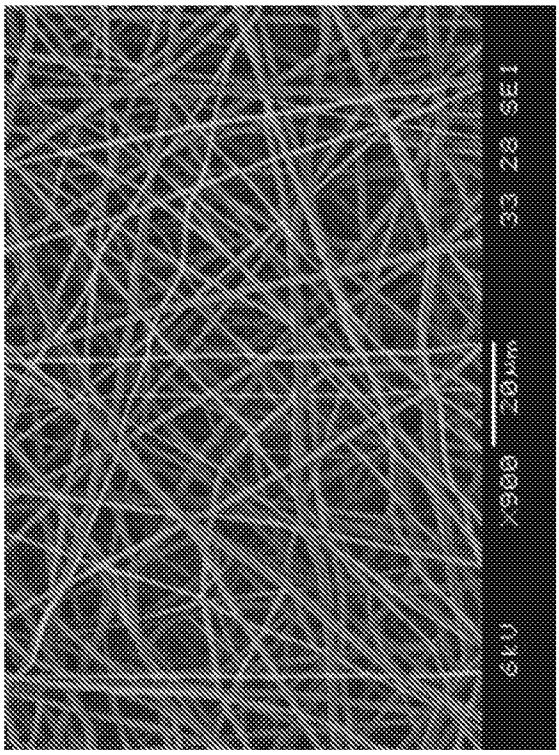


FIGURE 17

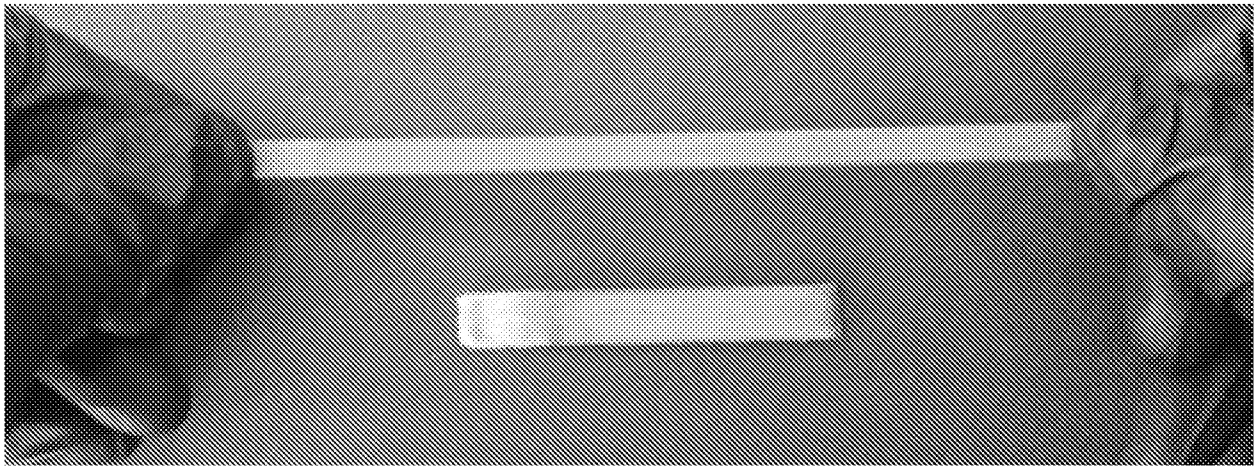


FIGURE 18

