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(71) Applicant: CORNELL UNIVERSITY [US/US]; Center for Technology Licensing ("CTL") at Cornell University, 395 Pine Tree Road, Suite 310, Ithaca, New York 14850 (US).

(72) Inventors: MA, Minglin; 105 Lisa Place, Ithaca, New York 14850 (US). PHAM, Tung T.; 68 Springbrook Circle, Ithaca, New York 14850 (US). BOWERS, Daniel; 113 Village Circle, Apt. A, Ithaca, New York 14850 (US). FLANDERS, James; 490 Snyder Hill Road, Ithaca, New York 14850 (US).

(74) Agent: MERKEL, Edwin et al.; 70 Linden Oaks, Suite 210, Rochester, New York 14625 (US).

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(54) Title: DRUG-ELUTING ANTI-FIBROTIC MACROENCAPSULATION (DREAM) DEVICES FOR DELIVERY OF THERAPEUTIC CELLS

(57) Abstract: Disclosed herein are an implantable therapeutic delivery system, methods of making the same, and methods of using the same. This system includes a hydrogel matrix comprising at least one therapeutic agent and a membrane that partially or fully encapsulates the hydrogel matrix. The membrane comprises a nitinol mesh-reinforced hydrogel or nanofibrous material.

DRUG-ELUTING ANTI-FIBROTIC MACROENCAPSULATION (DREAM) DEVICES FOR DELIVERY OF THERAPEUTIC CELLS

[0001] This application claims the priority benefit of U.S. Provisional Patent Application Serial No. 63/600,090, filed November 17, 2023, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to drug-eluting anti-fibrotic microencapsulation (DREAM) devices for delivery of therapeutic cells, the use of such devices for delivering a therapeutic agent to a subject in need thereof and thereby treating the subject for one or more diseases or conditions, as well as methods of making such devices.

BACKGROUND

[0003] Implantation of engineered therapeutic cells to continuously deliver biomolecules (e.g., insulin, antihemophilic factor, erythropoietin, dopamine) is a promising strategy for treating chronic diseases such as type 1 diabetes, hemophilia, anemia, and Parkinson's disease. However, the clinical applications of cell therapy are limited due to the requirement of lifelong immunosuppression to protect the implanted cells from the host immune system. In addition, engineered cells generally pose a risk of unwanted events such as teratoma. Therefore, it is critical to developing a strategy for immunoprotection and safe delivery of these cells. Over the past few decades, encapsulation of cells in semipermeable and retrievable systems has been proposed to tackle these issues. The perm-selectivity allows for diffusion of nutrients/oxygen and therapeutic biomolecules while preventing the penetration of immune cells. Besides, cell confinement within the systems could completely prevent cell escape, thus, averting the risks of unwanted events. The most intensively studied cell encapsulation system so far is hydrogel microcapsules, which can be implanted into the peritoneal cavity via a minimally invasive laparoscopic procedure. However, the inability to reliably retrieve all implanted capsules raises safety concerns in clinical applications. To address this issue, several retrievable cell encapsulation devices have been developed using different configurations such as hydrogel thread (Fukuda et al., "The Intraperitoneal Space is More Favorable than the Subcutaneous One for Transplanting Alginate Fiber Containing iPS-derived Islet-like Cells," *Regen. Ther.*, 11:65-72 (2019)), porous tubes, thread-reinforced hydrogel fiber (An et al., "Designing a Retrievable and Scalable Cell Encapsulation Device for Potential Treatment of Type 1 Diabetes," *Proc. Natl. Acad. Sci.*, 115(2):E263-E272 (2018)), hydrogel-incorporated nanofiber tubes (Wang et al., "A

Nanofibrous Encapsulation Device for Safe Delivery of Insulin-producing Cells to Treat Type 1 Diabetes," *Sci. Transl. Med.*, 13(596):eabb4601 (2021)). Though these devices were able to provide long-term survival of cells and retrievability in mouse models, they possess several limitations that may hinder clinical translation. First, cellular overgrowth and omentum adhesion after long-term implantation could aggravate cell survival and preclude retrievability. Second, devices made of mechanically weak materials (e.g., hydrogel and thin, porous membranes) are unable to maintain their original shapes after implantation and tend to be disrupted. In addition, device kink could further exacerbate the fibrotic responses. In contrast, rigid devices that avoid the use of weak materials (to overcome this specific problem) may potentially create an alternative problem: eliciting fibrosis and causing injuries to organs. Third, it is challenging to balance between scale up to deliver a clinical dose of cells while maintaining favorable conditions for their survival and function.

[0004] The present invention is directed to overcoming these and other deficiencies in the art.

SUMMARY

[0005] A first aspect of the present disclosure relates to an implantable therapeutic delivery system. This system comprises a hydrogel matrix comprising at least one therapeutic agent and a membrane that partially or fully encapsulates the hydrogel matrix. In one embodiment, the membrane includes a nitinol mesh-reinforced hydrogel. In another embodiment, the membrane includes a nitinol mesh-reinforced nanofibrous material. In yet another embodiment, the membrane includes a nitinol-reinforced hydrogel and nanofibrous material.

[0006] A second aspect of the present disclosure relates to a method of delivering a therapeutic agent to a subject in need thereof. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject.

[0007] A third aspect of the present disclosure relates to a method of treating diabetes in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having diabetes. The implanted therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating diabetes while the therapeutic delivery system remains implanted.

[0008] A fourth aspect of the present disclosure relates to a method of treating a bleeding disorder in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having a bleeding disorder. The implanted

therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating the bleeding disorder while the therapeutic delivery system remains implanted.

[0009] A fifth aspect of the present disclosure relates to a method of treating a lysosomal storage disease in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having the lysosomal storage disease. The implanted therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating the lysosomal storage disease while the therapeutic delivery system remains implanted.

[0010] A sixth aspect of the present disclosure relates to a method of treating a neurological disorder in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having the neurological disorder. The implanted therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating the neurological disorder while the therapeutic delivery system remains implanted.

[0011] A seventh aspect of the present disclosure relates to a method of treating a cancer in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having cancer. The implanted therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating the cancer while the therapeutic delivery system remains implanted.

[0012] An eighth aspect of the present disclosure relates to a method of treating a chronic eye disease in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having a chronic eye disease. The implanted therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating the chronic eye disease while the therapeutic delivery system remains implanted.

[0013] A ninth aspect of the present disclosure relates to a method of treating a kidney failure in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having a kidney failure. The implanted therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating kidney failure while the therapeutic delivery system remains implanted.

[0014] A tenth aspect of the present disclosure relates to a method of treating a chronic pain in a subject. This method involves implanting the implantable therapeutic delivery system according to the first aspect into the subject having a chronic pain condition. The implanted

therapeutic delivery system is capable of delivering to the subject one or more therapeutic agents effective for treating chronic pain while the therapeutic delivery system remains implanted.

[0015] An eleventh aspect of the present disclosure relates to a method of forming a cell encapsulation system suitable for implant. This method involves providing a hydrogel precursor solution comprising at least one therapeutic agent in the hydrogel precursor solution; and introducing the hydrogel precursor solution internally of a membrane comprising a nitinol mesh-reinforced hydrogel and/or nanofibrous material, and allowing the hydrogel precursor to form a hydrogel matrix that is partially or fully encapsulated by the membrane.

[0016] Disclosed herein and exemplified in the accompanying Examples are **DRug-Eluting Anti-fibrotic Macroencapsulation** devices, termed **DREAM** devices, which address the above-noted deficiencies of other cell encapsulation devices. To improve the mechanical properties of the devices, methods were first developed to reinforce hydrogel or nanofiber membranes with a thin shape-memory nitinol mesh to make elastic, soft, but durable membranes, namely **Nitinol-Reinforced Alginate (NIREA)** membrane and **Nitinol-Reinforced Nanofibrous (NIREN)** membrane. Devices made of these reinforced membranes effectively maintain their original shapes after implantation even with the thickness of a few tens of micrometers. This enables more efficient mass transportation, which is favorable for cell survival and function. In addition, the elasticity and softness of NIREA and NIREN membranes prevent device kink and cause minimal stress on intraperitoneal organs, thereby improving the safety of the devices and potentially reducing host responses to the devices. Second, different device configurations were designed to improve the encapsulation capacity of the device while maintaining the optimal mass transportation distance, which is crucial for functions of islets/ β cells. For example, the elasticity of NIREA and NIREN membranes allowed the establishment of a facile method to prepare devices having a tube-in-tube configuration where the islets/SC- β clusters are encapsulated within the thin wall of the device (*see* FIG. 1). This configuration facilitates scale-up in both radial and longitudinal directions while keeping encapsulated cells near the outermost surface of the device for efficient mass transport. Alternatively, devices can be prepared using a flat bar stock configuration with a thickness less than 800 μm , which results in a diffusion distance of < 400 μm (*see* FIG. 2). This device configuration can be scaled up by simply increasing width and length.

[0017] Also disclosed herein is a method for preparing crystalline particles of anti-fibrotic drugs, and their use to prevent foreign body response to a cell encapsulation device. To mitigate the foreign body response, crystalline particles of several anti-fibrotic drugs—including nintedanib, pirfenidone, and GW2580—were prepared and loaded into the inner lumen of the

devices. That is, the anti-fibrotic drug particles were loaded into the hydrogel matrix. The crystalline forms and particle sizes were optimized to achieve long-term and continuous drug release, maintaining a steady drug level in the vicinity of free-floating, *i.e.*, unanchored, devices in the intraperitoneal cavity to mitigate fibrotic reactions. Loading drugs into the hydrogel matrix core of device, instead of on the device surface, could avoid particle detachment and structural changes of the device surface after those crystalline drugs dissolve.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 shows schematic illustrations for proposed designs of tubular DREAM devices.

[0019] FIG. 2 shows proposed designs for flat bar DREAM devices and the encapsulation capacity of each version.

[0020] FIGs. 3A-3D show characterizations of nanofiber membranes made of different medical-grade elastomers. FIG. 3A shows SEM images of a nanofiber membrane prepared using different concentrations of PEBAX (5%, 7.5%, 10%, and 15%). FIGs. 3B-3C show fiber size of nanofiber membrane prepared using different concentrations of PEBAX (5%, 7.5%, 10%, and 15%). FIG. 3D shows SEM images and stretchability of PEBAX, QTHAN, and QFLEX membranes.

[0021] FIGs. 4A-4H show characterizations of NIREN tubes. FIG. 4A shows macroscopic images of tubular nitinol tubes prepared with different lengths. FIG. 4B shows a representative bright-field image of nitinol mesh. Scale bar: 1000 μm . FIGs. 4C-4D show representative SEM/EDS image showing the hierarchical structure of NIREN membrane. Scale bar: 50 μm (FIG. 4C) and 100 μm (FIG. 4D). FIG. 4E shows an image showing a 10-cm NIREN tube was bent without kink. FIGs. 4F-4H show the flexibility and elasticity of NIREN tube. The tube returned to its original shape after being twisted.

[0022] FIGs. 5A-5B show preparation and characterizations of flat bar NIREN tubes. FIG. 5A shows a digital image showing the installation of nitinol tubes on the stainless-steel mandrel for collecting nanofibers. FIG. 5B shows a NIREN tube maintained the open lumen while the neat nanofiber tube with the same thickness could not.

[0023] FIGs. 6A-6D show mechanical characteristics of flat bar NIREN tubes. FIGs. 6A-6B show macroscopic images showing the device could be bent without kink. FIGs. 6C-6D show shape-memory feature of the NIREN tube. The tube quickly returned to its original shape after being bent and twisted.

[0024] FIGs. 7A-7D show a method to load cells/islets in a tube-in-tube NIREN device. FIG. 7A shows that to load cells/islets in the space between 2 NIREN tubes, cell suspension is first deposited on the inner tube (diameter: 5 mm). FIG. 7B shows representative images showing the distribution of 150 μ m polystyrene beads used to mimic pancreatic islets between two nitinol tubes. FIG. 7C shows representative images showing the insertion of a 23-cm long NIREN tube into a 25-cm long NIREN tube. The diameter of both tubes was 5 mm. FIG. 7D shows the final device possessed the similar elasticity and shape memory feature of the NIREN tube.

[0025] FIGs. 8A-8C show preparation of NIREA tubes. FIG. 8A shows a schematic illustration demonstrating a method for preparation of NIREA tubes. FIG. 8B shows bright-field images of the flat bar (left) and tubular (right) NIREA devices. Scale bar: 5 mm. FIG. 8C shows stability of the alginate layer. The device could be bent without the detachment of alginate layer. Scale bar: 2 mm.

[0026] FIG. 9A-9I show mechanical characteristics of flat bar NIREA tubes. FIGs. 9A-9B show images showing a 25-cm NIREA tube. FIGs. 9C-9G show the elasticity of NIREA tube allows the devices to be bent without kink. FIGs. 9H-9I show the device could be twisted and rolled around a rod, which is beneficial for minimally invasive implantation of the device into intraperitoneal (IP) cavity by the laparoscopic procedure.

[0027] FIG. 10 shows a method for cell loading into a flat bar NIREA device. (1) The elasticity of the NIREA membrane allows for wider open of the device by applying pressure to the edges of the device. (2) Cell suspension can be loaded through the open end. (3) The device returns to its original shape after pressure is released. (4) The device can be sealed using alginate hydrogel.

[0028] FIGs. 11A-11B show preparation of crystalline anti-fibrotic drugs. FIG. 11 A shows a schematic illustration demonstrating the method for preparation of crystalline drugs. FIG. 11B shows bright-field images of crystalline nintedanib, GW2580, and pirfenidone prepared with different particle sizes.

[0029] FIGs 12A-12B show the effect of Nintedanib on the morphology and viability of human islets. FIG. 12A shows bright-field images of human islets incubated with nintedanib at different concentrations (0, 0.1, 0.2, 0.5, 1, and 2 μ M) for 24 h. Scale bar: 500 μ m (upper) and 300 μ m (lower). FIG. 12B shows viability assessment of islets incubated with nintedanib at different concentrations (0, 0.1, 0.2, 0.5, and 2 μ M) for 24 h using live/dead staining. Scale bar: 500 μ m.

[0030] FIGs. 13A-13C show post-implantation evaluation of Nylon 6 devices without drug and Nylon 6 devices containing 3.5 mg of either crystalline nintedanib or crystalline GW2580. FIG. 13A shows Masson's trichrome staining of devices retrieved 1 month after implantation. Scale bar: 100 μ m. FIG. 13B shows phase-contrast images of crystalline GW2580 in the core of the device retrieved 1 month after implantation. Scale bar: 2000 μ m (upper) and 400 μ m (lower). FIG. 13C shows phase-contrast images of crystalline nintedanib in the core of the device retrieved 1 month after implantation. Scale bar: 2000 μ m (upper) and 400 μ m (lower).

[0031] FIGs. 14A-14D show evaluation of nanofibrous DREAM devices after 6-week implantation in Göttingen minipigs. FIG. 14A shows laparoscopic images of devices with or without crystalline nintedanib at day 0 and day 42 after being implanted into the intraperitoneal cavity of Göttingen minipigs. FIG. 14B shows a macroscopic image (left) and Masson's trichrome staining (right) showing the fibrotic responses to the device without crystalline nintedanib. Scale bar: 500 μ m. FIG. 14C shows Masson's trichrome staining of the device containing crystalline nintedanib. Scale bar: 200 μ m. FIG. 14D shows images showing the presence and morphology of crystalline nintedanib in the core of the device. Scale bar: 5 mm (upper) and 400 μ m (lower).

[0032] FIGs. 15A-15G show evaluation of a nintedanib-eluting flat bar NIREA device after 2-month implantation in the intraperitoneal cavity of a farm pig. FIG. 15A shows a bright-field image of the device before implantation. FIG. 15B shows a laparoscopic image showing the location of the device after implantation. FIGs. 15C-15D show macroscopic images showing the device after 2-month implantation. FIG. 15E shows a bright-field image of the whole device retrieved after 2-month implantation. Scale bar: 5000 μ m. FIG. 15F shows a dark-field image of the alginate layer peeled off from the device. Scale bar: 2000 μ m. White arrows indicated the visible fibrotic layer. FIG. 15G shows phase-contrast images showing crystalline particles in the device.

