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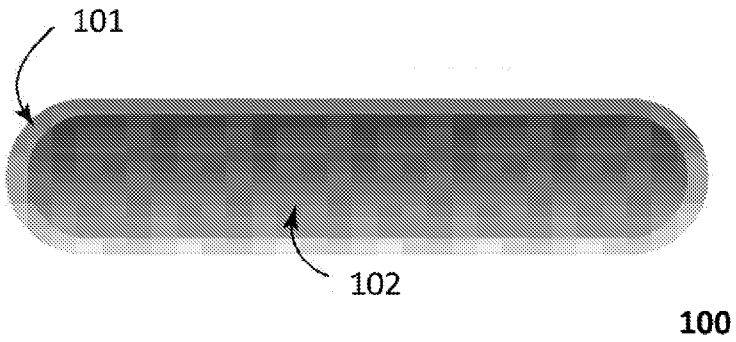


FIG. 1A

(57) Abstract: The present disclosure relates generally to wound inserts that may include an outer layer and an inner core of biopolymers that may be used in the therapy of tunneling wounds and for facilitating wound healing. Methods of use, methods for manufacture, and kits for use in practicing the methods are also provided.

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WOUND INSERTS FOR TREATMENT OF TUNNELING WOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Patent Application No. 62/868,629, filed on June 28, 2019, the contents of which are incorporated herein in their entirety.

TECHNICAL FIELD

[0002] The present technology relates generally to wound inserts and methods for facilitating wound healing. Methods of use, methods for manufacture, and kits for use in practicing the methods are also provided.

BACKGROUND

[0003] The following description of the background of the present technology is provided simply as an aid in understanding the present technology and is not admitted to describe or constitute prior art to the present technology.

[0004] A wide variety of materials and devices, generally characterized as "dressings," are generally known in the art for use in treating an injury or other disruption of tissue. Such wounds may be the result of trauma, surgery, or disease, and may affect skin or other tissues. In general, dressings may control bleeding, absorb wound exudate, ease pain, assist in debriding the wound, protect wound tissue from infection, or otherwise promote healing and protect the wound from further damage.

[0005] Healing wounds with complex configurations, such as lengthy tunneling wounds, can be very challenging since some of such wounds do not respond to mainstream wound care treatment. Wounds that do not respond to treatment can not only lead to a chronic wound, but also patient mortality.

SUMMARY

[0006] In an aspect, a wound insert is provided that includes an outer layer and an inner core. The outer layer includes a photocrosslinked biopolymer, a reagent-crosslinked biopolymer, or both (collectively, "crosslinked biopolymer"), and the inner core includes a

biopolymer. Further, the outer layer exhibits a modulus of elasticity from about 0.5 MPa to about 5.0 MPa; and the inner core exhibits a lower modulus of elasticity.

[0007] In a related aspect, a method for treating a wound in a subject is provided, where the method includes administering a wound insert of any embodiment disclosed herein to the wound.

[0008] In a further related aspect, a kit is provided that includes a wound insert of any embodiment disclosed herein as well as instructions for use.

[0009] In a further related aspect, a method of manufacturing a wound insert of any embodiment of the present technology is provided. The method includes fabricating an outer layer of the wound insert from a first slurry comprising one or more biopolymers, wherein the outer layer is in a shape having a hollow center; photo-crosslinking and/or reagent-crosslinking the outer layer to obtain one or more photocrosslinked and/or reagent-crosslinked biopolymers; drying the outer layer of the wound insert; depositing a second slurry into the hollow center of the outer layer to form an inner core of the wound insert; and removing residual moisture from the inner core, where the shape of the outer layer may be a cylinder, a sphere, a cube, a cuboid, a hexagonal prism, a cone, a square-based pyramid, triangular-based pyramid, or a triangular prism; the second slurry includes a biopolymer; the outer layer exhibits a modulus of elasticity from about 0.5 MPa to about 5.0 MPa; and the inner core exhibits a lower modulus of elasticity than the outer layer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIGs. 1A-1B show cross-sectional views of a diagrammatic representation of an embodiment of an insert of the present technology having a cylindrical shape.

[0011] FIGs. 2A-2B show cross-sectional views of a diagrammatic representation of an embodiment of an insert of the present technology having a cuboidal shape with rounded edges.