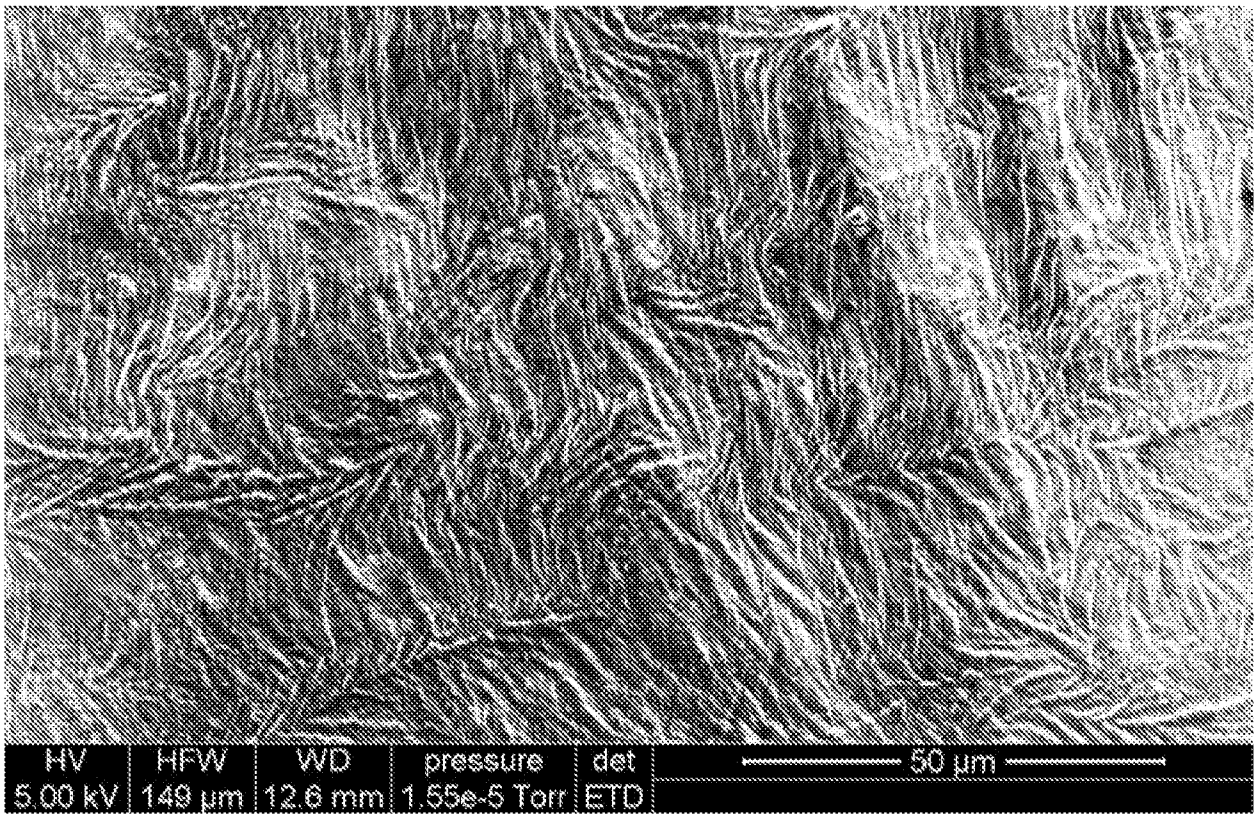


FIGURE 19

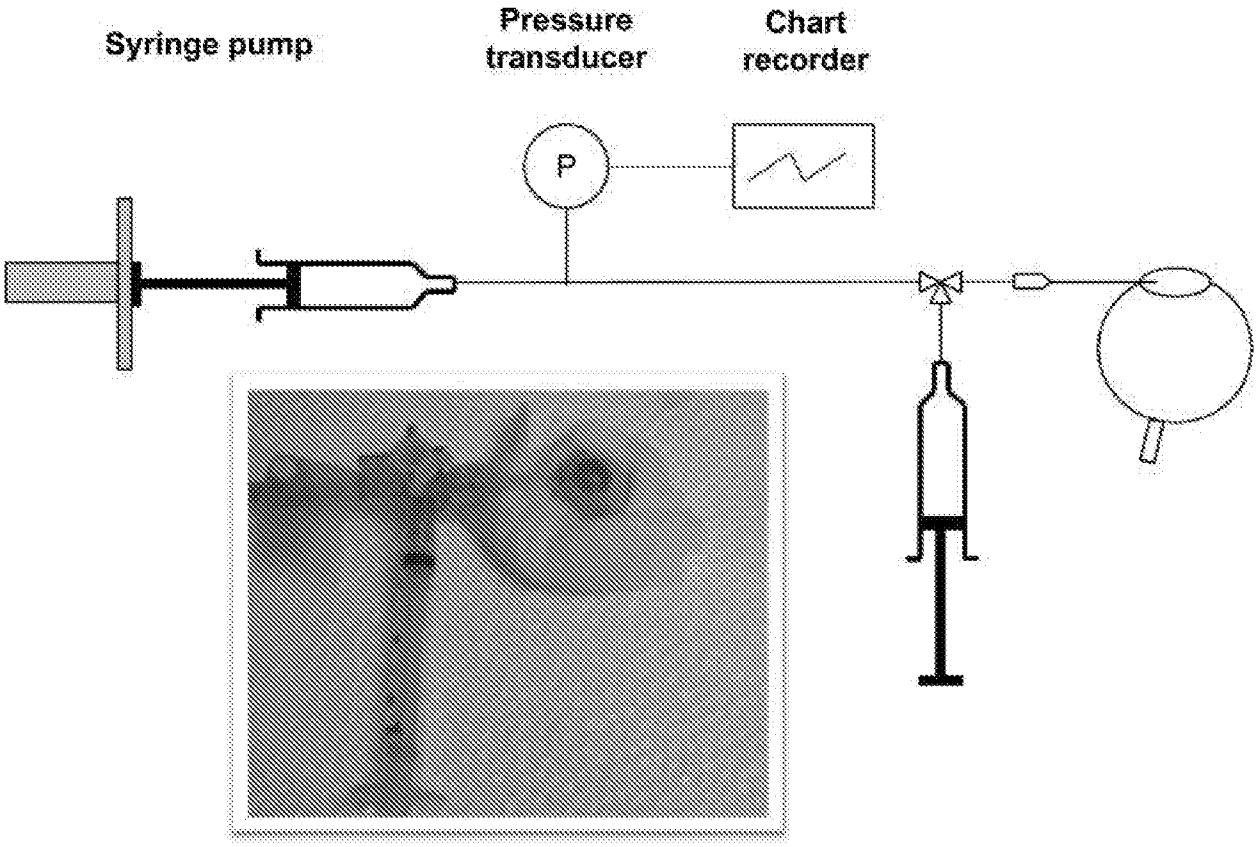


FIGURE 20