[0033] FIG. 16 shows that one example of using 2 layers of the nanofibrous membrane is the integration of a nitinol mesh between two layers of nanofibrous material to mitigate delamination issues arising from suboptimal interaction between the nanofibrous layers and the nitinol mesh. In this configuration, the fibers from the outer nanofibrous layer can infiltrate the pores of the nitinol mesh and bond with the inner nanofibrous layer, thereby preventing the detachment of the outer fibrous layer.

[0034] FIG. 17 shows that the thickness of the nitinol mesh could fall within the 10 to 100 μ m range. This mesh could be crafted from nitinol wire with a diameter ranging from 10 to

100 μm , where the thickness of the mesh aligns with the wire's diameter used for its construction.

DETAILED DESCRIPTION

[0035] The present disclosure relates to implantable cell therapeutic delivery systems, methods of producing these systems, and methods of using the same.

[0036] One aspect of the disclosure relates to an implantable therapeutic delivery system. This implantable therapeutic delivery system includes a hydrogel matrix comprising at least one therapeutic agent and a membrane that partially or fully encapsulates the hydrogel matrix. The membrane includes a nitinol mesh-reinforced hydrogel and/or nanofibrous material.

[0037] The nitinol reinforced membrane is elastic, soft but durable to maintain the original shape and avoid kink as well as potential injuries to vital organs after implantation. The membrane is also thin enough for efficient mass transport. In certain embodiments, the membrane includes a nitinol mesh-reinforced hydrogel. In another embodiment, the membrane includes a nitinol mesh-reinforced nanofibrous material. In yet another embodiment, the membrane includes a nitinol-reinforced hydrogel and nanofibrous material.

[0038] In certain embodiments, the membrane fully encapsulates the hydrogel matrix such that the hydrogel matrix and its contents are immuno-isolated. That is, immune cells of the subject into which the implantable cell therapeutic delivery system is implanted cannot infiltrate the hydrogel matrix. This can be achieved by physically sealing any opening used during assembly of the implantable cell therapeutic delivery system, such as by thermally sealing the opening.

[0039] The variety of membrane constructions are not limited to any particular shape or configuration. Exemplary shapes or configurations are presented in the accompanying examples and include tubular and flat bar configurations. In a preferred embodiment, the nitinol reinforced membrane is used to prepare a device with a tube-in-tube configuration.

[0040] In some embodiments, the membrane comprises a nitinol mesh-reinforced hydrogel material. In some embodiments the nitinol mesh-reinforced hydrogel material comprises one or more nitinol mesh layers. The hydrogel material can comprise a natural polymeric material, a synthetic polymeric material, or a combination thereof.

[0041] Suitable natural polymeric materials that can be used include, without limitation, collagen, hyaluronate, fibrin, alginate, agarose, chitosan, bacterial cellulose, elastin, keratin, derivatives thereof, and combinations thereof. In some embodiments, the hydrogel material

comprises a pure alginate, a modified alginate, or a mixture of pure and modified alginate. In some embodiments, the modified alginate is a zwitterionically modified alginate.

[0042] Suitable synthetic polymeric materials that can be used include, without limitation, polyethylene glycol (PEG), poly(acrylic acid), poly(ethylene oxide), poly(vinyl alcohol), polyphosphazene, poly(hydroxyethyl methacrylate), triazole-zwitterion hydrogels (TR-qCB, TR-CB, TR-SB), poly(sulfobetaine methacrylate), carboxybetaine methacrylate, poly[2-methacryloyloxyethyl phosphorylcholine, N-hydroxyethyl acrylamide, a copolymer thereof, a derivatives thereof, and a combination thereof.

[0043] In some embodiments, the nitinol mesh-reinforced hydrogel material has a thickness of about 10 to about 200 μm , about 10 to about 50 μm , about 50 to about 100 μm , about 100 to about 150 μm , or about 150 to about 200 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm , about 100 to about 110 μm , about 110 to about 120 μm , about 120 to about 130 μm , about 130 to about 140 μm , about 140 to about 150 μm , about 150 to about 160 μm , about 160 to about 170 μm , about 170 to about 180 μm , about 180 to about 190 μm , or about 190 to about 200 μm .

[0044] In some embodiments of the nitinol mesh-reinforced hydrogel material, the nitinol mesh is present at or adjacent to an internal surface thereof and the hydrogel material extends from the internal surface to an external surface thereof.

[0045] In some embodiments, the membrane comprises a nitinol mesh-reinforced nanofibrous material. The nitinol mesh-reinforced nanofibrous material can comprise one or more nitinol mesh layers. In some embodiments, the nitinol mesh-reinforced nanofibrous material comprises one or more nanofiber layers, such as first and second nanofibrous layers with the nitinol mesh sandwiched between the first and second nanofibrous layers, optionally wherein fibers of the first and second nanofibrous layers are bonded to another via pores in the nitinol mesh. This is illustrated in FIG. 16. The one or more nanofiber layers can be formed of one or more medical-grade elastomers. Suitable medical-grade elastomers that can be used include, without limitation, polyether block amide, polycarbonate urethane, thermoplastic silicon-polycarbonate-urethane, polyether urethane, and combinations thereof.

[0046] In some embodiments, the nitinol mesh-reinforced nanofibrous material has a thickness of about 10 to about 100 μm , about 10 to about 50 μm , or about 50 to about 100 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to

about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm .

[0047] In some embodiments, the nitinol mesh is present at or adjacent to an internal surface thereof and the nanofiber layer is present at or adjacent to an external surface thereof.

5 **[0048]** In some embodiments, the membrane is porous but impermeable to cellular migration.

[0049] In some embodiments, the nitinol mesh has a thickness of about 10 to about 100 μm , about 10 to about 50 μm , or about 50 to about 100 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm .

[0050] In some embodiments, the nitinol mesh is formed of nitinol wire having a diameter of about 10 to about 100 μm , about 10 to about 50 μm , or about 50 to about 100 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm .

[0051] In some embodiments, the nitinol mesh has a pore size from about 50 to 5000 μm , including about 50 to about 150 μm , about 150 to about 250 μm , about 250 to about 500 μm , about 500 to about 750 μm , about 750 to about 1000 μm , about 1000 to about 1500 μm , about 1500 to about 2000 μm , about 2000 to about 2500 μm , about 2500 to about 3000 μm , about 3000 to about 3500 μm , about 3500 to about 4000 μm , about 4000 to about 4500 μm , or about 4500 to about 5000 μm . Several embodiments in these ranges are illustrated in FIG. 17.

[0052] In some embodiments, the delivery system has a tube-like configuration having a diameter of about 100 μm to about 1 cm, including about 100 to about 500 μm , about 500 to about 1000 μm , about 1000 to about 2000 μm , about 3000 to about 4000 μm , about 4000 to about 5000 μm , about 5000 to about 6000 μm , about 6000 to about 7000 μm , about 7000 to about 8000 μm , about 8000 to about 9000 μm , or about 9000 to about 10000 μm .

[0053] In some embodiments, the implantable therapeutic delivery system comprises a tube-in-tube configuration, wherein the inner and outer tubes independently comprise a membrane comprising a nitinol mesh-reinforced hydrogel or nanofibrous material, wherein a hydrogel matrix is positioned between the inner and outer tubes. In some embodiments, elastic, shape-memory NIREN or NIREA tubes are used for device construction.

[0054] In some embodiments, the hydrogel matrix is a natural polymeric material, a synthetic polymeric material, or a combination thereof. Suitable natural and synthetic polymeric

materials include those of the present disclosure, as defined herein with respect to the hydrogel material used to form NIREA membranes.

[0055] In some embodiments, the at least one therapeutic agent of the hydrogel matrix comprises a drug. In some embodiments, the at least one therapeutic agent is released from a preparation of cells positioned within the hydrogel matrix. In some embodiments, there is a first therapeutic agent in the hydrogel matrix, and a second therapeutic agent released from a preparation of cells positioned within the hydrogel material.

[0056] In some embodiments, the membrane that partially or fully encapsulates the hydrogel matrix comprises a first nitinol mesh-reinforced nanofibrous material, and the delivery system further comprises a second hydrogel matrix external of the first nitinol mesh-reinforced nanofibrous material, which is partially or fully encapsulated by a nitinol mesh-reinforced hydrogel or nanofibrous material.

[0057] In some embodiments, the second hydrogel matrix includes a preparation of cells, which release a therapeutic agent. The preparation of cells can include a preparation of single cells or a preparation of cell aggregates. In some embodiments, the preparation of cells includes a preparation of primary cells or a preparation of immortalized cells.

[0058] In some embodiments, the preparation of cells can include mammalian cells. Suitable mammalian cells that can be used include, without limitation, primate cells, rodent cells, canine cells, feline cells, equine cells, bovine cells, and porcine cells. In some embodiments, the preparation of cells includes human cells.

[0059] In some embodiments, the preparation of cells can include stem cells or stem cell derived cells. The stem cells can be pluripotent, multipotent, oligopotent, or unipotent stem cells. Suitable stem cells that can be used include, without limitation, embryonic stem cells, epiblast cells, primitive ectoderm cells, primordial germ cells, and induced pluripotent stem cells.

[0060] In some embodiments, the preparation of cells can include, one or more of smooth muscle cells, cardiac myocytes, platelets, epithelial cells, endothelial cells, urothelial cells, fibroblasts, embryonic fibroblasts, myoblasts, chondrocytes, chondroblasts, osteoblasts, osteoclasts, keratinocytes, hepatocytes, bile duct cells, islet cells, thyroid, parathyroid, adrenal, hypothalamic, pituitary, ovarian, testicular, salivary gland cells, adipocytes, embryonic stem cells, mesenchymal stem cells, neural cells, endothelial progenitor cells, hematopoietic cells, precursor cells, mesenchymal stromal cells, Baby Hamster Kidney (BHK) cells, Chinese Hamster Ovary cells, Human Amniotic Epithelial (HAE) cells, choroid plexus cells, chromaffin cells, adrenal chromaffin cells, pheochromocytoma cell line PC12, human retinal pigment epithelium cells, recombinant human retinal pigment epithelium cells, NGF-secreting Baby

Hamster Kidney (BHK) cells, human bone marrow-derived stem cells transfected with GLP-1, BDNF-producing fibroblasts, NGF-producing cells, CNTF-producing cells, BDNF-secreting Schwann cells, IL-2-secreting myoblasts, endostatin-secreting cells, and cytochrome P450 enzyme overexpressed feline kidney epithelial cells, myogenic cells, embryonic stem cell-derived neural progenitor cells, irradiated tumor cells, proximal tubule cells, neural precursor cells, astrocytes, genetically engineered cells.

[0061] In some embodiments, the preparation of cells includes a preparation of islet cells that release insulin and glucagon. The preparation of islet cells can be a preparation of human cells, porcine cells, or rodent islets. In some embodiments, the preparation of islets comprises a density between about 1×10^3 to 2×10^6 islet equivalents (IEQs)/mL. For example, the preparation of islets can comprise a density ranging between about 1×10^3 up to about 5×10^3 , 1×10^3 up to about 1×10^4 , 1×10^3 up to about 5×10^4 , 1×10^3 up to about 1×10^5 , 1×10^3 up to about 5×10^5 , 1×10^3 up to about 1×10^6 , 5×10^3 up to about 1×10^4 , 5×10^3 up to about 5×10^4 , 5×10^3 up to about 1×10^5 , 5×10^3 up to about 5×10^5 , 5×10^3 up to about 1×10^6 , 5×10^3 up to about 2×10^6 , 1×10^4 up to about 5×10^4 , 1×10^4 up to about 1×10^5 , 1×10^4 up to about 5×10^5 , 1×10^4 up to about 1×10^6 , 1×10^4 up to about 2×10^6 , 5×10^4 up to about 1×10^5 , 5×10^4 up to about 5×10^5 , 5×10^4 up to about 1×10^6 , 5×10^4 up to about 2×10^6 , 1×10^5 up to about 5×10^5 , 1×10^5 up to about 1×10^6 , 1×10^5 up to about 2×10^6 , 5×10^5 up to about 1×10^6 , 5×10^5 up to about 2×10^6 , or 1×10^6 up to about 2×10^6 islet equivalents (IEQs)/mL.

[0062] The therapeutic agent can include one or more cell factors or biologically active agents to enhance cell growth, differentiation, and/or survival of the cells positioned within the hydrogel matrix. Suitable biologically active agents include, without limitation, a protein, peptide, antibody or antibody fragment thereof, antibody mimetic, a nucleic acid, a small molecule, a hormone, a growth factor, an angiogenic factor, a cytokine, an anti-inflammatory agent, an anti-fibrotic agent, and combinations thereof.

[0063] Exemplary growth factors include, without limitation, fibroblast growth factors (FGFs) such as FGF1, FGF4, FGF19, and FGF21; nerve growth factors (NGFs), epiderma growth factors (EGFs), transforming growth factors, hepatocyte growth factors (HGFs), platelet-derived growth factors (PDGFs), insulin-like growth factors (IGFs), IGF binding proteins, basic fibroblast growth factors, and vascular endothelial growth factors (VEGF).

[0064] Exemplary angiogenic factors include, without limitation, VEGF, bFGF, HGF, PDGF, ANG-1, and IGF-1.

[0065] Exemplary cytokines include, without limitation, interleukins, lymphokines, monokines, colony stimulating factors, chemokines, interferons and tumor necrosis factor (TNF).

[0066] Exemplary anti-inflammatory agents include, without limitation corticosteroids such as prednisone, cortisone, and methylprednisolone; and non-steroidal anti-inflammatory agents (NSAIDs) such as ibuprofen, naproxen, celecoxib, diclofenac, indomethacin, oxaprozin, and piroxicam.

5 **[0067]** Exemplary antifibrotic agents include, without limitation, nintedanib, GW2580 (the cFMS Receptor Tyrosine Kinase Inhibitor 5-[[3-methoxy-4-[(4-methoxyphenyl)methoxy]-phenyl]methyl]pyrimidine-2,4-diamine), and pirfenidone. In some embodiments, the anti-fibrotic agent can be in crystalline form. While several of these agents have previously been evaluated for preventing fibrotic responses against intraperitoneally inserted alginate
10 microcapsules (*see* Farah et al., "Long-term Implant Fibrosis Prevention in Rodents and Non-human Primates Using Crystallized Drug Formulations," *Nat. Mater.*, 18(8):892-904 (2019); PCT Publ. No. WO 2017/176804, each of which is hereby incorporated by reference in its entirety), these prior reports raise several potential problems. The inability to reliably retrieve all capsules raises safety concerns and issues associated with the regulatory approval process.
15 Because the microcapsules are randomly distributed in the intraperitoneal cavity, the drug concentration is highly varied and depends on the density of capsules. Thus, it is difficult to reliably control the drug concentration in the vicinity of all capsules within the therapeutic window. Finally, co-encapsulation of cells and crystalline drugs in microcapsules raises concern that the empty space left after the drug dissolves may devastate the integrity of any immuno-
20 isolation barrier. Indeed, others have used degradable materials to release pirfenidone for the treatment of corneal abrasion (Tawfik et al., "Dual Drug-loaded Coaxial Nanofibers for the Treatment of Corneal Abrasion," *Internat'l J Pharmaceutics*, 581:119296 (2020), which is hereby incorporated by reference in its entirety), but the degradable materials precluded immuno-isolation, afforded limited drug-loading capacity, and achieved a fairly short (< 10 h)
25 drug release period that was incompatible with long-term delivery.

[0068] Referring now to specific embodiments of the implantable therapeutic delivery system, reference is made to specific figures and the construction of the delivery systems shown therein.

[0069] FIG. 1 illustrates an exemplary embodiment of the therapeutic delivery system **10**
30 having a tube-in-tube construction. The system **10** includes an inner NIREN membrane **12** containing crystalline drugs **14** dispersed in a hydrogel matrix **16** and an outer NIREA or NIREN membrane **18** for immunoisolation and shape maintenance. The outer tube is made of the NIREN membrane if cell escape prevention is desired. Pancreatic islets or beta-cell clusters **20** are suspended in alginate hydrogel **22**, which is loaded in the space between the inner tube and the

outer tube. The devices can be scaled up in both radial and longitudinal directions to achieve different encapsulation capacities. A device with diameter of 10 mm and length of 250 mm is estimated to be able to accommodate a clinical dose (~400,000 IEQ) of islets to cure diabetes in humans at cell encapsulation density of 35,000 IEQ.