[0012] FIG. 3 shows a cross-sectional view of a diagrammatic representation of an embodiment of an insert of the present technology having a cuboidal shape with rounded edges and perforations in the outer layer.

[0013] FIG. 4 shows a cross-sectional view of a diagrammatic representation of an embodiment of an insert of the present technology having a cuboidal shape with rounded edges and though-holes.

[0014] It should be noted that the representative illustrations provided in the figures set forth herein is intended to illustrate the general features and/or characteristics of exemplary embodiments to aid in describing the present technology in full. The figures may not precisely reflect the characteristics of any given embodiment, and are not necessarily intended to define or limit the scope of the claimed subject matter. Further, the present technology may or may not include or incorporate therewith any one or more features of characteristics set provided in any one or more figures.

DETAILED DESCRIPTION

[0015] It is to be appreciated that certain aspects, modes, embodiments, variations, and features of the present methods are described below in various levels of detail in order to provide a substantial understanding of the present technology.

Definitions

[0016] The definitions of certain terms as used in this specification are provided below. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this present technology belongs.

[0017] The following terms are used throughout as defined below.

[0018] As used herein and in the appended claims, singular articles such as “a”, “an”, and “the” and similar referents in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or

exemplary language (*e.g.*, "such as") provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0019] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art, given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term – for example, "about 10 wt.%" would mean "9 wt.% to 11 wt.%." It is to be understood that when "about" precedes a term, the term is to be construed as disclosing "about" the term as well as the term without modification by "about" – for example, "about 10 wt.%" discloses "9 wt.% to 11 wt.%" as well as discloses "10 wt.%."

[0020] As used herein, the term "modulus of elasticity" (also known as "Young's modulus") refers to the measure of an object or a substance's resistance to being deformed elastically (*i.e.*, non-permanently) upon the application of a stress. The modulus of elasticity of an object is defined by the following formula:

$$E = \frac{tensile\ stress\ (\sigma)}{tensile\ strain\ (\varepsilon)}$$

wherein "stress" is the force causing the deformation divided by the area to which the force is applied, and wherein "strain" is the ratio of the change in some parameter caused by the deformation to the original value of the parameter.

[0021] As used herein, the term "radiant power" or "irradiance" refers to the radiant flux or power received by a surface (*e.g.*, a biopolymer of an outer layer of a wound insert as disclosed herein) per unit area. The SI unit of irradiance is the watt per square meter (W/m^2).

[0022] As used herein, the "administration" of a wound insert to a subject includes any route of introducing or delivering to a subject a wound insert to perform its intended function. Administration can be carried out by any suitable route, including, but not limited to, topical administration. Administration includes self-administration and the administration by another.

[0023] As used herein, the term "effective amount" refers to a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, *e.g.*, an amount which results in the decrease

in a wound described herein or one or more signs or symptoms associated with a wound described herein. In the context of therapeutic and/or prophylactic applications, the amount of an insert administered to the subject will vary depending on the composition, the degree, type, and severity of the wound and on the characteristics of the individual. The inserts can also be administered in combination with one or more additional therapeutic compounds. In the methods described herein, the therapeutic inserts may be administered to a subject having one or more wounds.

[0024] As used herein, the terms "individual", "patient", or "subject" can refer to an individual organism, a vertebrate, a mammal, or a human. In some embodiments, the individual, patient, or subject is a human.

[0025] "Treating" or "treatment" as used herein covers the treatment of a wound described herein, in a subject, such as a human, and includes: (i) inhibiting a wound, *i.e.*, arresting its development; (ii) relieving a wound, *i.e.*, causing regression of the wound; (iii) slowing progression of the wound; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the wound. In some embodiments, treatment means that the symptoms associated with the wound are alleviated, reduced, cured, or placed in a state of remission.

[0026] It is also to be appreciated that the various modes of treatment of wounds as described herein are intended to mean "substantial," which includes total but also less than total treatment, and wherein some biologically or medically relevant result is achieved. The treatment may be a continuous prolonged treatment for a chronic wound or a single administration, or a few administrations for the treatment of an acute wound.

The Present Technology

[0027] A lengthy tunneling wound can be very challenging to heal since such wounds do not respond to mainstream wound care treatment. Such wounds can not only lead to chronic wound formation, but also patient mortality.