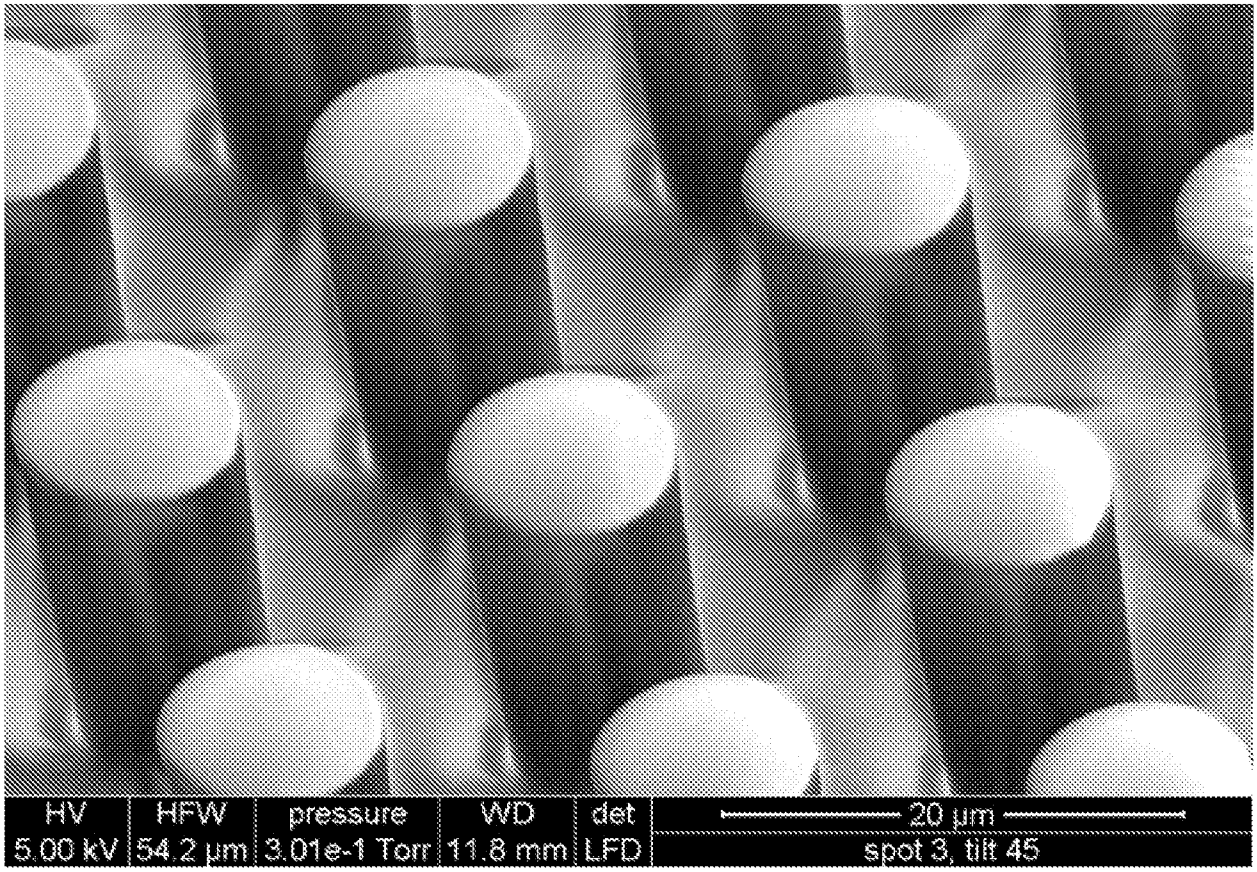

HV
5.00 kV
HFW
54.2 µm
pressure
3.01e-1 Torr
WD
11.8 mm
det
LFD
20 µm
spot 3, tilt 45