5 **[0070]** FIG. 2 illustrates several exemplary embodiments of therapeutic delivery systems **40**, **50**, **60**, and **70**, which generally have a flat bar shape construction. The system **40** includes a NIREA membrane that encapsulates a hydrogel matrix containing a crystalline anti-fibrotic drug and pancreatic islets or beta-cell clusters. The system **50** includes a NIREA membrane that encapsulates a hydrogel matrix containing a crystalline anti-fibrotic drug. Externally of the
10 NIREA membrane is a thicker alginate matrix containing pancreatic islets or beta-cell clusters. As shown, the system does not possess an external NIREN membrane that surrounds the alginate matrix containing the pancreatic islets or beta-cell clusters; however, such a NIREN membrane can be included. The system **60** includes a NIREN membrane that encapsulates a hydrogel matrix containing a crystalline anti-fibrotic drug and pancreatic islets or beta-cell clusters. The
15 system **70** includes a membrane that includes a nitinol mesh reinforced with both a nanofibrous layer and a cross-linked alginate layer. In this system, the membrane encapsulates a hydrogel matrix containing a crystalline anti-fibrotic drug and pancreatic islets or beta-cell clusters.

[0071] Another aspect of the present disclosure relates to a method of forming a cell encapsulation system suitable for implant. This method involves providing a hydrogel precursor
20 solution comprising at least one therapeutic agent in the hydrogel precursor solution; and introducing the hydrogel precursor solution internally of a membrane comprising a nitinol mesh-reinforced hydrogel or nanofibrous material, and allowing the hydrogel precursor to form a hydrogel matrix that is partially or fully encapsulated by the membrane.

[0072] Initial membrane assembly can be carried out as described in the Examples.
25 During membrane formation, the membranes are typically presented on a support structure, which may just be a support structure that is of a similar size and configuration of the final device shape, or alternatively can be a rotatable mandrel or shaft.

[0073] NIREN membranes can be prepared by first coating the nitinol mesh with a polymer solution to facilitate binding of electrospun polymer fibers to the nitinol mesh. This can
30 be carried before or after placement of the nitinol mesh on the support structure. Thereafter, electrospinning of polymer fibers is carried out to achieve a polymer nanofiber membrane of desired dimension and pore properties formed on the nitinol mesh. With the use of a mandrel as a support structure, it is possible to obtain tubular-shaped NIREN membranes. Regardless of its

final shape or configuration, the NIREN membrane can be removed from the support structure for subsequent use in device assembly.

[0074] NIREA membranes can be prepared by first soaking a support structure in a solution that will facilitate coating of the support structure with a cross-linking agent. By way of example, a calcium and polyethylene glycol solution can be used to promote cross-linking of an alginate solution. Once the support structure is coated with cross-linking agent, a nitinol mesh can be installed onto the support structure and then immersed in the alginate precursor solution to facilitate formation of the NIREA membrane. Thereafter, the NIREA membrane can be removed from the support structure for subsequent use in device assembly. This process is illustrated in FIG. 8A.

[0075] In certain embodiments, the support structure can take the form of an inner nitinol mesh that is installed over a mandrel or other support, which is then soaked in the solution containing the cross-linking agent. In this embodiment, a second (outer) nitinol mesh is installed onto the support structure prior to immersing in the alginate precursor solution. When the NIREA membrane is removed from the support structure, the inner nitinol mesh remains on the mandrel or other support, such that the NIREA membrane contains only the hydrogel material and the outer nitinol mesh.

[0076] Similar procedures used in forming the NIREA membranes can also be used to form other nitinol mesh-reinforced hydrogel membranes containing hydrogel materials other than alginate. Other cross-linking agent solutions can, of course, be used to support cross-linking of other hydrogel precursor solutions as is well known in the art.

[0077] In addition to the above, in certain embodiments, both processes can be used to form nitinol mesh-reinforced hydrogel and nanofibrous material membranes.

[0078] After forming the membrane but before forming the hydrogel matrix internally thereof, the membrane at one end (or side) of the device can be sealed closed using, e.g., a thermal sealer or a material that otherwise completely seals that end (or side) of the device closed to maintain the capacity for immuno-separation.

[0079] Forming the hydrogel matrix can be achieved by causing cross-linking of the hydrogel precursors as disclosed herein. Briefly, the hydrogel precursor solution containing one or more therapeutic agent(s) dispersed therein can be introduced into the region internally of the membrane and then cross-linking of the hydrogel precursors can be carried out to form the hydrogel. As is well known in the art, the cross-linking agent will differ depending on the type of hydrogel precursors used and hydrogel matrix to be formed. Nevertheless, once the hydrogel matrix is formed internally of the membrane, the other end (or side) of the membrane can sealed

closed using the same approach. This ensures that the interior of the device is closed to maintain the capacity for immuno-separation while also allowing molecules to pass through the membrane.

[0080] As an alternative to sealing one end before and one end after forming the

5 hydrogel matrix internally of the membrane, both ends can be sealed after forming the hydrogel matrix.

[0081] One exemplary process for forming the implantable therapeutic delivery system is illustrated in FIG. 7A, which shows a method for loading cells/islets in the space between two NIREN tubes. The inner tube can first be coated with a cell suspension (containing cells and a solution of hydrogel precursors) and then cross-linking affords the cells/islets embedded in a hydrogel matrix form outside the inner tube. Because the NIREN membrane is elastic in nature, the NIREN inner tube can be stretched, thereby reducing its diameter, which allows the NIREN inner tube to be inserted into a NIREN outer tube. After the stretching force is released, the inner tube returns to its original shape, pushing the cells to the area near the surface of the device, i.e., adjacent to the inner surface of the NIREN outer tube. The thickness of cell encapsulation layer is dictated by the volume of alginate solution. Thereafter, the NIREN outer tube can optionally be coated with an additional hydrogel layer, if desired, and the interior space of the NIREN inner tube can be loaded with a hydrogel matrix containing anti-fibrotic agent. Thereafter, the ends can be sealed as described herein.

20 **[0082]** Once the implantable therapeutic delivery system has been completely assembled, the delivery system can then be implanted in a subject for delivery of therapeutic agent(s) to the subject while the device remains implanted.

[0083] In particular, the devices can be implanted using laproscopic surgical procedures or open surgical sites, and the devices can be placed subcutaneously, transcutaneously, preperitoneally, transperitoneally, or intraperitoneally. In some embodiments, implanting involves suturing the device or system to a body wall of the subject; anchoring the device to a body wall of the subject via a transabdominal portal; wrapping the delivery device or system in omentum of the subject; positioning the device in a cavity between the liver and the diaphragm; or anchoring the device to the diaphragm. Unanchored implantation is also contemplated.

30 **[0084]** Both veterinary and medical uses are contemplated. Thus, exemplary subjects include, without limitation, a human, a mouse, a rat, a dog, a cat, a pig, a sheep, a cow, a horse, and a nonhuman primate.

[0085] By implanting the implantable therapeutic delivery system, the systems can be used to deliver a therapeutic agent to a subject in need thereof. The treatment by implantation

can be carried out for a limited duration over a period of days, weeks, or months. Thus, it is also contemplated that the method of treatment further involves retrieving the implantable cell containing device from the subject when no longer needed or when the device needs replacement, and optionally implanting a replacement implantable therapeutic deliver system after the initial device is retrieved.

[0086] The introduction of one or more contrast agents allows for monitoring of the device. Methods of *in vivo* monitoring include but are not limited to confocal microscopy, 2-photon microscopy, high frequency ultrasound, optical coherence tomography (OCT), photoacoustic tomography (PAT), computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET). These alone or combined can provide useful means to monitoring the implantable device. Monitoring of the device may be used to determine when to remove and replace a device, as necessary.

[0087] According to one embodiment, the subject has diabetes, is in need of diabetes treatment, and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein, which comprises a preparation of cells that release insulin, glucagon, or a combination thereof for the treatment of diabetes in the subject. Exemplary cells that release the therapeutic agent include one or more of islet cells, islets derived from a preparation of stem cells such as pluripotent, multipotent, oligopotent, or unipotent stem cells, including embryonic stem cells, epiblast cells, primitive ectoderm cells, primordial germ cells, and induced pluripotent stem cells.

[0088] According to one embodiment, the subject has a bleeding disorder, is in need of treatment for the bleeding disorder, and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein, which comprises a preparation of cells that release a therapeutic agent that treats the bleeding disorder. In accordance with this embodiment, the bleeding disorder can be any bleeding disorder, such as hemophilia A, hemophilia B, von Willebrand disease, Factor I deficiency, Factor II deficiency, Factor V deficiency, Factor VII deficiency, Factor X deficiency, Factor XI deficiency, Factor XII deficiency, and Factor XIII deficiency, and the therapeutic agent is a blood clotting factor selected from the group of Factor I, Factor II, Factor V, Factor VII, Factor VIII, Factor IX, Factor X, Factor XI, Factor XII, Factor XIII, and combinations thereof. Exemplary cells that release the therapeutic agent include one or more of recombinant myoblasts, mesenchymal stromal cells, endothelial cells, induced pluripotent stem cell derived

endothelial cells, induced pluripotent stem cell derived mesenchymal stromal cells, and a combination thereof.

[0089] In another embodiment, the subject has a lysosomal storage disorder, is in need of treatment for the lysosomal storage disorder, and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein into the subject having the lysosomal storage disorder. In accordance with this embodiment, the therapeutic agent is an enzyme selected from the group of α -L-iduronidase, Iduronate-2-sulfatase, α -glucuronidase, Arylsulfatase A, alpha-Galactosidase A, and combinations thereof. Exemplary cells that release the therapeutic agent include one or more of hematopoietic stem cells, fibroblasts, myoblasts, Baby Hamster Kidney (BHK) cells, Chinese Hamster Ovary cells, Human Amniotic Epithelial (HAE) cells, mesenchymal stromal cells, induced pluripotent stem cell derived mesenchymal stromal cells, and combinations thereof.

[0090] According to one embodiment, the subject has a neurological disorder, is in need of treatment for the neurological disorder, and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein, which comprises a preparation of cells that release a therapeutic agent that treats the neurological disorder. In accordance with this embodiment, the neurological disorder is Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Amyotrophic lateral sclerosis, chronic pain, a sensory disorder such as visual loss, hearing loss, peripheral nerve injury, and spinal cord injury, and the therapeutic agent is selected from the group of cerebrospinal fluid, extracellular fluid, levodopa, nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), BLP-1, brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), enkephalin, adrenaline, catecholamine, and combinations thereof. Exemplary cells that release the therapeutic agent include one or more of choroid plexus cells, chromaffin cells, pheochromocytoma cell line PC12, human retinal pigment epithelial cells, NGF-secreting Baby Hamster Kidney (BHK) cells, myoblasts, human bone marrow-derived stem cells transfected with GLP-1, BDNF-producing fibroblasts, NGF-producing cells, CNTF-producing cells, adrenal chromaffin cells, BDNF-secreting Schwann cells, myogenic cells, embryonic stem cell-derived neural progenitor cells, and combinations thereof.

[0091] In another embodiment, the subject has a cancerous condition, is in need of treatment for the cancerous condition, and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein into the subject having the cancerous condition. In accordance with this embodiment, the therapeutic agent is one or more of IL-2, endostatin, cytochrome P450 enzyme, a tumor antigen, a cytokine,

and combinations thereof. Exemplary cells that release the therapeutic agent include one or more of IL-2-secreting myoblasts, endostatin-secreting cells, Chinese Hamster Ovary cells, cytochrome P450 enzyme overexpressed feline kidney epithelial cells, irradiated tumor cells, and combinations thereof.

5 **[0092]** In another embodiment, the subject has a chronic eye disease, is in need of treatment for the chronic eye disease, and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein into the subject having the chronic eye disease. The chronic eye disease may be any one of age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, glaucoma, macular telangiectasia, and combinations thereof. In accordance with this embodiment, the therapeutic agent is one or more trophic factors that protect compromised retinal neurons and restore neural circuits, such as any one or more of ciliary neurotrophic factor, antagonists against vascular endothelial growth factor and platelet-derived growth factor, and combinations thereof. Exemplary cells that release the therapeutic agent include one or more of human retinal pigment epithelium cells, recombinant human retinal pigment epithelium cells, and combinations thereof.

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[0093] In one embodiment, the subject has kidney disease (kidney failure), is in need of treatment for the kidney disease (kidney failure), and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein into the subject having the kidney disease (kidney failure). In accordance with this embodiment, the therapeutic agent is dopamine, atrial natriuretic peptide, and combinations thereof. Exemplary cells that release the therapeutic agent include one or more of renal proximal tubule cells, mesenchymal stem cells, and combinations thereof.

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[0094] In one embodiment, the subject has chronic pain, is in need of treatment for the chronic pain, and the method of delivering a therapeutic agent to the subject involves implanting an implantable therapeutic delivery system as described herein into the subject having the chronic pain. The chronic pain can be any chronic pain condition including, without limitation, those caused by degenerative back and knee, neuropathic back and knee, or cancer. In accordance with this embodiment, the therapeutic agent is catecholamine, opioid peptides, enkephalins, and combinations thereof. Exemplary cells that release the therapeutic agent include one or more of chromaffin cells, neural precursor cells, mesenchymal stem cells, astrocytes, and genetically engineered cells, and combinations thereof.

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[0095] Wherever the word “about” is employed herein in the context of dimensions (e.g. distances, sizes), time, amounts (relative amounts, concentration, etc.), cell densities, etc., it will

be appreciated that such variables are approximate and as such may vary by $\pm 10\%$, for example $\pm 5\%$ and preferably $\pm 2\%$ (e.g., $\pm 1\%$) from the numbers specified herein.

EXAMPLES

[0096] The examples below are intended to exemplify the practice of embodiments of the disclosure but are by no means intended to limit the scope thereof.

Materials and Methods for Examples 1-7

Materials

[0097] Nintedanib and GW2580 were purchased from LC Laboratories (Woburn, MA). Pirfenidone was purchased from Neta Scientific, Inc (Hainesport, NJ). Braided nitinol tubes were supplied by Secant Medical, LLC (Telford, PA). Polyamide 6 (Nylon 6), barium chloride, calcium chloride, formic acid, and tetrahydrofuran were purchased from Sigma Aldrich (St. Louis, MO). Polyamide 12 (Rilsamid Aesno Med) and polyether block amide (PEBAX 2533 SA 01 MED) were provided by Arkema (Colombes, France). Polycarbonate urethane (QTHAN-ARC-95A), thermoplastic silicon-polycarbonate-urethane (QSIL-ARCS-90A), and polyether urethane (QFLEX-ARE-93A) are generous sample gifts from Biomerics (Salt Lake City, UT). Thermoplastic silicon-polycarbonate-urethane (TSPU; Carbosil 20 90A) was purchased from DSM Biomedical Inc (Berkely, CA). Ultrapure sodium alginate (PRONOVA SLG100) was supplied by Novamatrix (Sandvika, Norway). 1,1,1,3,3,3-hexafluoro-2-propanol was purchased from Oakwood Chemical (Estill, SC).

Effects of Nintedanib on Human Pancreatic Islets

[0098] A stock solution of nintedanib was prepared by dissolving nintedanib in cell-grade DMSO at 5.82 mg/mL. The solution was filtered through a sterile 0.22 μm syringe filter and diluted with CMRL 1066 (supplemented with 10% FBS) to a series of solutions (0.1 μM , 0.2 μM , 0.5 μM , 1 μM , 2 μM). Approximately 300 IEQ of human islets was incubated in 3 mL of each solution for 48 hours. Islet viability was assessed by dual fluorescence staining using a LIVE/DEAD viability/toxicity kit. The fluorescence images were captured using an EVOS fl microscope.