[0028] The present disclosure is directed to wound inserts that include an outer layer and an inner core of biologically-active biopolymers. The wound inserts of the present technology advantageously may exhibit reduced wound packing pressure on the sides of the wound tunnel and may decrease bioburden due to antimicrobial properties of the wound insert. The wound insert of the present technology may further help prevent the collapse of the wound.

The components of the wound insert may stimulate tissue growth and/or prevent bacterial infection. The components of the wound insert may reduce the inflammatory phase, may stimulate granulation tissue growth, and/or may reduce bacterial bioburden. The wound insert of the present technology may further be configured, due to the nature of the outer layer, with a bioresorbable suture thread to facilitate removal of the wound insert for wound assessment.

[0029] Thus, in an aspect, a wound insert is provided that includes an outer layer and an inner core. The outer layer includes a crosslinked biopolymer, such as a photocrosslinked biopolymer, a reagent-crosslinked biopolymer, or both, and the inner core includes a biopolymer. Further, in any embodiment herein, the outer layer exhibits a modulus of elasticity from about 0.5 MPa to about 5.0 MPa; and the inner core exhibits a lower modulus of elasticity. Therefore, the outer layer of any embodiment disclosed herein may exhibit a modulus of elasticity of about 0.5 MPa, about 0.6 MPa, about 0.7 MPa, about 0.8 MPa, about 0.9 MPa, about 1.0 MPa, about 1.3 MPa, about 1.4 MPa, about 1.5 MPa, about 1.6 MPa, about 1.7 MPa, about 1.8 MPa, about 1.9 MPa, about 2.0 MPa, about 2.1 MPa, about 2.2 MPa, about 2.3 MPa, about 2.4 MPa, about 2.5 MPa, about 2.6 MPa, about 2.7 MPa, about 2.8 MPa, about 2.9 MPa, about 3.0 MPa, about 3.1 MPa, about 3.2 MPa, about 3.3 MPa, about 3.4 MPa, about 3.5 MPa, about 3.6 MPa, about 3.7 MPa, about 3.8 MPa, about 3.9 MPa, about 4.0 MPa, about 4.1 MPa, about 4.2 MPa, about 4.3 MPa, about 4.4 MPa, about 4.5 MPa, about 4.6 MPa, about 4.7 MPa, about 4.8 MPa, about 4.9 MPa, about 5.0 MPa, or any range including and/or in between any two of these values. As discussed above, the inner core exhibits a lower modulus of elasticity than the outer layer. In any embodiment disclosed herein, the inner core may exhibit a modulus of elasticity of about 0.0 MPa, about 0.1 MPa, about 0.2 MPa, about 0.3 MPa, about 0.5 MPa, or any range including and/or in between any two of these values.

[0030] FIGs. 1A-1B and 2A-2B provide non-limiting representative illustrations of embodiments of a wound insert of the present technology, illustrating the outer layer (101 and 201, respectively) and of the inner core (102 and 202, respectively) of such a wound insert. FIG. 1A provides an illustrative side view illustration of a wound insert 100 having a cylindrical shape that includes an outer layer 101 and an inner core 102. FIG. 1B provides an illustrative cross-sectional view of the wound insert 100 having a cylindrical shape. FIG. 2A provides an illustrative side view illustration of a wound insert 200 having a cuboidal shape

with rounded edges that includes an outer layer 201 and an inner core 202. FIG. 2B provides an illustrative cross-sectional view illustration of the wound insert 200 having a cuboidal shape with rounded edges.

The Outer Layer

[0031] In any embodiment disclosed herein, the outer layer may include an inner core facing side and a side facing away from the inner core (*i.e.*, outer facing side). The outer-facing side of the outer layer may be configured to be in contact with a wound when in use. In any embodiment disclosed herein, it may be that the outer layer envelopes the inner core.