FIGURE 21

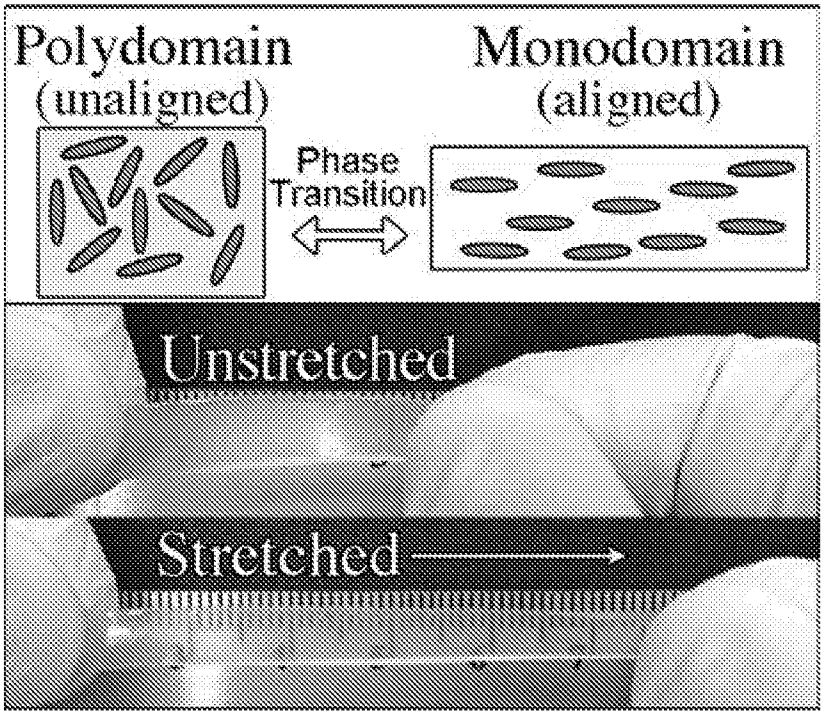

Polydomain
(unaligned)
Monodomain
(aligned)
Phase
Transition
Unstretched
Stretched

FIGURE 22

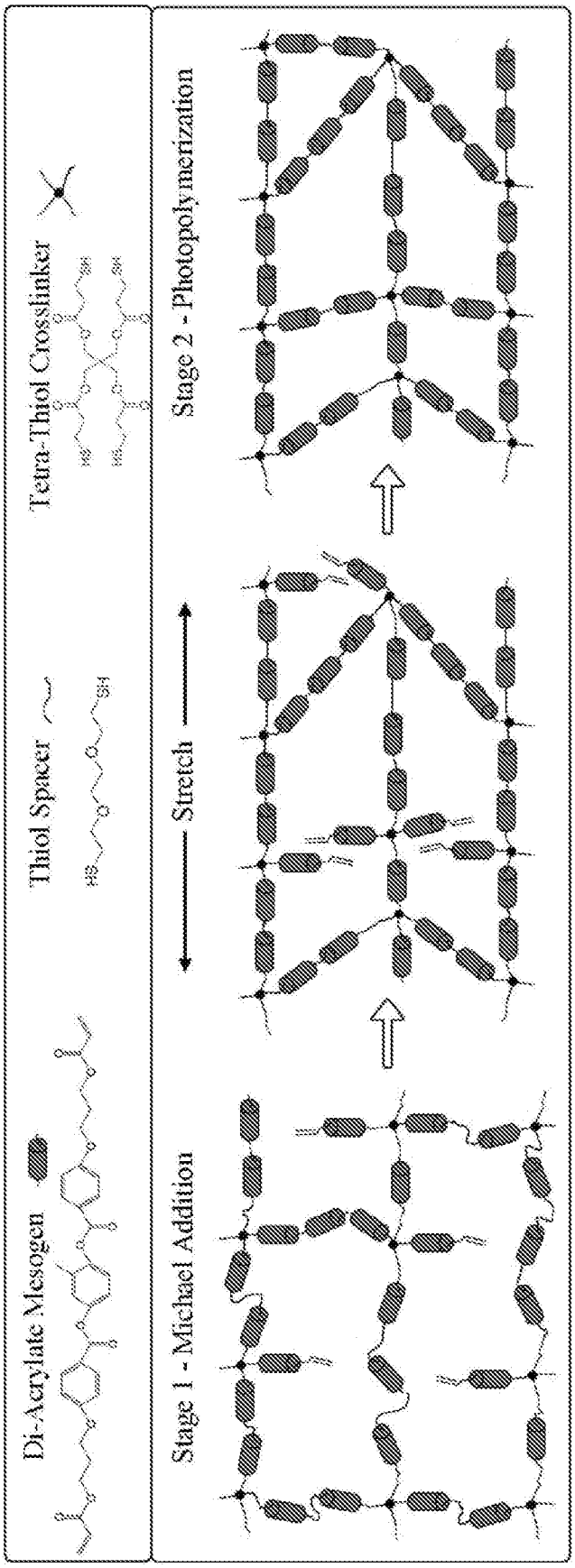

Di-Acrylate Mesogen
Thiol Spacer
Tetra-Thiol Crosslinker
Stage 1 - Michael Addition
Stretch
Stage 2 - Photopolymerization