Preparation of Nanofibrous Tubes

[0099] Nanofibrous membranes were prepared using custom-built electrospinning system consisting of a syringe pump (Harvard Apparatus, MA), a constantly moving needle holder, and a rotating collector connected to a high voltage supply (Gamma High Voltage, Ormond Beach, FL). Different polymers including polyamide 6 (Nylon 6), polyamide 12 (Rilsamid Aesno Med),

polyether block amide (PEBAX 2533 SA 01 MED), polycarbonate urethane (QTHAN-ARC-95A), thermoplastic silicon-polycarbonate-urethane (TSPU; Carbosil 20 90A or QSIL-ARCS-90A), polyether urethane (QFLEX-ARE-93A) were used to achieve different characteristics.

Polyamide 6, PEBAX, QFLEX was dissolved in a hexafluoroisopropanol (HFIP)/formic acid (FA) blend (8/2; v/v). Carbosil was dissolved in a tetrahydrofuran (THF)/dimethylformamide (DMF) blend (3/2; v/v). Polyamide 12 and QTHAN were dissolved in HFIP. Polymer concentrations, pumping rates, spinneret, voltage, working distance listed in Table 1 were optimized beforehand to achieve targeted fiber size and good reproducibility (Table 1).

Conductive stainless-steel rods and flat bars were used to collect fibers to prepare tubular tubes and flat tubes, respectively.

Table 1: Electrospinning Conditions for the Preparation of Nanofibrous Membranes Made of Different Polymers

Polymer	Concentration (%; w/v)	Spinneret (G)	Pumping Rate (mL/hr)	Voltage (kV)
Nylon 6	20	20	2.4	15
	25	20	1.2	18
PEBAX	5	23	1	20
	7.5	23	1	20
	10	23	1	20
	15	23	1	20
QTHAN	7.5	23	1	18
QFLEX	5	23	2	20
	10	23	2	20
	20	23	2	20
QSIL	16	23	0.5	18
Carbosil	8	23	0.5	13

Preparation of Crystalline Anti-fibrotic Drugs

[0100] Preparation of Crystalline Nintedanib: Nintedanib (100 mg) was added to 200 mL of ethyl acetate. The solution was heated to 75°C until the drug was completely dissolved. Then, 50 to 400 mL of hexanes was added to the solution to prepare crystalline particles of different sizes. The mixture was briefly mixed for 5 seconds and incubated at 25°C for 12 hours. After that, the supernatant was decanted, and the particles were washed twice with hexanes followed by drying under vacuum for 12 hours to remove organic solvents.

[0101] Preparation of Crystalline GW2580: GW2580 (100 mg) was dissolved in 150 mL of ethyl acetate and heated to 75°C. Then, 0 to 150 mL of hexanes was added to the drug solution to prepare crystalline particles of different sizes. The mixture was briefly mixed for 5 seconds

and incubated at 25°C for 24 hours. After that, the supernatant was decanted, and the particles were washed twice with hexanes followed by drying under vacuum for 12 hours. The particles were submerged in ethanol for 1 hour and dried in a biosafety hood.

[0102] Preparation of Crystalline Pirfenidone: Pirfenidone (1 gram) was dissolved in 5 to 10 mL of ethyl acetate and heated to 40-75°C depending on the targeted size of crystalline particles. Then, 0-10 mL hexanes were added to the drug solution; the mixture was briefly mixed for 5 seconds and incubated at 25°C for 4 hours. After that, the supernatant was decanted and the particles were washed twice with hexanes, followed by drying under vacuum for 12 hours.

Preparation of NIREN Tubes

[0103] To prepare NIREN tubes, nitinol tubes were first soaked in 0.5% polymer solution to facilitate better binding of polymeric fibers to nitinol wires. The tube was then installed on a stainless steel mandrel, which has the same size and morphology as the nitinol tube. The mandrel was used to collect electrospun fibers. The electrospinning time was optimized beforehand to get ~25- μ m thick nanofiber membrane on the nitinol tube. After that, the tube was removed from the mandrel and dried in a vacuum oven at RT for 24 hours to remove residual solvents.

Preparation of NIREA Tubes

[0104] A nitinol tube was installed on a stainless-steel mandrel, which has the same size and morphology as the nitinol tube. The tube and the mandrel were then immersed in a calcium solution (0.5 g/mL) containing polyethylene glycol (PEG) 6000 (0.13 g/mL). The tube was dried out in an oven at 80°C for 15 minutes. The dried tube fixed on the mandrel was then inserted into a second nitinol tube. The system was then immersed in a 3% alginate solution for 10 seconds to facilitate the formation of alginate hydrogel. The outer tube was detached from the inner tube and washed 3 times with normal saline.

Anti-fibrotic Effects of Crystalline Drugs in a Mouse Model

[0105] A previously developed Nylon 6 device was chosen as a model to evaluate the anti-fibrotic effect of crystalline drugs (Liu et al., "A Safe, Fibrosis-Mitigating, and Scalable Encapsulation Device Supports Long-Term Function of Insulin-Producing Cells," *Small*, 18(8):e2104899 (2021), which is hereby incorporated by reference in its entirety). The device was designed using a concentric configuration where a fibrous tube was inserted into another fibrous tube. The length, diameter, pore size, and thickness of the outer tube were 2.5 cm, 3.2 mm, 1.05 μ m, and 70 μ m whereas those of the inner tube were 2 cm, 2 mm, 1.70 μ m, and 100 μ m. This device was known to cause severe fibrotic reactions after being implanted into the intraperitoneal cavity of C57BL/6 mice (Liu et al., "A Safe, Fibrosis-Mitigating, and Scalable

Encapsulation Device Supports Long-Term Function of Insulin-Producing Cells," *Small*, 18(8):e2104899 (2021), which is hereby incorporated by reference in its entirety). For drug loading (nintedanib or GW2580) into the core of the device, crystalline particles were dispersed in 0.75% SLG100 at 50 mg/mL; 70 μ L of drug suspension was injected into the inner tube with one end sealed using a thermal sealer. The tube was then immersed in a saline solution containing 95 mM Ca^{2+} and 5 mM Ba^{2+} for cross-linking. The excess liquid on the tube was observed using sterile tissue papers, and the open end of the tube was sealed using a thermal sealer. The tube containing the drug was inserted into the other tube, followed by thermally sealing the ends of the outer tube. To prepare control devices, 70 μ L of 0.75% SLG100 was injected into the inner tube. The devices were stored in 50 mL of normal saline until implantation.

[0106] The devices were retrieved 1-month post-implantation and washed 3 times with saline. The outer tubes were fixed in 4% PFA at room temperature for 12 hours. The tubes were then dehydrated using a series of graded ethanol solutions, embedded in paraffin, sectioned, and stained by Cornell Histology Core Facility. The inner tube was peeled off to expose the alginate core containing crystalline drugs. The morphology and mass reduction of the particles was observed under an inverted microscope (EVOS fl).

Laparoscopic Implantation and Retrieval of Tubular DREAM Devices in Gottingen Minipigs

[0107] DREAM devices made of NIREN Carbosil membrane were used to evaluate the effect of crystalline nintedanib in female Gottingen minipigs. For device preparation, a nitinol tube (diameter: 5 mm, length: 10 cm) was installed on a stainless-steel rod (diameter: 5 mm). The rod was then used to collect electrospun fibers. Carbosil was used at 8% (w/v) in a THF:DMF (8:2) blend. The nanofibers were spun at 0.5 mL/h under the voltage of 13 kV. A 23G blunt needle was used as the spinneret. The spinning time was 4 hours. The tubes were then removed from the mandrel and placed in a vacuum oven for 24 hours to remove residual solvents. The tube was sterilized by soaking in 70% ethanol for 1 hour and UV radiation for 1 hour. One end of the tube was thermally sealed using a commercial thermal sealer (Impulse Sealer Supply, CA). Crystalline nintedanib was dispersed in 0.75% SLG100 solution at 100 mg/mL; approximately 2 mL of the suspension was loaded into the device. After that, the device was immersed in a normal saline solution containing 95 mM Ca^{2+} and 5 mM Ba^{2+} for crosslinking. The excess liquid was absorbed using sterile tissue papers prior to sealing the open end. For the control device, 2 mL of SLG100 (0.75%) was loaded into the device.

[0108] For laparoscopic implantation of devices, a 10-mm laparoscopic camera port and two 5-mm instrument ports were percutaneously inserted into the abdomen. The abdomen was insufflated with CO₂. The device was inserted into the abdomen through the left-sided instrument port and placed onto the great omentum. The remaining ports were then removed, and the port sites were closed with 3-0 polydioxanone suture material. For retrieval of the devices, the procedure was similar using one 10-mm camera port and one or two 5-mm instrument ports.

Laparoscopic Implantation and Retrieval of a Flat Bar DREAM Device in Farm Pigs

[0109] An 8-cm flat bar DREAM device made of NIREA membrane was loaded with 0.6 mL crystalline nintedanib suspension in 0.75% SLG100 (27 mg/mL). The device was placed onto the omentum of a female farm pig through a 5-mm instrument port inserted percutaneously into the abdomen. Then, the port sites were closed using a 3-0 polydioxanone suture. After 2 months, the device was retrieved through an incision generated through the abdomen wall.

Example 1 – Reinforcement of Nanofibrous Membrane with Nitinol Mesh

[0110] Several criteria were considered in designing NIREN membrane. The membrane should be elastic, soft but durable to maintain the original shape and avoid kink as well as potential injuries to vital organs after implantation into the abdomen. Meanwhile, the membrane should be thin enough for efficient mass transport. To this end, different medical-grade elastomers including polyether block amide (PEBAX 2533 SA 01 MED), polycarbonate urethane (QTHAN-ARC-95A), thermoplastic silicon-polycarbonate-urethane (Carbosil 20 90A or QSIL-ARCS-90A), polyether urethane (QFLEX-ARE-93A) were first screened for preparing nanofibrous membranes. SEM examination revealed the nonwoven structure with interconnected pores of these membranes (FIGs. 3A, 3D). Devices made of PEBAX, QTHAN, and QLEX could be stretched more than 3 times of their original lengths and were able to return to their original shapes after the force was released (FIG. 3D). Of note, the fiber size and porosity of these membranes could be tuned by adjusting the polymer concentrations. For example, increased fiber sizes and porosity were achieved when the concentrations of PEBAX increased from 5% to 15%. The fiber sizes were 146.03 ± 55.95 nm, 286.87 ± 79.61 nm, 376.11 ± 111.16 nm, and 787.05 ± 164.84 nm when PEBAX was used at 5%, 7.5%, 10%, and 15%, respectively (FIGs. 3B-3C).

[0111] Shape-memory, braided nitinol tubes were used to reinforce the nanofibrous membrane. The shape, diameter, and length of the tube could be easily tuned to adapt to different animal models and encapsulation volume. Tubular nitinol tubes with a diameter of 5 mm were used for preparation of tubular NIREN versions (FIGs. 1, 4A-4H) and flat bar nitinol tubes (1 cm

x 800 μm cross-section) were used for flat bar NIREN versions (FIGs. 2, 5A-5B, 6A-6D). The thickness and pore size of the nitinol mesh were $\sim 25\text{ }\mu\text{m}$ and 100-150 μm , which negligibly affect the mass transport (FIGs. 4A-4B). SEM/EDS was used to confirm the hierarchical structure of NIREN membrane, in which a thin layer of nanofibrous membrane was firmly coated on braided nitinol tube (FIGs. 4C-4D). Of note, NIREN membrane could maintain the shape even when the thickness of the membrane was lower than 50 μm (FIG. 5B). Meanwhile, the neat nanofiber membranes with the same thickness were not able to keep the lumen open. Interestingly, the NIREN tube could be bent without kink and quickly returned to the original shape after being twisted (FIGs. 4E-4H, 6A-6D).

Example 2 – Tube-in-tube NIREN Device

[0112] In a previous study, a concentric configuration was used for designing a SHIELD encapsulation device, in which cells are encapsulated within the device cylindrical wall (Liu et al., "A Safe, Fibrosis-Mitigating, and Scalable Encapsulation Device Supports Long-Term Function of Insulin-Producing Cells," *Small*, 18(8):e2104899 (2021), which is hereby incorporated by reference in its entirety). SHIELD device consisted of two rigid Nylon 6 tubes: an inner tube with a diameter of 2 mm and an outer tube with a diameter of 3.2 mm. A thin layer of cell-laden alginate hydrogel ($\sim 500\text{ }\mu\text{m}$) was deposited on the inner tube and inserted into the outer tube. This configuration allows for device scale-up in the radial direction while keeping cells near the device surface for efficient mass transfer. However, the insertion of a rigid Nylon 6 tube into another tube with the same diameter without affecting the cell-laden hydrogel layer remained challenging, especially for long devices desired for clinical translation. This limitation diminishes the feasibility of device scale-up. To address this issue, elastic, shape-memory NIREN tubes were used for device construction. The elasticity of the NIREN tube allowed it to be stretched to reduce its diameter, enabling facile insertion of the inner tube into the outer tube without affecting the cell-laden layer (FIG. 7A). 150- μm polystyrene beads were used to mimic pancreatic islets to demonstrate the cell loading process. After being stretched along a 2-cm rod, the inner tube was easily inserted into the outer tube. There was no visible loss of beads deposited on the inner tube, and all the beads were positioned in a peripheral area where the distance from them to the device surface was less than 300 μm (FIG. 7B). To demonstrate the scalability of this method, a 25-cm long device was prepared by inserting a 23 cm NIREN tube into another 25 cm NIREN tube. The diameter of both tubes was 5 mm. It is important to note that this device could accommodate half of the established islet dose to cure diabetes in humans at an encapsulation density of 35,000 IEQ/mL. It was anticipated that a device with a diameter of

10 mm and a length of 25 cm prepared by the same method could accommodate a clinical dose of human islets (FIG. 1). The final device maintained the perfect cylindrical shape and possessed similar elasticity and shape-memory features of the NIREN single tube, which could be beneficial for preventing device kink and injuries to organs after implantation (FIGs. 7C-7D).

5 **Example 3 – Reinforcement of Alginate Hydrogel Membrane with Nitinol Mesh**

[0113] Alginate hydrogel has been widely used for cell encapsulation. However, its intrinsic mechanical weakness raises concerns for clinical applications as the breakage of hydrogel after long-term implantation could affect the immunoprotection and preclude the complete retrieval. To overcome this challenge, a simple and facile method was developed to
10 reinforce the alginate hydrogel membrane with a nitinol mesh (FIG. 8A). A similar tube-in-tube structure from Example 2 was used for NIREA membranes. First, the inner nitinol mesh tube was pre-coated with calcium by simply submerging it in a calcium/PEG solution. The trellis nature of the nitinol membrane facilitated homogenous absorption of Ca^{2+} into its pores. When the tube-in-tube device was dipped in an alginate solution, the liquid penetrated through the outer
15 tube, triggering the release of calcium absorbed in the inner tube. This allows for quick gelation of alginate in the pores and on both sides of the outer tube, preventing the detachment of hydrogel. Thin, smooth, and uniform alginate layers were achieved on both flat bar and tubular NIREA versions (FIG. 8B). The NIREA membrane/tube could be bent, twisted, or rolled around a small rod without the detachment of hydrogel (FIGs. 8C, 9C-9I). The scalability of the flat bar
20 NIREA device was demonstrated by preparing a 25-cm long device, which could accommodate ~80,000 IEQ islets at an encapsulation density of 35,000 IEQ/mL (FIGs. 9A-9B). A 2-cm wide, 50-cm long device with an encapsulation capacity of ~300,000 IEQ islets can be prepared easily using the same method. Cells can be loaded in the alginate coating layer by dispersing cells in alginate solution before gelation (FIG. 1) or loaded in the lumen of the device by simply
25 injecting cell suspension in 0.75% SLG solution, followed by crosslinking in an isotonic 10 mM Ca^{2+} solution (FIG. 10).