[0032] In any embodiment disclosed herein, the wound insert may further include a suture thread connected to and extending from the outer layer and advantageously allowing for the removal of the wound insert if, for example, such removal is desired to assess the healing progress of a wound. The suture thread may be a bioresorbable suture thread. Bioresorbable suture thread materials include, but are not limited to, a poly(glycolic acid), a poliglycaprone (a copolymer of glycolide and a caprolactone, such as a copolymer of glycolide and ε-caprolactone), a polydioxanone, a collagen, or a combination of any two or more thereof. Further exemplary materials are poliglycaprone 25 and polyglactin 910. Suture threads of any embodiment herein may be monofilament or polyfilament suture threads, where polyfilament suture threads may be braided. The length of the suture thread as measured extending from the outer layer (*i.e.*, not including the portion of suture thread connected to the outer layer) may be about 0.1 centimeters (cm) to about 10 cm.

[0033] The thickness of the outer layer of any embodiment herein may be about 20 μM to about 300 μM. Thus, the thickness of the outer layer may be about 20 μM, about 22 μM, about 24 μM, about 26 μM, about 28 μM, about 30 μM, about 32 μM, about 34 μM, about 36 μM, about 38 μM, about 40 μM, about 42 μM, about 44 μM, about 46 μM, about 48 μM, about 50 μM, about 55 μM, about 60 μM, about 65 μM, about 70 μM, about 75 μM, about 80 μM, about 85 μM, about 90 μM, about 95 μM, about 100 μM, about 110 μM, about 120 μM, about 130 μM, about 140 μM, about 150 μM, about 160 μM, about 170 μM, about 180 μM, about 190 μM, about 200 μM, about 220 μM, about 240 μM, about 260 μM, about 280 μM, about 300 μM, or any range including and/or in between any two of these values.

[0034] The crosslinked biopolymer of the outer layer may include a collagen, an oxidized cellulose, an oxidized regenerated cellulose (ORC), a polysaccharide, chitosan, gelatin,

hyaluronic acid, or a combination of any two or more thereof. The outer layer may include about 0.01 wt.% to 100 wt.% of crosslinked biopolymer. Thus, the outer layer may include crosslinked biopolymer in an amount (based on the total weight of the outer layer) of about 0.01 wt.%, about 0.1 wt.%, about 1 wt.%, about 2 wt.%, about 3 wt.%, about 4 wt.%, about 5 wt.%, about 6 wt.%, about 7 wt.%, about 8 wt.%, about 9 wt.%, about 10 wt.%, about 12 wt.%, about 14 wt.%, about 16 wt.%, about 18 wt.%, about 20 wt.%, about 25 wt.%, about 30 wt.%, about 35 wt.%, about 40 wt.%, about 45 wt.%, about 50 wt.%, about 55 wt.%, about 60 wt.%, about 65 wt.%, about 70 wt.%, about 75 wt.%, about 80 wt.%, about 85 wt.%, about 90 wt.%, about 95 wt.%, 100 wt.%, or any range including and/or in between any two of these values. In any embodiment herein, the outer layer may include from about 50 wt.% to about 100 wt.% gelatin. In any embodiment herein, the outer layer may include collagen and ORC. In any embodiment herein, the outer layer may include collagen, ORC, and gelatin.

[0035] Photocrosslinked biopolymers are to be understood as biopolymers that have been crosslinked due to light and that do not include a cross-linking compound (cross-linking compounds are used to produce the reagent-crosslinked biopolymers, as discussed herein). The photocrosslinked biopolymer of the outer layer may be produced from a biopolymer that is photocrosslinked by exposure to light with a wavelength from about 360 nm to about 370 nm. The total radiant power of all wavelengths of light used to crosslink the biopolymer of the outer layer may be from about 10 mW/cm^2 to about 1000 mW/cm^2. Thus, the total radiant power of all wavelengths of light used to crosslink the biopolymer of the outer layer may be from about 10 mW/cm^2, about 15 mW/cm^2, about 20 mW/cm^2, about 25 mW/cm^2, about 30 mW/cm^2, about 35 mW/cm^2, about 40 mW/cm^2, about 45 mW/cm^2, about 50 mW/cm^2, about 55 mW/cm^2, about 60 mW/cm^2, about 65 mW/cm^2, about 70 mW/cm^2, about 75 mW/cm^2, about 80 mW/cm^2, about 85 mW/cm^2, about 90 mW/cm^2, about 95 mW/cm^2, about 100 mW/cm^2, about 110 mW/cm^2, about 120 mW/cm^2, about 130 mW/cm^2, about 140 mW/cm^2, about 150 mW/cm^2, about 160 mW/cm^2, about 170 mW/cm^2, about 180 mW/cm^2, about 190 mW/cm^2, about 200 mW/cm^2, about 210 mW/cm^2, about 220 mW/cm^2, about 230 mW/cm^2, about 240 mW/cm^2, about 250 mW/cm^2, about 260 mW/cm^2, about 270 mW/cm^2, about 280 mW/cm^2, about 290 mW/cm^2, about 300 mW/cm^2, about 310 mW/cm^2, about 320 mW/cm^2, about 330 mW/cm^2, about 340 mW/cm^2, about 350 mW/cm^2, about 360 mW/cm^2, about 370 mW/cm^2, about 380 mW/cm^2, about 390 mW/cm^2, about 400 mW/cm^2, about 410 mW/cm^2, about 420 mW/cm^2, about 430 mW/cm^2, about 440 mW/cm^2, about 450 mW/cm^2, about 460 mW/cm^2, about 470 mW/cm^2, about 480 mW/cm^2, about 490 mW/cm^2, about 500