FIGURE 23

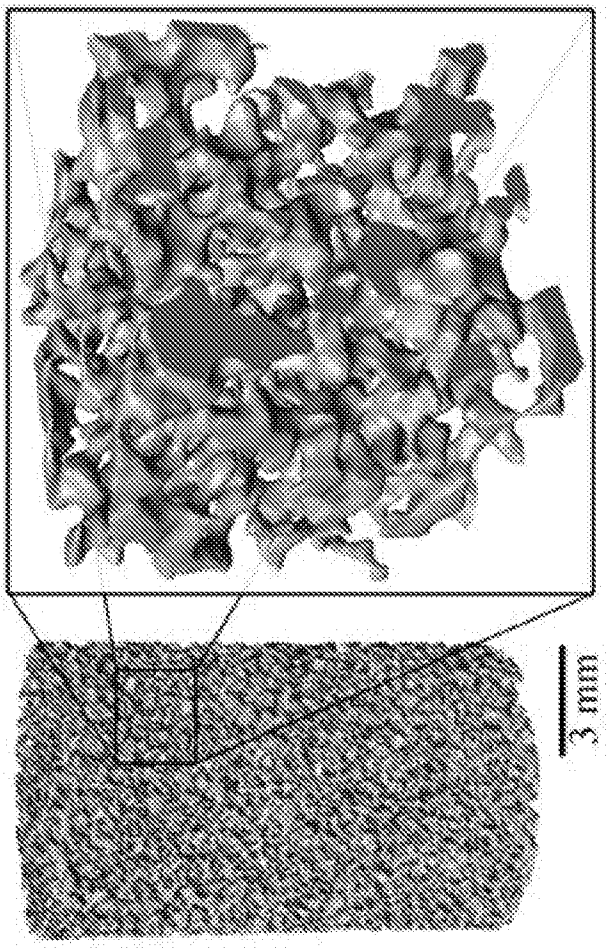


FIGURE 24

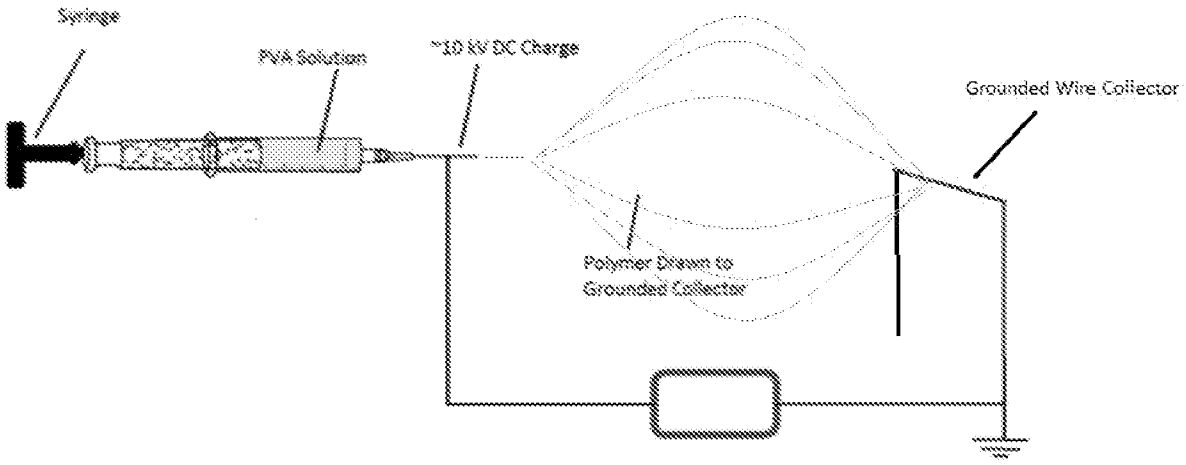


FIGURE 25