Example 4 – Preparation of Crystalline Anti-fibrotic Drugs

[0114] Foreign body response (FBR) is one of the greatest obstacles for the clinical translation of cell encapsulation systems. Fibrotic encapsulation involving cellular overgrowth
30 and dense collagen deposition could lead to diminished mass transfer and eventually graft failure. Another issue for devices implanted in the abdominal cavity is omentum adhesion, which potentially precludes minimally invasive retrievability. Efforts have been made to tackle these

problems. Of these, local controlled release of small molecules targeting different pathways involved in fibrotic response and tissue adhesion has been reported as a promising and reproducible means. Corticoids and anti-proliferative drugs have been shown to reduce fibroblast proliferation and collagen depositions on stents, pacemakers (Singarayar et al., "A Comparative Study of the Action of Dexamethasone Sodium Phosphate and Dexamethasone Acetate in Steroid-Eluting Pacemaker Leads," *Pacing Clin. Electrophysiol.*, 28(4):311-315 (2005), which is hereby incorporated by reference in its entirety), biosensors (Friedl, "Corticosteroid Modulation of Tissue Responses to Implanted Sensors," *Diabetes Technol Ther.*, 6(6):898-901 (2004), which is hereby incorporated by reference in its entirety). Recently, Anderson's group at MIT reported that selective targeting macrophage-expressed colony stimulation factor 1 receptor (CSF1R) using GW2580 was shown to suppress FBR on different implanted materials in rodents in non-human primates (Farah et al., "Long-term Implant Fibrosis Prevention in Rodents and Non-human Primates Using Crystallized Drug Formulations," *Nat. Mater.*, 18(8):892-904 (2019); Doloff et al., "Colony Stimulating Factor-1 Receptor is a Central Component of the Foreign Body Response to Biomaterial Implants in Rodents and Non-Human Primates," *Nat. Mater.*, 16(6):671-680 (2017); which are hereby incorporated by reference in their entirety). However, the effect and safety profiles of GW2580 is not validated in humans. Instead, in these examples the effects of nintedanib and pirfenidone were investigated because these are the only two drugs with validated anti-fibrotic effects for reducing fibrosis and scars in humans. The drugs were prepared in crystalline form for long-term release and loaded into the core of the device to locally modulate the host reactions to the device while minimizing the systemic exposure to prevent unwanted side effects.

[0115] A solvent displacement method was used to prepare crystalline drugs (FIG. 11A). In general, nintedanib, GW2580, or pirfenidone was first dissolved in ethyl acetate. The crystallization was initiated by adding hexanes to the drug solution. Drug concentration, temperature, solvent/anti-solvent ratio, and time were adjusted to achieve different sizes and morphology of crystalline particles (FIG. 11B). In most of the experiments, crystalline nintedanib was used with the size distribution in a range of 200-300 μm prepared by adding 1 volume of hexanes to 4 volumes of nintedanib solution (0.5 mg/mL) at 70°C. The mixture was then kept at room temperature for 12 hours.

Example 5 – Effect of Nintedanib on the Viability of Human Islets

[0116] One criterion in this example is that the drug should not negatively affect the encapsulated cells. To investigate the potential detrimental effects of nintedanib, human islets

were incubated with different drug concentrations for 48 hours (FIGs. 12A-12B). The islet viability was evaluated by dual fluorescence staining using a LIVE/DEAD viability/toxicity kit. No significant changes in islet morphology and the number of dead cells were observed in all conditions (up to 2 μ M), indicating the compatibility of nintedanib with the islet encapsulation devices.

Example 6 – Anti-fibrotic Effects of Nintedanib-eluting Devices in Mice

[0117] A tube-in-tube Nylon 6 device was chosen as a model to evaluate the anti-fibrotic effect of crystalline drug given that it previously caused severe fibrotic response after implantation in IP of C57BL/6 mice. 3.5 mg of either crystalline nintedanib or crystalline GW2580 was loaded in the inner tube, which enables continuous dissolution of the drug thanks to the high porosity of both tubes. After 1 month, the devices without drugs elicited strong fibrotic response, evidenced by thick layers of host cells and dense collagen matrix deposited on the device surface. Considerable reductions in the thickness of the fibrotic layer and collagen density were observed for both nintedanib-eluting and GW2580-eluting devices, indicating the potential anti-fibrotic effect of the drugs (FIG. 13A). Notably, only a small portion (< 10%) of crystalline drugs in the periphery of the alginate matrix was dissolved, indicating that the release of the drug from these devices could possibly last for many months (FIGs. 13B-13C). This would be beneficial for the long-term suppression of fibrotic responses.

Example 7 – Anti-fibrotic Effects of DREAM Devices in Pigs

[0118] To confirm whether the anti-fibrotic effects of drug-eluting devices could be translated to a high-order animal model, 200 mg of crystalline nintedanib was loaded into a 10-cm long DREAM device made of Carbosil NIREN membrane (diameter: 5 mm) and implanted into IP cavity of a Göttingen minipig by a minimally invasive laparoscopic procedure. A device loaded with neat alginate hydrogel was used as a control. Laparoscopic retrieval was performed 6 weeks after implantation. The device without crystalline nintedanib was completely wrapped by the omentum, which only could be invasively retrieved by incising a part of the omentum (FIGs. 14A-14B). Masson's trichrome staining revealed a thick fibrotic layer (~500 μ m) firmly covered the nanofiber layer. In contrast, the nintedanib-eluting DREAM device was not wrapped by the omentum (FIGs. 14A, 14C). However, the two ends of the device were adhered to the liver, possibly due to the sharpness and stiffness of the thermal-sealed ends. A majority part of the device was found less or free of fibrosis although significant collagen deposition was observed at the adhesion interface between the device and the liver (FIG. 14C). Very slow

dissolution of crystalline nintedanib was observed in the core of the device, in which most of the particles remained intact, confirming the feasibility of long-term drug release from the device (FIG. 14D).

[0119] The anti-fibrotic effect of a nintedanib-eluting NIREA flat bar device in a farm

5 pig was next confirmed. An 8-cm flat bar DREAM device made of NIREA membrane containing 16.2 mg of crystalline nintedanib was implanted into the IP cavity of a 2-month-old farm pig by a minimally invasive laparoscopic procedure (FIGs. 15A-15B). The device was explanted by a non-survival procedure after 2 months to evaluate the fibrotic response.

Interestingly, the device was found free-floating in the IP space and no tissue adhesion was

10 observed (FIG. 15C). More than 70% of the device surface was not microscopically covered by a fibrotic layer (FIGs. 15D-15F). Of note, the fibrotic response mainly occurred at the two sealed ends and the edges of the device. Most of the crystalline drug was found intact with less than 10% mass reduction (FIG. 15G).

15 **[0120]** Although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions, and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the claims which follow.

WHAT IS CLAIMED IS:

1. An implantable therapeutic delivery system comprising:
a hydrogel matrix comprising at least one therapeutic agent; and
a membrane that partially or fully encapsulates the hydrogel matrix, the membrane
5 comprising a nitinol mesh-reinforced hydrogel or nanofibrous material.
2. The implantable therapeutic delivery system of claim 1, wherein the membrane
comprises a nitinol mesh-reinforced hydrogel material.
3. The implantable therapeutic delivery system of claim 2, wherein the nitinol mesh-
reinforced hydrogel material comprises one or more nitinol mesh layers.
- 10 4. The implantable therapeutic delivery system of claim 2 or 3, wherein hydrogel
material comprises a natural polymeric material, a synthetic polymeric material, or a combination
thereof.
5. The implantable therapeutic delivery system of any one of claims 2 to 4, wherein
the hydrogel material comprises a natural polymeric material selected from the group consisting
15 of collagen, hyaluronate, fibrin, alginate, agarose, chitosan, bacterial cellulose, elastin, keratin,
derivatives thereof, and combinations thereof.
6. The implantable therapeutic delivery system of claim 5, wherein the hydrogel
material comprises a pure alginate, a modified alginate, or a mixture of pure and modified alginate.
7. The implantable therapeutic delivery system of claim 6, wherein the modified
20 alginate is a zwitterionically modified alginate.
8. The implantable therapeutic delivery system of any one of claims 2 to 4, wherein
the hydrogel material comprises a synthetic polymeric material selected from polyethylene glycol
(PEG), poly(acrylic acid), poly(ethylene oxide), poly(vinyl alcohol), polyphosphazene,
poly(hydroxyethyl methacrylate), triazole-zwitterion hydrogels (TR-qCB, TR-CB, TR-SB),
25 poly(sulfobetaine methacrylate), carboxybetaine methacrylate, poly[2-methacryloyloxyethyl
phosphorylcholine, N-hydroxyethyl acrylamide, a copolymer thereof, a derivative thereof, and a
combination thereof.
9. The implantable therapeutic delivery system of any one of claims 2 to 8, wherein
the nitinol mesh-reinforced hydrogel material has a thickness of about 10 to about 200 μm , about
30 10 to about 50 μm , about 50 to about 100 μm , about 100 to about 150 μm , or about 150 to about

200 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm , about 100 to about 110 μm , about 110 to about 120 μm , about 120 to about 130 μm , about 130 to about 140 μm , about 140 to about 150 μm , about 150 to about 160 μm , about 160 to about 170 μm , about 170 to about 180 μm , about 180 to about 190 μm , or about 190 to about 200 μm .

10. The implantable therapeutic delivery system of any one of claims 2 to 8, wherein in the nitinol mesh-reinforced hydrogel material, the nitinol mesh is present at or adjacent to an internal surface thereof and the hydrogel material extends from the internal surface to an external surface thereof.

11. The implantable therapeutic delivery system of claim 1, wherein the membrane comprises a nitinol mesh-reinforced nanofibrous material.

12. The implantable therapeutic delivery system of claim 11, wherein the nitinol mesh-reinforced nanofibrous material comprises one or more nitinol mesh layers.

13. The implantable therapeutic delivery system according to claim 12, wherein the nitinol mesh-reinforced nanofibrous material comprises one or more nanofiber layers, such as first and second nanofibrous layers with the nitinol mesh sandwiched between the first and second nanofibrous layers, optionally wherein fibers of the first and second nanofibrous layers are bonded to another via pores in the nitinol mesh.

14. The implantable therapeutic delivery system according to claim 13, wherein the one or more nanofiber layers are formed of one or more medical-grade elastomers.

15. The implantable therapeutic delivery system according to claim 14, wherein the one or more medical-grade elastomers are selected from the group of polyether block amide, polycarbonate urethane, thermoplastic silicon-polycarbonate-urethane, polyether urethane, and combinations thereof.

16. The implantable therapeutic delivery system of any one of claims 11 to 15, wherein the nitinol mesh-reinforced nanofibrous material has a thickness of about 10 to about 100 μm , about 10 to about 50 μm , or about 50 to about 100 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm .

17. The implantable therapeutic delivery system of any one of claims 10 to 16, wherein in the nitinol mesh-reinforced nanofibrous material, the nitinol mesh is present at or adjacent to an internal surface thereof and the nanofiber layer is present at or adjacent to an external surface thereof.

5 18. The implantable therapeutic delivery system of any one of claims 1 to 17, wherein the membrane is porous but impermeable to cellular migration.

19. The implantable therapeutic delivery system of any one of claims 1 to 18, wherein the hydrogel matrix is a natural polymeric material, a synthetic polymeric material, or a combination thereof, as defined in one of claims 4 to 8.

10 20. The implantable therapeutic delivery system of any one of claims 1 to 19, wherein the nitinol mesh has a thickness of about 10 to about 100 μm , about 10 to about 50 μm , or about 50 to about 100 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm .

15 21. The implantable therapeutic delivery system of any one of claims 1 to 19, wherein the nitinol mesh is formed of nitinol wire having a diameter of about 10 to about 100 μm , about 10 to about 50 μm , or about 50 to about 100 μm , such as about 10 to about 20 μm , about 20 to about 30 μm , about 30 to about 40 μm , about 40 to about 50 μm , about 50 to about 60 μm , about 60 to about 70 μm , about 70 to about 80 μm , about 80 to about 90 μm , about 90 to about 100 μm .

20 22. The implantable therapeutic delivery system of any one of claims 1 to 19, wherein the nitinol mesh has a pore size from about 50 to 5000 μm , including about 50 to about 150 μm , about 150 to about 250 μm , about 250 to about 500 μm , about 500 to about 750 μm , about 750 to about 1000 μm , about 1000 to about 1500 μm , about 1500 to about 2000 μm , about 2000 to about 2500 μm , about 2500 to about 3000 μm , about 3000 to about 3500 μm , about 3500 to about 4000
25 μm , about 4000 to about 4500 μm , or about 4500 to about 5000 μm .

23. The implantable therapeutic delivery system of any one of claims 1 to 19, wherein the delivery system has a tube-like configuration having a diameter of about 100 μm to about 1 cm, including about 100 to about 500 μm , about 500 to about 1000 μm , about 1000 to about 2000 μm , about 3000 to about 4000 μm , about 4000 to about 5000 μm , about 5000 to about 6000 μm ,
30 about 6000 to about 7000 μm , about 7000 to about 8000 μm , about 8000 to about 9000 μm , or about 9000 to about 10000 μm .

24. The implantable therapeutic delivery system of any one of claims 1 to 19, wherein the implantable therapeutic delivery system comprises a tube-in-tube configuration, wherein the inner and outer tubes independently comprise a membrane comprising a nitinol mesh-reinforced hydrogel or nanofibrous material, wherein a hydrogel matrix is positioned between the inner and outer tubes.

25. The implantable therapeutic delivery system of any one of claims 1 to 24, wherein the at least one therapeutic agent comprises a drug.

26. The implantable therapeutic delivery system of any one of claims 1 to 25, wherein the at least one therapeutic agent is released from a preparation of cells positioned within the hydrogel matrix.

27. The implantable therapeutic delivery system of any one of claims 2 to 10, wherein the at least one therapeutic agent comprises a first therapeutic agent in the hydrogel matrix, and wherein the device further comprises a second therapeutic agent released from a preparation of cells positioned within the hydrogel material.

28. The implantable therapeutic delivery system of claim 1 wherein:
the membrane that partially or fully encapsulates the hydrogel matrix comprises a first nitinol mesh-reinforced nanofibrous material; and
the delivery system further comprises a second hydrogel matrix external of the first nitinol mesh-reinforced nanofibrous material, which is partially or fully encapsulated by a nitinol mesh-reinforced hydrogel or nanofibrous material.

29. The implantable therapeutic delivery system of claim 28, wherein the second hydrogel matrix comprises a preparation of cells positioned therein, which preparation of cells release a therapeutic agent.

30. The implantable therapeutic delivery system of any one of claims 1 to 29, wherein the preparation of cells comprises a preparation of single cells or a preparation of cell aggregates.

31. The implantable therapeutic delivery system of any one of claims 1–30, wherein the preparation of cells comprises a preparation of primary cells or a preparation of immortalized cells.

32. The implantable therapeutic delivery system of any one of claims 1–31, wherein the preparation of cells comprises a preparation of mammalian cells.

33. The implantable therapeutic delivery system of claim 32, wherein the preparation of cells comprise a preparation of mammalian cells selected from the group consisting of primate cells, rodent cells, canine cells, feline cells, equine cells, bovine cells, and porcine cells.

34. The implantable therapeutic delivery system of claim 33, wherein the preparation
5 of cells comprises human cells.

35. The implantable therapeutic delivery system of any one of claims 1–34, wherein the preparation of cells comprise a preparation of stem cells or stem cell derived cells.

36. The implantable therapeutic delivery system of claim 35, wherein the stem cells are pluripotent, multipotent, oligopotent, or unipotent stem cells.

10 37. The implantable therapeutic delivery system of claim 35, wherein the preparation of stem cells is selected from the group consisting of embryonic stem cells, epiblast cells, primitive ectoderm cells, primordial germ cells, and induced pluripotent stem cells.

38. The implantable therapeutic delivery system of any one of claims 1–34, wherein the preparation of cells comprise cells selected from the group consisting of smooth muscle cells,
15 cardiac myocytes, platelets, epithelial cells, endothelial cells, urothelial cells, fibroblasts, embryonic fibroblasts, myoblasts, chondrocytes, chondroblasts, osteoblasts, osteoclasts, keratinocytes, hepatocytes, bile duct cells, islet cells, thyroid, parathyroid, adrenal, hypothalamic, pituitary, ovarian, testicular, salivary gland cells, adipocytes, embryonic stem cells, mesenchymal stem cells, neural cells, endothelial progenitor cells, hematopoietic cells, precursor cells,
20 mesenchymal stromal cells, Baby Hamster Kidney (BHK) cells, Chinese Hamster Ovary cells, Human Amniotic Epithelial (HAE) cells, choroid plexus cells, chromaffin cells, adrenal chromaffin cells, pheochromocytoma cell line PC12, human retinal pigment epithelium cells, recombinant human retinal pigment epithelium cells, NGF-secreting Baby Hamster Kidney (BHK) cells, human bone marrow-derived stem cells transfected with GLP-1, BDNF-producing
25 fibroblasts, NGF-producing cells, CNTF-producing cells, BDNF-secreting Schwann cells, IL-2-secreting myoblasts, endostatin-secreting cells, and cytochrome P450 enzyme overexpressed feline kidney epithelial cells, myogenic cells, embryonic stem cell-derived neural progenitor cells, irradiated tumor cells, proximal tubule cells, neural precursor cells, astrocytes, genetically engineered cells.

30 39. The implantable therapeutic delivery system of claim 38, wherein the preparation of cells comprises a preparation of islet cells that release insulin and glucagon.

40. The implantable therapeutic delivery system of claim 39, wherein the preparation of islet cells is a preparation of human cells, porcine cells, or rodent islets.

41. The implantable therapeutic delivery system of claim 39 or 40, wherein the preparation of islets comprises a density between 1×10^3 to 2×10^6 islet equivalents (IEQs)/mL.

5 42. The implantable therapeutic delivery system of any one of claims 1–40, wherein the therapeutic agent comprises one or more biologically active agents selected from the group consisting of a protein, peptide, antibody or antibody fragment thereof, antibody mimetic, a nucleic acid, a small molecule, a hormone, a growth factor, an angiogenic factor, a cytokine, an anti-inflammatory agent, an anti-fibrotic agent, and combinations thereof.

10 43. The implantable therapeutic delivery system of any one of claims 1–41, wherein the therapeutic agent comprises an anti-fibrotic agent.

44. The implantable therapeutic delivery system of claim 43, wherein the anti-fibrotic agent is in crystalline form.

15 45. The implantable therapeutic delivery system of claim 43, wherein the anti-fibrotic agent is nintedanib, GW2580, or pirfenidone.

46. A method of delivering a therapeutic agent to a subject in need thereof, said method comprising:

implanting the implantable therapeutic delivery system according to any one of claims 1–45 into the subject.

20 47. A method of treating diabetes in a subject, said method comprising:
implanting the implantable therapeutic delivery system according to any one of claims 39–42 into the subject having diabetes.

25 48. The method of claim 47, wherein the hydrogel matrix comprises a preparation of cells that release insulin, glucagon, or a combination thereof for the treatment of diabetes in the subject.

49. The method of claim 47 or claim 48, wherein the preparation of cells is a preparation of islets.

50. The method of claim 49, where the preparation of islets is a preparation of primate islets, rodent islets, canine islets, feline islets, equine islets, bovine islets, or porcine islets.

51. The method of claim 49, wherein the preparation of islets is derived from a preparation of stem cells.

52. The method of claim 49, wherein the preparation of stem cells is selected from the group consisting of embryonic stem cells, epiblast cells, primitive ectoderm cells, primordial germ
5 cells, and induced pluripotent stem cells.

53. A method of treating a bleeding disorder in a subject, said method comprising:

implanting the implantable therapeutic delivery system of any one of claims 1–45 into the subject having a bleeding disorder.

54. The method of claim 53, wherein the bleeding disorder is selected from the group
10 consisting of hemophilia A, hemophilia B, von Willebrand disease, Factor I deficiency, Factor II deficiency, Factor V deficiency, Factor VII deficiency, Factor X deficiency, Factor XI deficiency, Factor XII deficiency, and Factor XIII deficiency.

55. The method of claim 53 or claim 54, wherein the hydrogel matrix comprises a preparation of cells that release one or more blood clotting factors selected from the group
15 consisting of Factor I, Factor II, Factor V, Factor VII, Factor VIII, Factor IX, Factor X, Factor XI, Factor XII, and Factor XIII for treatment of the bleeding disorder.

56. The method of claim 53, wherein the preparation of cells comprises recombinant myoblasts, mesenchymal stromal cells, induced pluripotent stem cell derived endothelial cells, or a combination thereof.

20 57. A method of treating a lysosomal storage disease in a subject, said method comprising:

implanting the implantable therapeutic delivery system of any one of claims 1–45 into the subject having the lysosomal storage disease.

58. The method of claim 57, wherein the hydrogel matrix comprises a preparation of
25 cells that release an enzyme selected from the group consisting of α -L-iduronidase, Iduronate-2-sulfatase, α -glucuronidase, Arylsulfatase A, alpha-Galactosidase A, and combinations thereof, for treating the lysosomal storage disease in the subject.

59. The method of claim 58, wherein the preparation of cells comprises hematopoietic stem cells, fibroblasts, myoblasts, Baby Hamster Kidney (BHK) cells, Chinese Hamster Ovary
30 cells, Human Amniotic Epithelial (HAE) cells, or combinations thereof.

60. A method of treating a neurological disorder in a subject, said method comprising:
implanting the implantable therapeutic delivery system of any one of claims 1–45 into the
subject having the neurological disorder.

61. The method of claim 60, wherein the neurological disorder is selected from the
5 group consisting of Parkinson's disorder, Alzheimer's disease, epilepsy, Huntington's disease,
Amyotrophic lateral sclerosis, chronic pain, visual loss, hearing loss, peripheral nerve injury, and
spinal cord injury.

62. The method of claim 60 or claim 61, wherein the hydrogel matrix comprises a
preparation of cells that release a molecule selected from cerebrospinal fluid, extracellular fluid,
10 levodopa, nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), BLP-1, brain-derived
neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), enkephalin, adrenaline,
catecholamine, and combinations thereof, for treating the neurological disorder.

63. The method of claim 62, wherein the preparation of cells comprises choroid plexus
cells, chromaffin cells, pheochromocytoma cell line PC12, human retinal pigment epithelial cells,
15 NGF-secreting Baby Hamster Kidney (BHK) cells, myoblasts, human bone marrow-derived stem
cells transfected with GLP-1, BDNF-producing fibroblasts, NGF-producing cells, CNTF-
producing cells, adrenal chromaffin cells, BDNF-secreting Schwann cells, myogenic cells,
embryonic stem cell-derived neural progenitor cells, or combinations thereof.

64. A method of treating a cancer in a subject, said method comprising:
20 implanting the implantable therapeutic delivery system of any one of claims 1–45 into the
subject having cancer.

65. The method of claim 64, wherein the hydrogel matrix comprises a preparation of
cells that release a molecule selected from IL-2, endostatin, cytochrome P450 enzyme, tumor
antigens, a cytokine, and combinations thereof, for treating cancer in the subject.

66. The method of claim 65, wherein the preparation of cells comprises IL-2-secreting
myoblasts, endostatin-secreting cells, Chinese Hamster Ovary cells, and cytochrome P450 enzyme
overexpressed feline kidney epithelial cells, irradiated tumor cells, or combinations thereof.

67. A method of treating a chronic eye disease in a subject, said method comprising:
implanting the implantable therapeutic delivery system of any one of claims 1–45 into the
30 subject having a chronic eye disease.

68. The method of claim 67, wherein the chronic eye disease is selected from the group consisting of age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, glaucoma, macular telangiectasia, and combinations thereof.

5 69. The method of claim 67 or claim 68, wherein the hydrogel matrix comprises a preparation of cells that release a molecule selected from ciliary neurotrophic factor, antagonists against vascular endothelial growth factor and platelet-derived growth factor, and combinations thereof, for treating the chronic eye disease.

10 70. The method of claim 69, wherein the preparation of cells comprises human retinal pigment epithelium cells, recombinant human retinal pigment epithelium cells, or a combination thereof.

71. A method of treating a kidney failure in a subject, said method comprising:
implanting the implantable therapeutic delivery system of any one of claims 1–45 into the subject having a kidney failure.

15 72. The method of claim 71, wherein the hydrogel matrix comprises a preparation of cells that release a therapeutic molecule suitable for treating the kidney failure.

73. The method of claim 71 or 72, wherein the hydrogel matrix comprises a preparation of renal proximal tubule cells, mesenchymal stem cells, and a combination thereof.

20 74. A method of treating a chronic pain in a subject, said method comprising:
implanting the implantable therapeutic delivery system of any one of claims 1–45 into the subject having a chronic pain.

75. The method of claim 74, wherein the chronic pain is chronic pain caused by degenerative back and knee, neuropathic back and knee, or cancer.

25 76. The method of claim 74 or claim 75, wherein the hydrogel matrix comprises a preparation of cells that release a molecule selected from the group consisting of catecholamine, opioid peptides, enkephalins, and combinations thereof.

77. The method of claim 76, wherein the preparation of cell comprises chromaffin cells, neural precursor cells, mesenchymal stem cells, astrocytes, and genetically engineered cells, or a combination thereof.

30 78. The method according to any one of claims 46-77, wherein said implanting is carried out via a laparoscopic procedure.

79. The method according to any one of claims 46-77, wherein said implantable therapeutic delivery system is implanted intraperitoneally, percutaneously, or subcutaneously.

80. The method according to any one of claims 46-77, wherein said method further comprises retrieving the implantable therapeutic delivery system from the subject.

5 81. The method according to claim 80, wherein said method further comprises implanting a replacement implantable therapeutic delivery system after said retrieving.

82. A method of forming a cell encapsulation system suitable for implant, the method comprising:

10 providing a hydrogel precursor solution comprising at least one therapeutic agent in the hydrogel precursor solution; and

introducing the hydrogel precursor solution internally of a membrane comprising a nitinol mesh-reinforced hydrogel or nanofibrous material, and allowing the hydrogel precursor to form a hydrogel matrix that is partially or fully encapsulated by the membrane.

15 83. The method according to claim 82 further comprising:
forming the nitinol mesh-reinforced hydrogel membrane prior to said introducing.

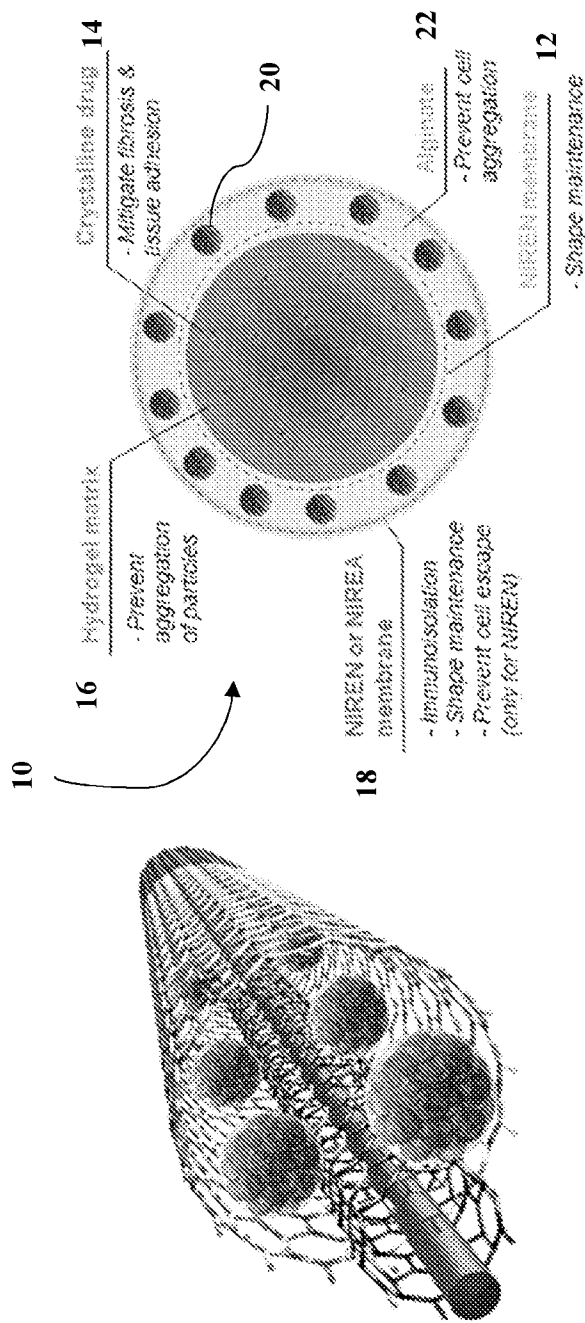
20 84. The method according to claim 83, wherein said forming the nitinol mesh-reinforced hydrogel membrane comprises exposing a nitinol mesh to a hydrogel precursor solution under conditions to cause cross-linking of the hydrogel precursors, thereby forming a hydrogel layer supported on the nitinol mesh.

85. The method according to claim 82 further comprising:
forming the nitinol mesh-reinforced nanofibrous membrane prior to said introducing.

25 86. The method according to claim 85, wherein said forming the nitinol mesh-reinforced nanofibrous membrane comprises electrospinning a nonwoven web of polymeric nanofibers on one or both sides of a nitinol mesh.

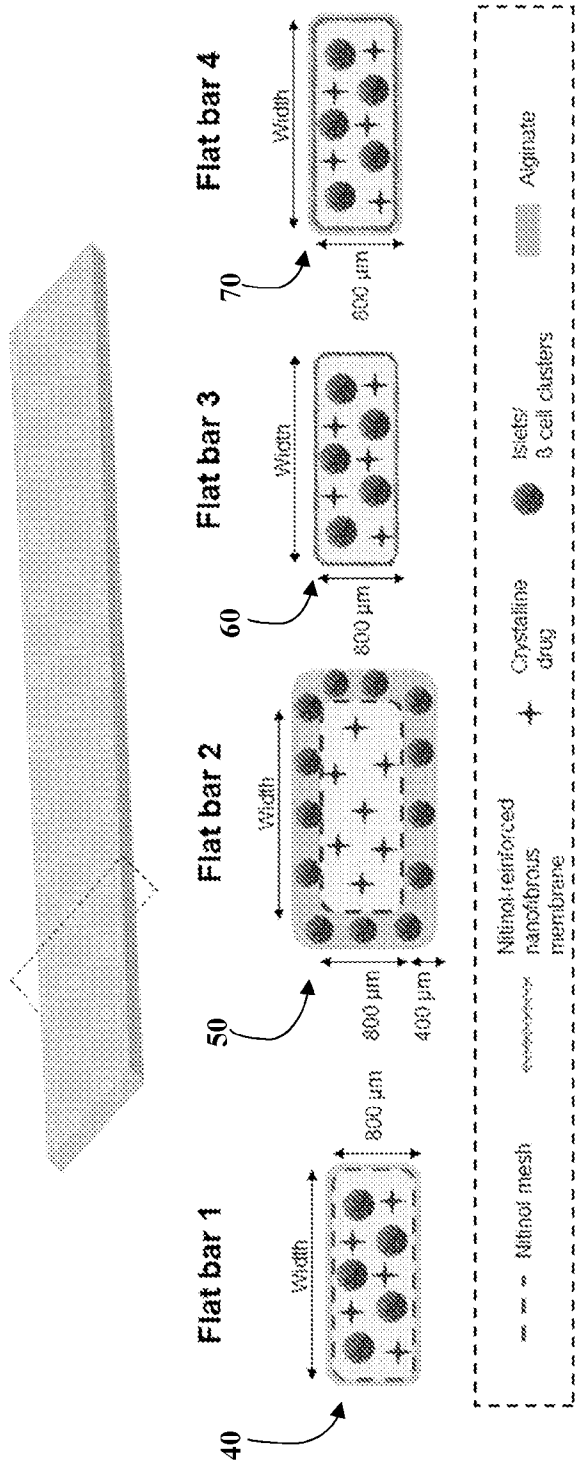
30 87. The method according to claim 85 further comprising:
exposing a nitinol mesh-reinforced nanofibrous membrane to a hydrogel precursor solution under conditions to cause cross-linking of the hydrogel precursors, thereby forming a hydrogel layer supported on the nitinol mesh-reinforced nanofibrous membrane.