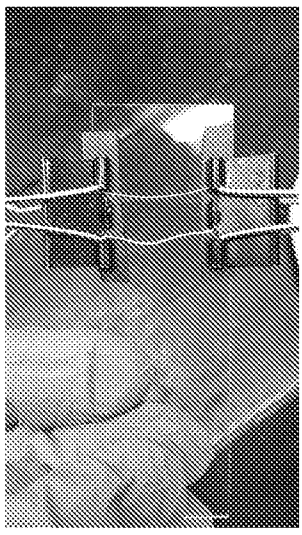


FIGURE 26

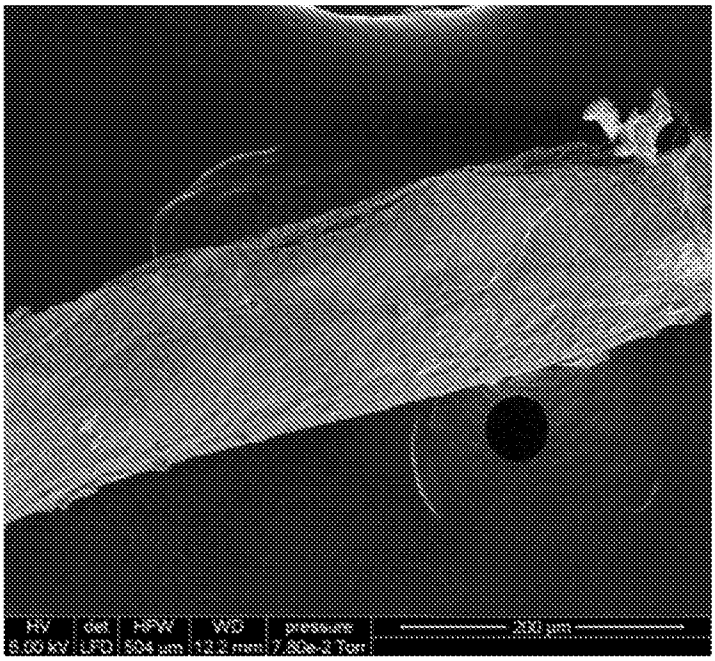


FIGURE 27

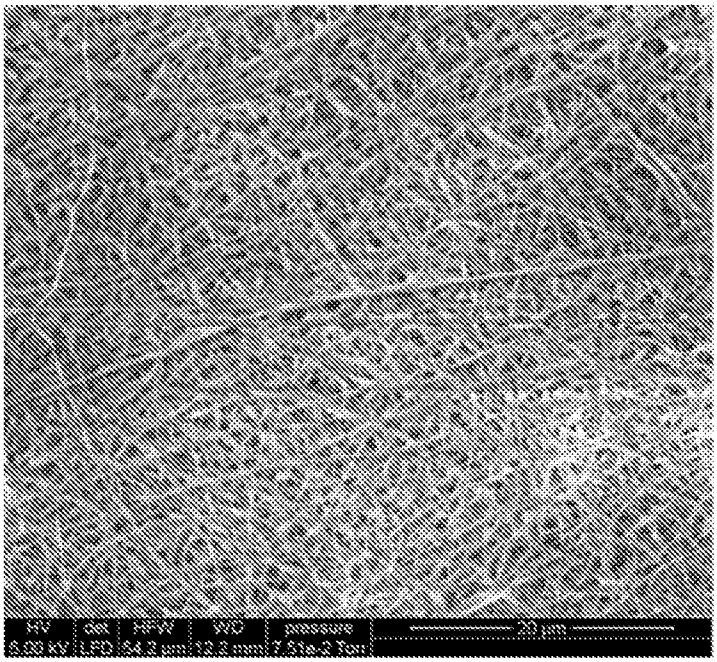


FIGURE 28