88. The method according to claim 82 further comprising:
sealing the membrane to fully encapsulate the hydrogel matrix.



Outer diameter (mm)	Diffusion distance (mm)	Length (mm)	Volume of cell encapsulation zone (mL)
5	0.3	250	4.429
	0.4	250	5.780
6	0.3	250	5.375
	0.4	250	7.038
8	0.3	250	7.258
	0.4	250	9.550
10	0.3	250	9.142
	0.4	250	12.064

FIG. 1



Width (mm)	Length (mm)	Volume for cell encapsulation (mL)			
		Flat bar 1	Flat bar 2	Flat bar 3	Flat bar 4
10	250	2	2.32	2	2
10	500	4	4.64	4	4
20	250	4	4.32	4	4
20	500	8	8.64	8	8

FIG. 2

FIG. 3A

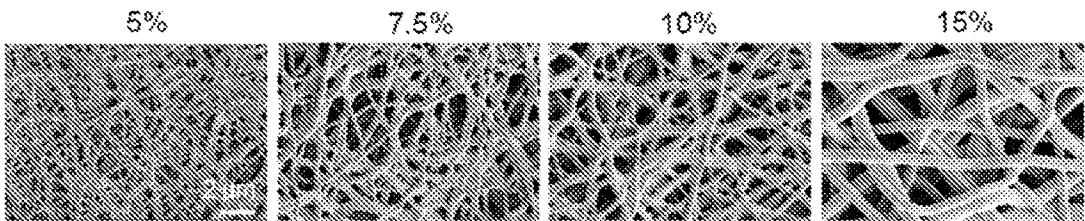


FIG. 3B

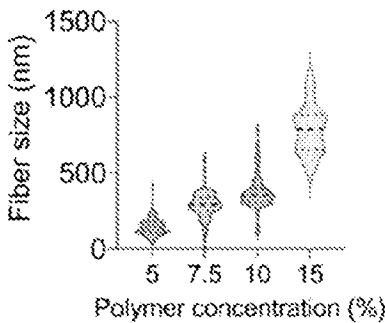


FIG. 3C

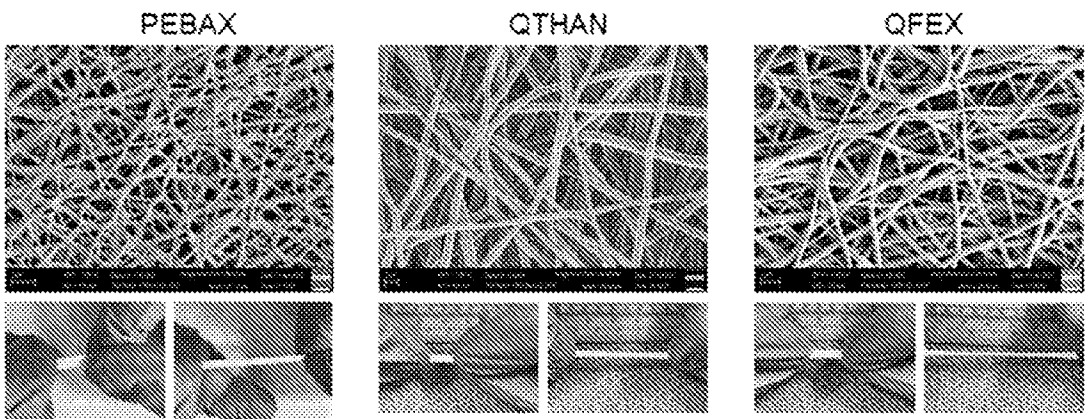
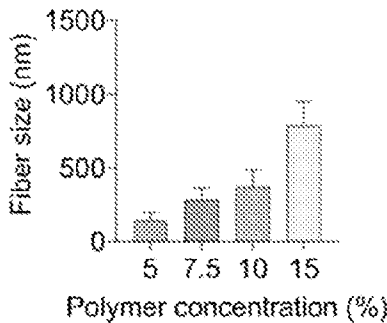


FIG. 3D

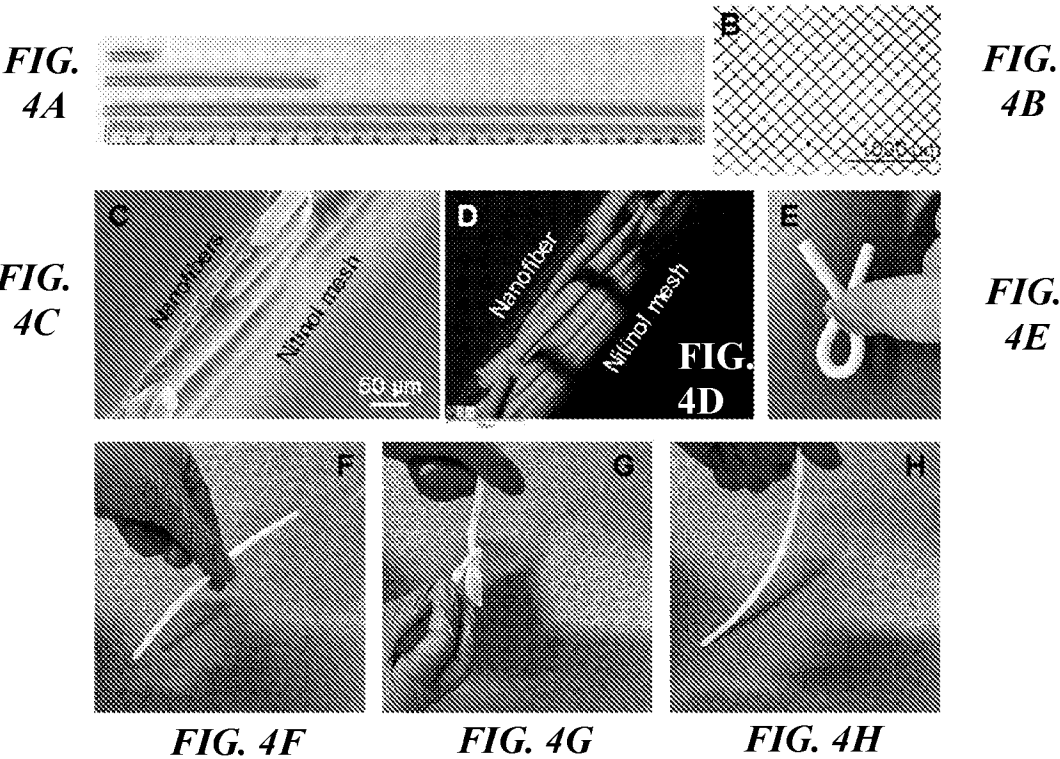


FIG. 6A

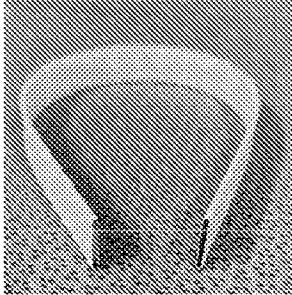


FIG. 6C

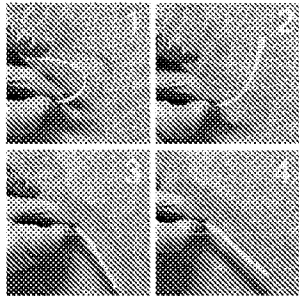


FIG. 6D

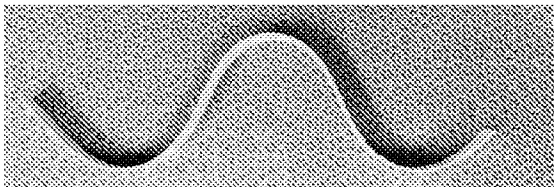
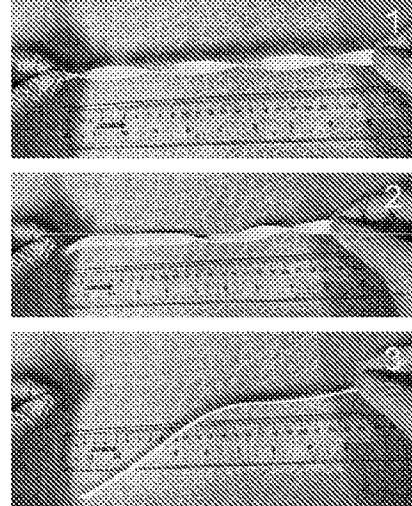


FIG. 6B

FIG. 7A

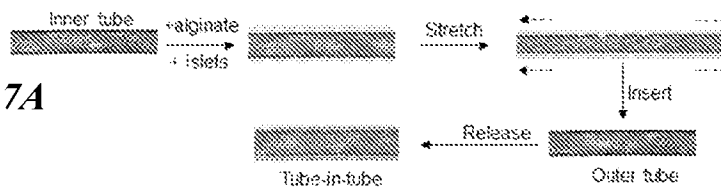


FIG. 7B

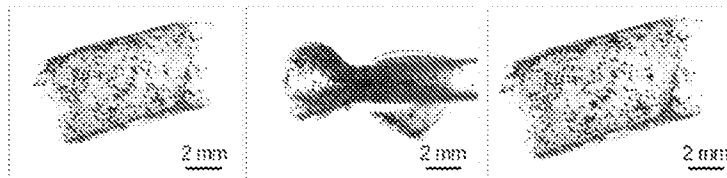


FIG. 7C

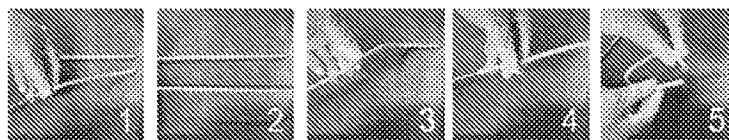
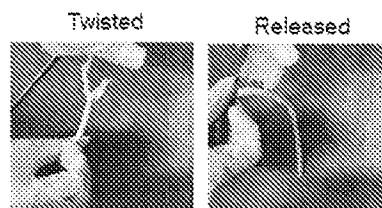


FIG. 7D



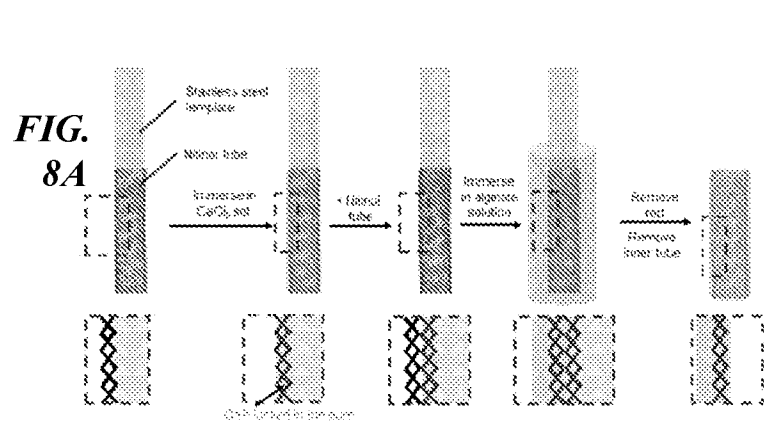


FIG. 8B

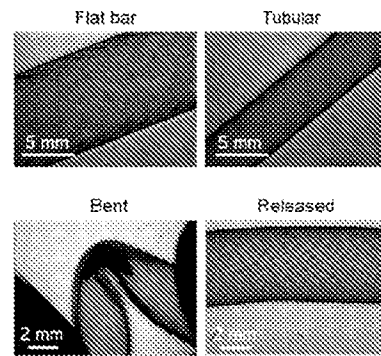


FIG. 8C

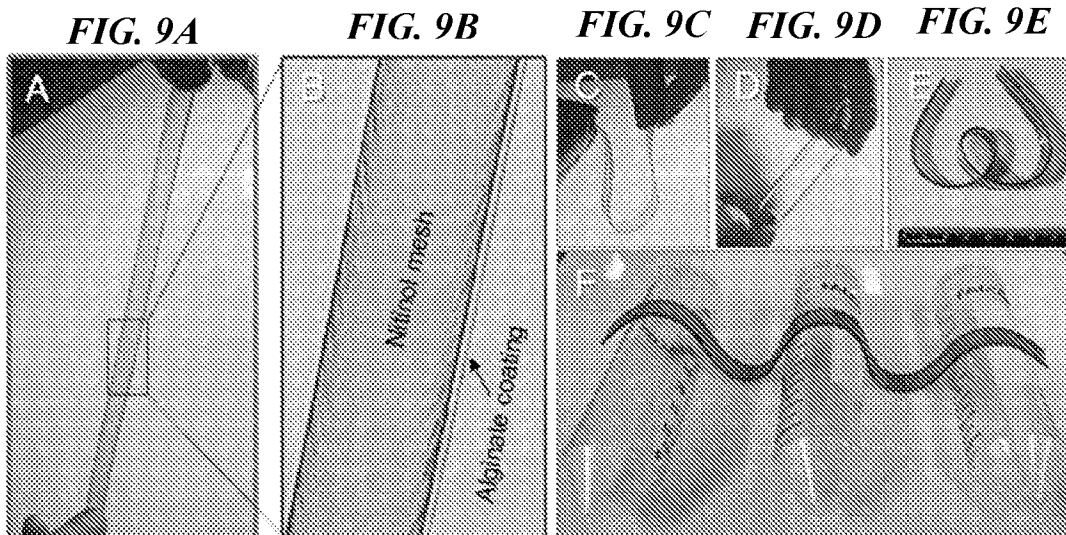


FIG. 9F

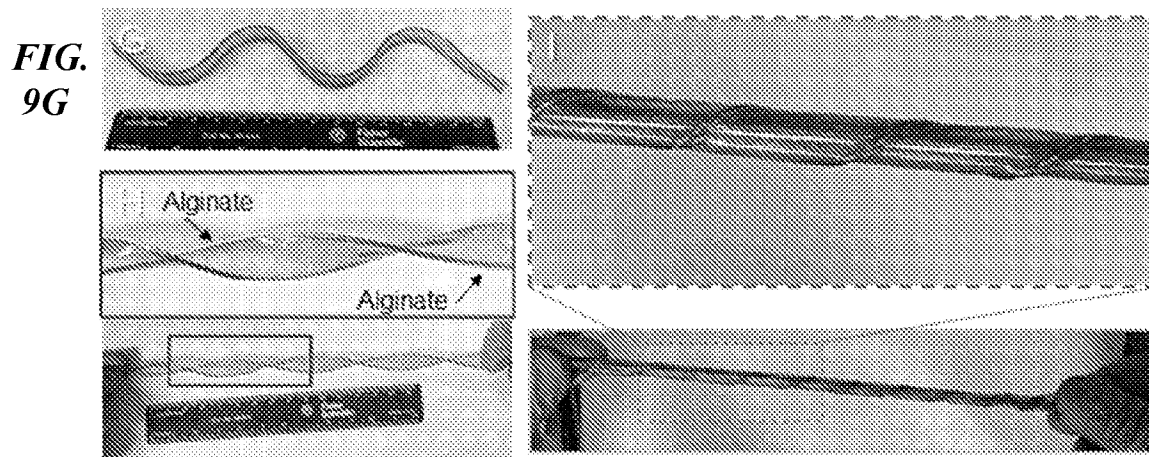


FIG. 9H

FIG. 9I

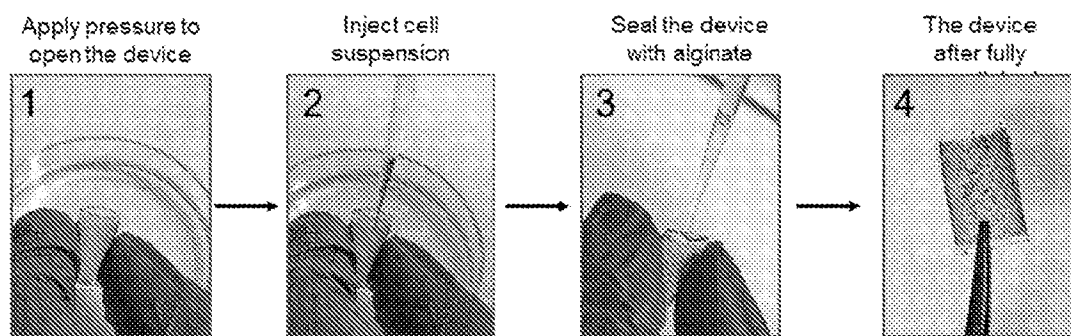


FIG. 10

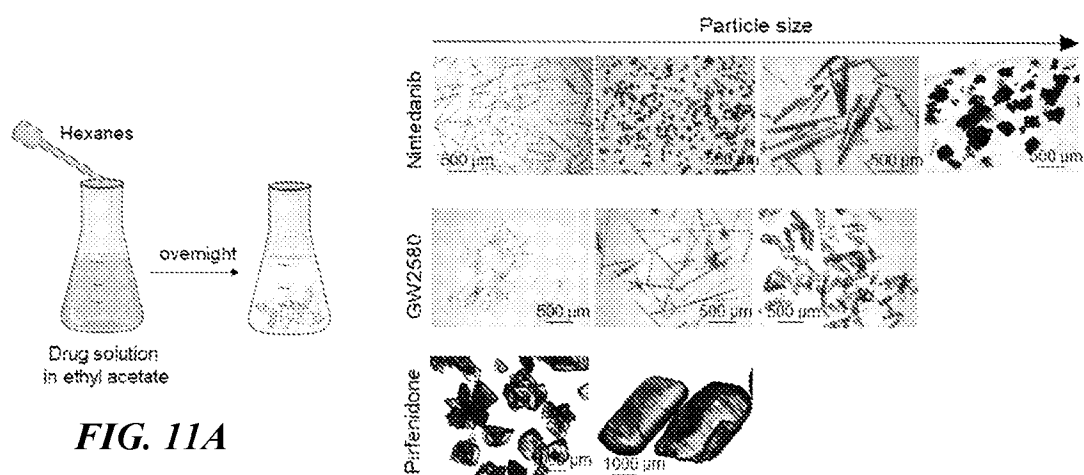
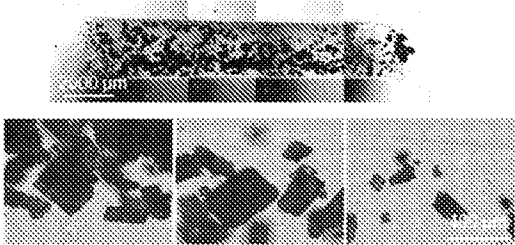
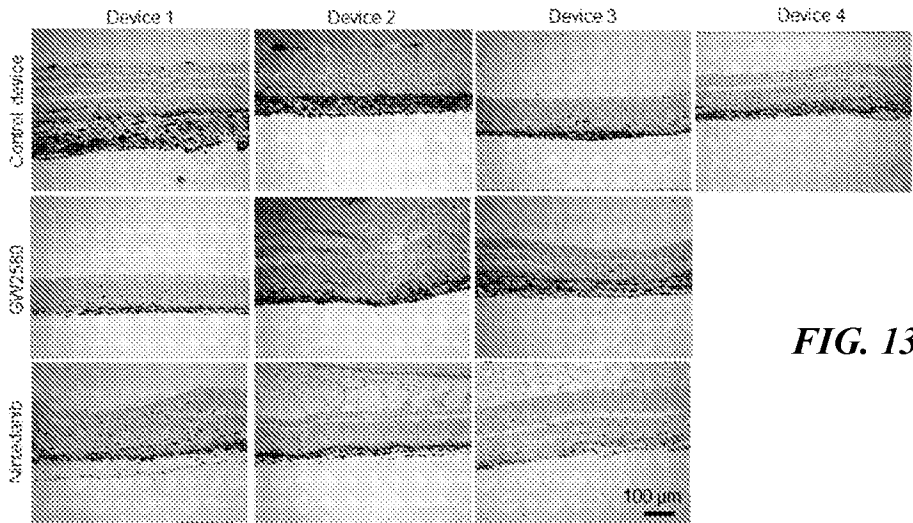
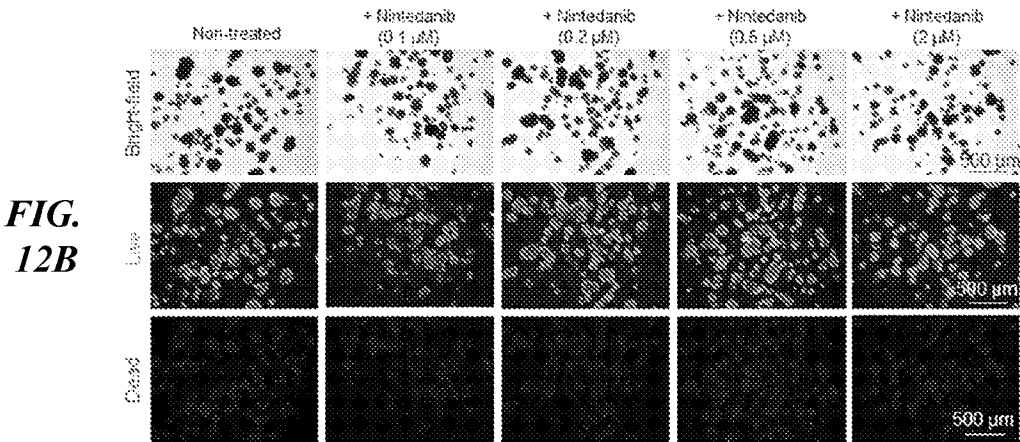
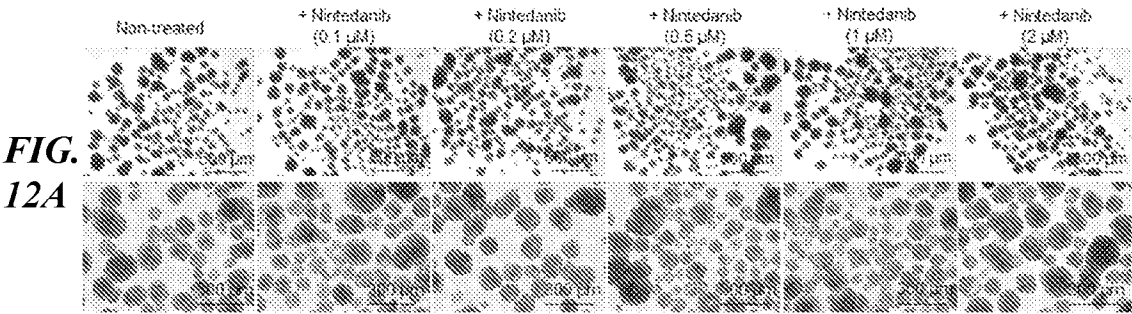


FIG. 11B



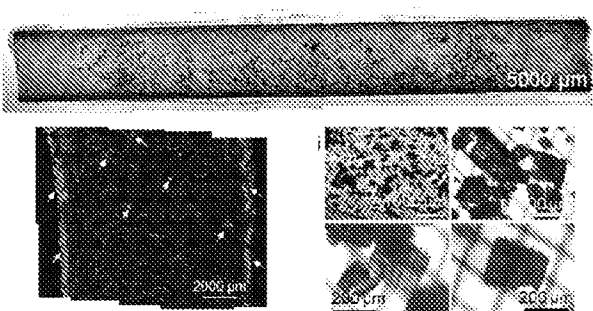
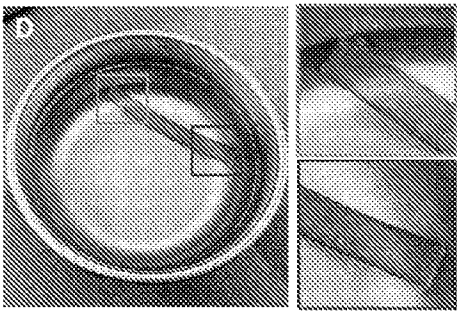
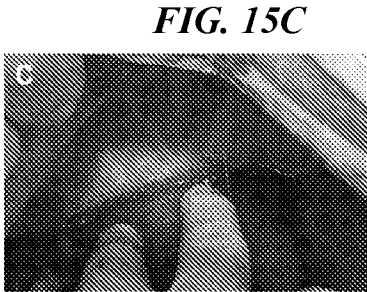
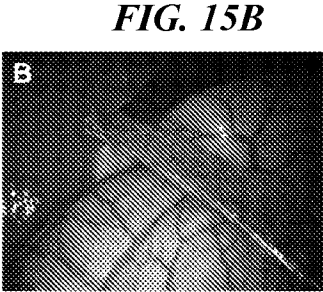
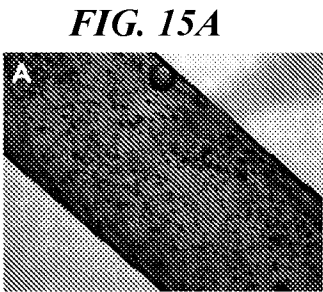
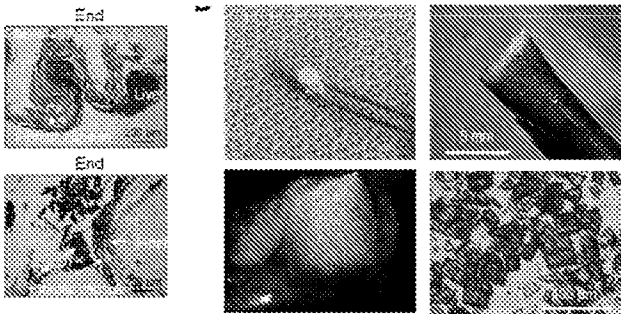
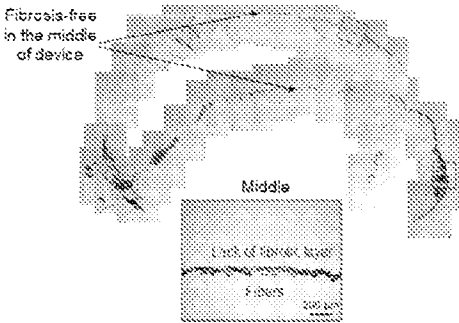
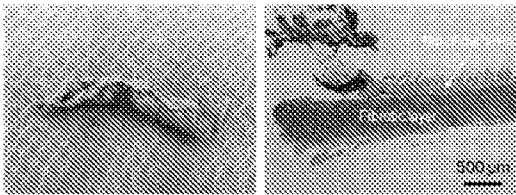
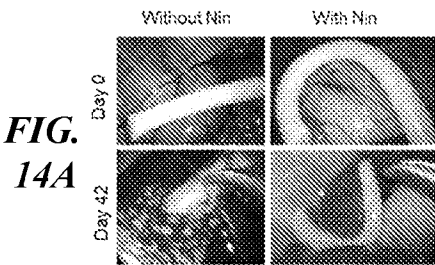
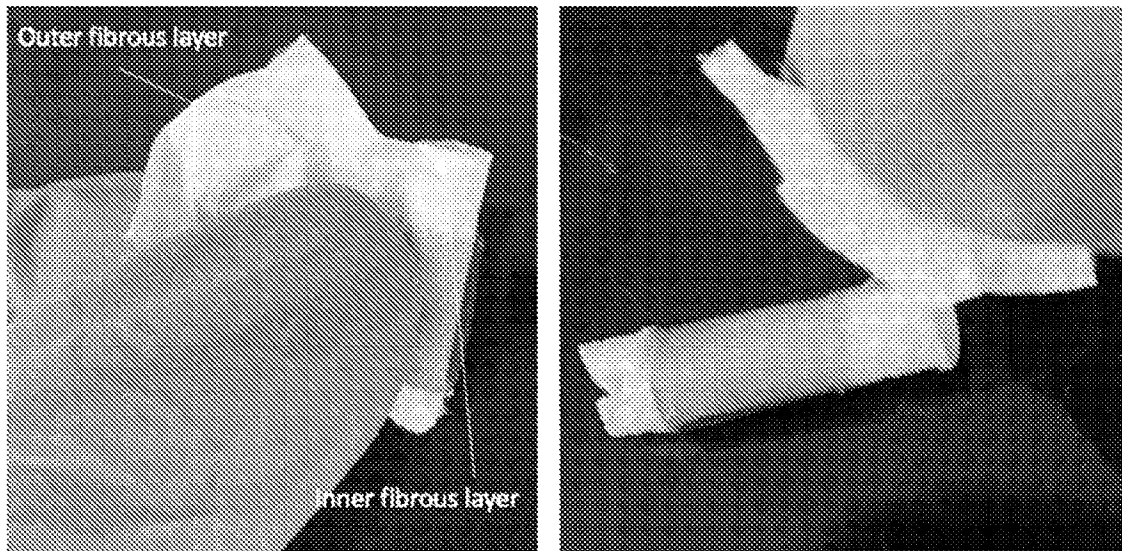
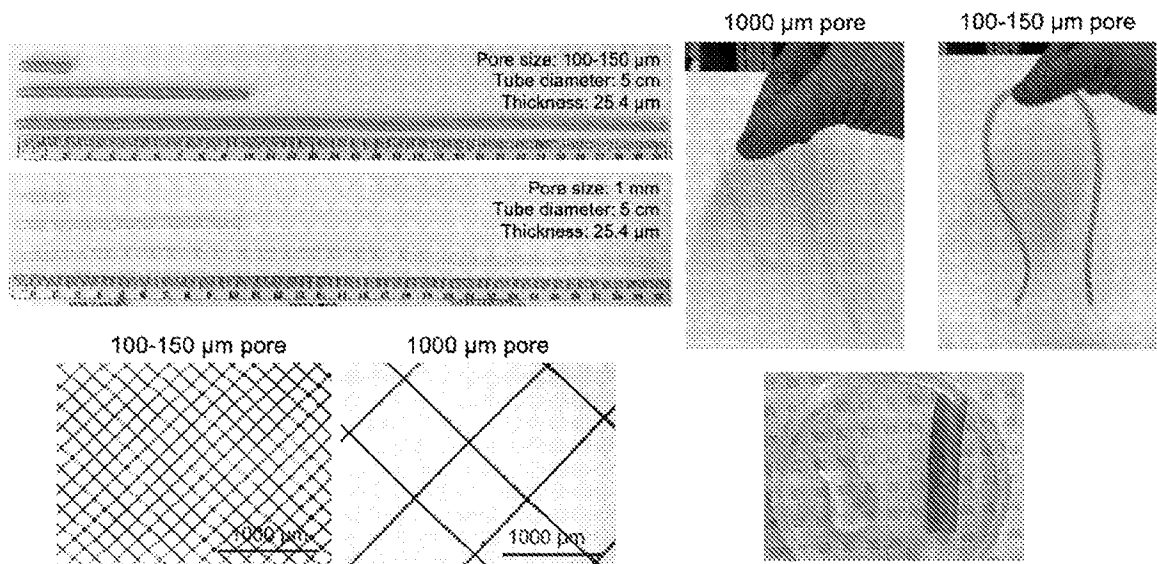


FIG. 15F

FIG. 15G

**FIG. 16****FIG. 17**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/056396

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61L 27/52** (2023.01); **A61L 29/14** (2023.01); **A61F 2/86** (2023.01); **A61F 2/30** (2023.01); **A61F 2/90** (2023.01);
A61F 2/852 (2023.01)CPC: **A61L 27/52**; **A61L 29/145**; **A61F 2/86**; **A61F 2002/30092**; **A61F 2/90**; **A61F 2/852**

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)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2023/0017150 A1 (THE ASAN FOUNDATION) 19 January 2023 (19.01.2023) abstract, claims 1-7	1-4
Y	US 2019/0247306 A1 (W. L. Gore & Associates, Inc.) 15 August 2019 (15.08.2019) abstract, [0024]	1-4
A	US 2023/0338035 A1 (MicroVention Inc) 26 October 2023 (26.10.2023) entire document	1-4
A	US 2016/0030360 A1 (Massachusetts Institute of Technology) 02 April 2016 (02.04.2016) entire document	1-4
A	Bhagavatula et al., "Self-Expanding Anchors for Stabilizing Percutaneously Implanted Microdevices in Biological Tissues", 06 April 2021, Micromachines 2021, 12, 404. https://doi.org/10.3390/mi12040404 entire document	1-4

☒ 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
"D" document cited by the applicant in the international application
"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

24 March 2025 (24.03.2025)

Date of mailing of the international search report

17 March 2025 (17.03.2025)

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SHANE THOMAS

Telephone No. (571)272-4188

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/056396

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **5-10, 17-27, 30-81**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-4, 11-16, 28-29, directed to an implantable therapeutic delivery system. The implantable therapeutic delivery system will be searched to the extent that it encompasses the first choice of a membrane that partially or fully encapsulates the hydrogel matrix of instant claim 1, a nitinol mesh-reinforced hydrogel material.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-4**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/056396

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Kalairaj et al., "Hydrogel-matrix encapsulated Nitinol actuation with self-cooling mechanism", 25 October 2019, RSC Adv., 2019, 9, 34244, DOI: 10.1039/c9ra05360c entire document	1-4