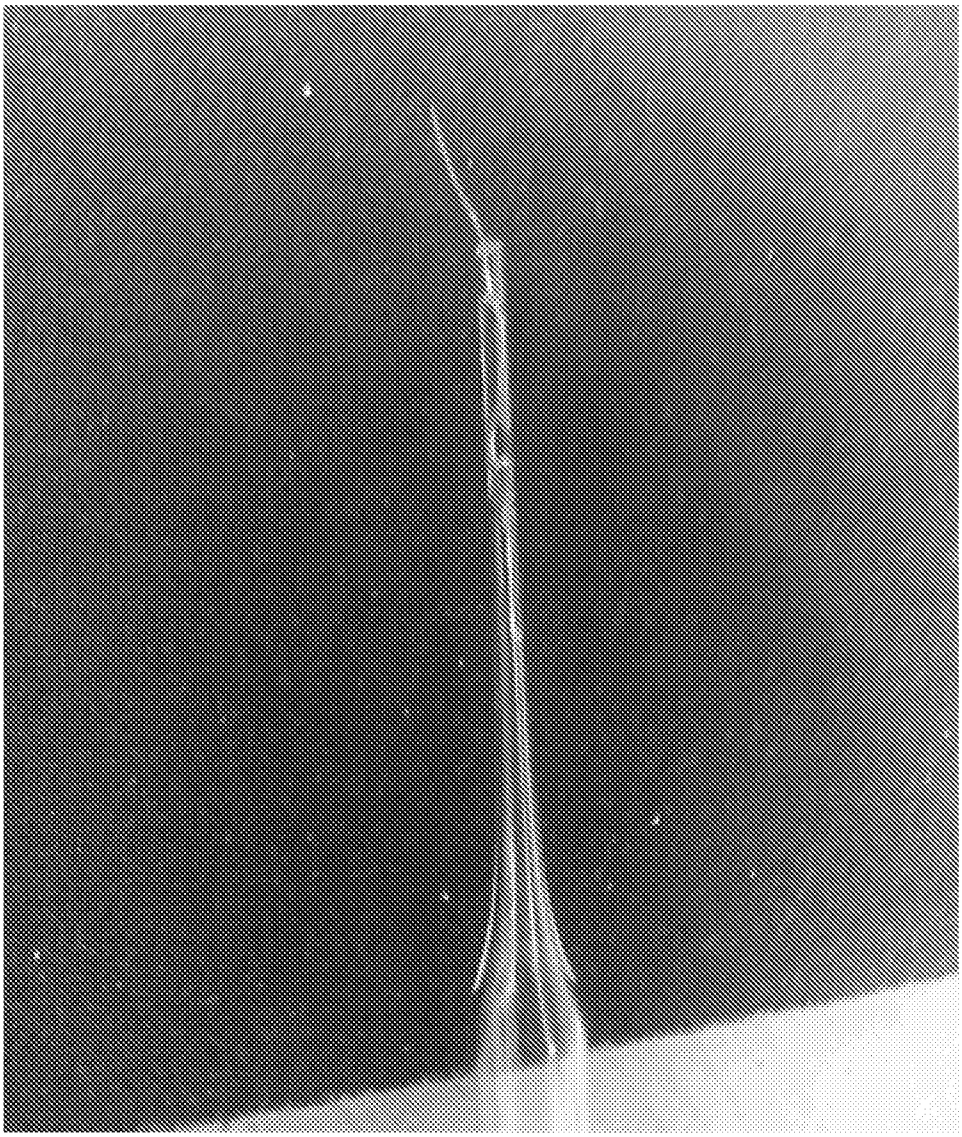


FIGURE 29

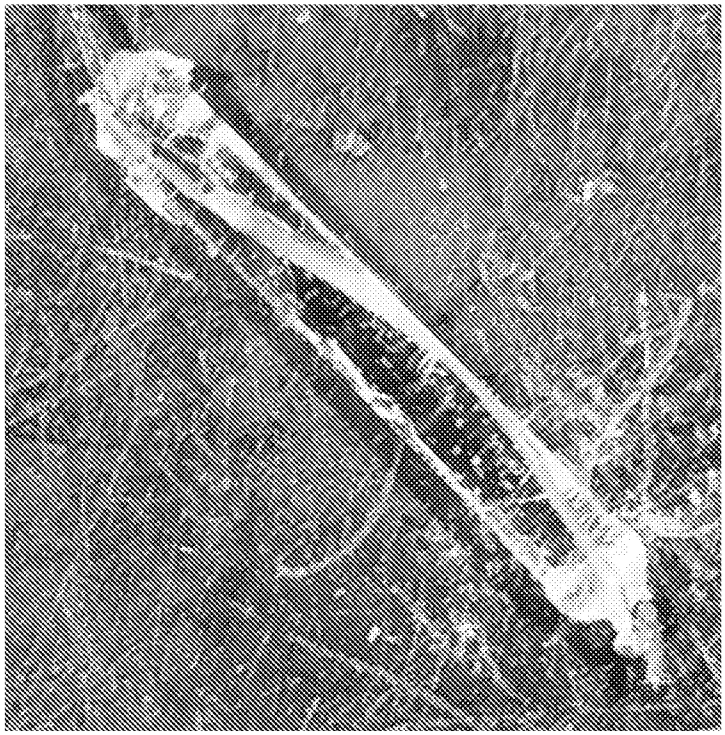
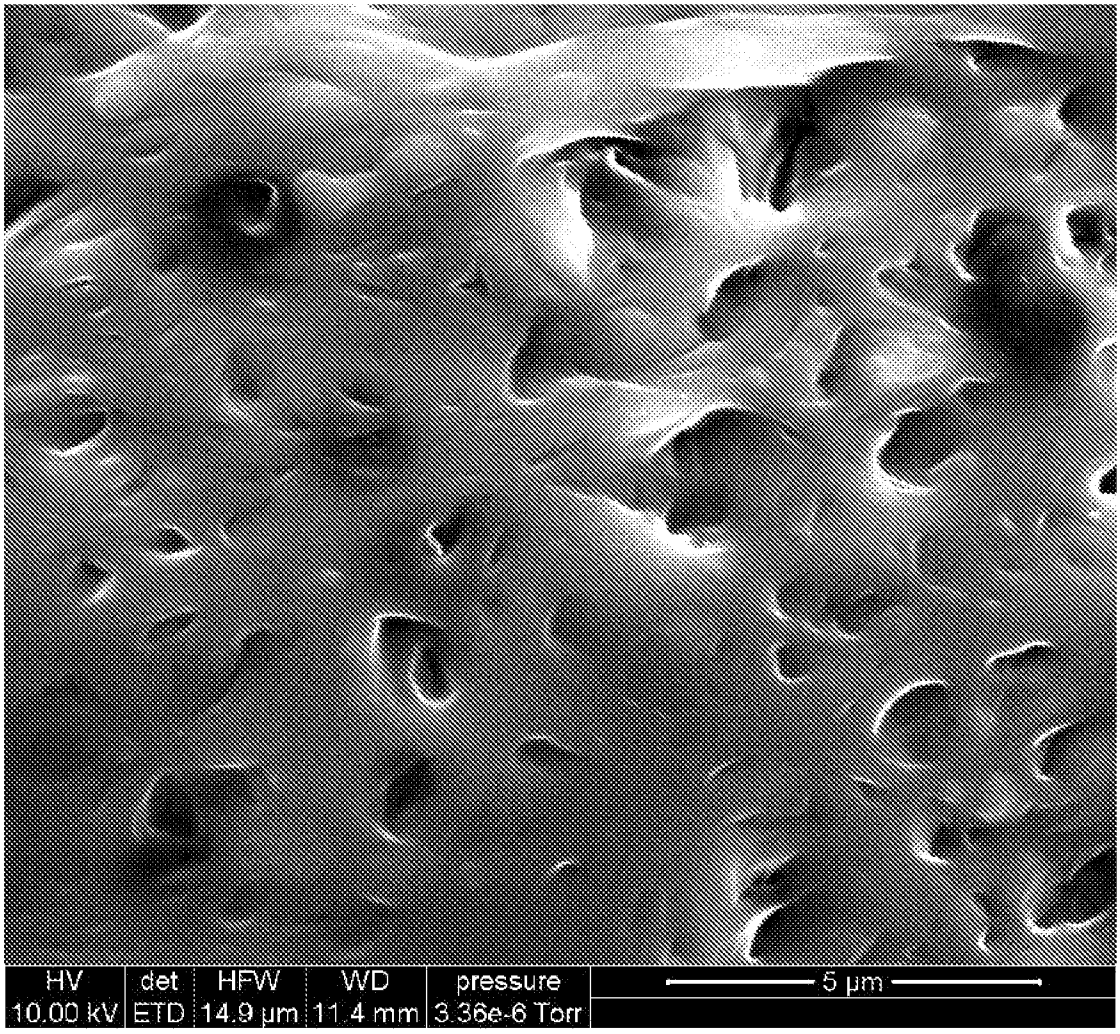


FIGURE 30



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/66068

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61F9/007, A61M27/00 (2016.01)
CPC - A61F9/00781, A61M1/0094, A61F9/0017
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)
CPC: A61F9/00781, A61F9/0017, A61F9/022, A61M1/0001, A61M1/0094, A61M1/0096, A61M27/00, A61M27/002;
IPC(8): A61F9/007, A61M1/00, A61M27/00 (2016.01)

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Orbit; PubMed; EBSCO; Google/Google Scholar; KEYWORDS: ocular, eye, pressure, glaucoma, opthalm*, drain*, shunt, cylind*, channel, tube, anti_microbial, filter, hollow, conduit, titanium dioxide, liquid crystal, elastom*, pore, porous, elastomer, cool*, chill, temperature, degrees, polymer*, diameter

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 2008/0161741 A1 (BENE, E et al.) 03 July 2008; figures 1, 2, 23, 43-44; paragraphs 30, 32-33, 36, 39, 44-46, 53, 56, 60, 65, 67, 71-72, 87	1,4, 6-9, 11-12, 17, 19, 22, 24, 26, 28, 30-32 ---------- 2-3, 5, 10, 13, 15, 18, 20-21, 23, 25, 27, 29
Y	US 2004/0193095 A1 (SHADDUCK, J) 30 September 2004; figures 3, 5, paragraphs 23, 25	2-3, 18, 20
Y	EP 1,741,457 A1 (OTTAWA HEALTH RESEARCH INSTSTITUE, et al.) 10 January 2007; claims 1, 3; paragraphs 90, 99-100	5
Y	US 2003/0212383 A1 (COTE, D et al.) 13 November 2003; paragraphs 17, 30, 37	13
Y	US 4,849,223 A (PRATT, A et al.) 18 July 1989; column 4, lines 33-38; claims 4, 9	10
Y	US 2010/0168644 A1 (BROWN, D) 01 July 2010; figure 3A-B, paragraphs 13-14, 31, 41, 56-57	21, 29
Y	US 2003/0229303 A1 (HAFFNER, D et al.) 11 December 2003; figure 3; paragraphs 55, 69-70, 110, 112	23
Y	US 5,868,697 A (RICHTER, J et al.) 09 February 1999; column 5, lines 21-27	25
Y	US 2014/0236067 A1 (AQUESYS, INC) 21 August 2014; paragraph 122	27
Y	US 2004/0111111 A1 (LIN, H) 10 June 2004; paragraphs 39, 56	15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2016 (05.02.2016)	04 MAR 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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