mW/cm^2, about 550 mW/cm^2, about 600 mW/cm^2, about 650 mW/cm^2, about 750 mW/cm^2, about 800 mW/cm^2, about 850 mW/cm^2, about 900 mW/cm^2, about 950 mW/cm^2, about 1000 mW/cm^2, or any range including and/or in between any two of these values. The biopolymer of the outer layer may be photo-crosslinked with light for a period of about 1 minute to about 100 minutes.

[0036] Reagent-crosslinked biopolymer are biopolymers that are crosslinked via cross-linking compounds where part of the cross-linking compound is incorporated to generate the reagent-crosslinked biopolymer. Exemplary reagent-crosslinked biopolymers are biopolymers crosslinked by one or more of disuccinimidyl suberate (DSS), disuccinimidyl tartrate (DST), dithiobis succinimidyl propionate (DSP), bismaleimidoethane (BMOE), dithiobismaleimidoethane (DTME), *m*-maleimidobenzoyl-*N*-hydroxysuccinimide ester (MBS), *N*-γ-maleimidobutyryl-oxysuccinimide ester (GMBS), *N*-ε-maleimidocaproyloxy-succinimide ester (EMCS), and *N*-ε-maleimidocaproyl-oxysulfosuccinimide ester (sulfo-EMCS). Other exemplary reagent-crosslinked biopolymers are biopolymers crosslinked in the presence of light (*e.g.*, 250-350 nm light) with *N*-((2-pyridyldithio)ethyl)-4-azidosalicylamide and/or *N*-5-azido-2-nitrobenzyloxysuccinimide – thus, light may be used to initiate the crosslinking reaction of the cross-linking compound with a biopolymer.

[0037] In any embodiment disclosed herein, the outer layer may include at least one plasticizer. The at least one plasticizer may be included in the amount of about 2 wt.% to about 30 wt.% within the outer layer. Thus, the at least one plasticizer may be included in the amount of about 2 wt.%, about 3 wt.%, about 4 wt.%, about 5 wt.%, about 6 wt.%, about 7 wt.%, about 8 wt.%, about 9 wt.%, about 10 wt.%, about 11 wt.%, about 12 wt.%, about 13 wt.%, about 14 wt.%, about 15 wt.%, about 16 wt.%, about 17 wt.%, about 18 wt.%, about 19 wt.%, about 20 wt.%, about 21 wt.%, about 22 wt.%, about 23 wt.%, about 24 wt.%, about 25 wt.%, about 26 wt.%, about 27 wt.%, about 28 wt.%, about 29 wt.%, about 30 wt.%, or any range including and/or in between any two of these values. Exemplary plasticizers include, but are not limited to, an acetylated monoglyceride, an alkyl citrate, methyl ricinoleate, glycerol, or a combination of any two or more thereof. Examples of alkyl citrates include, but are not limited to, triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate, trioctyl citrate, acetyl trioctyl citrate, trihexyl citrate, acetyl trihexyl citrate, butyryl trihexyl citrate, trimethyl citrate, or a combination of any two or more thereof.

[0038] In any embodiment disclosed herein, the outer layer may include one or more additional materials. Suitable additional materials may include, but are not limited to, biocompatible dyes, non—steroidal anti-inflammatory drug (*e.g.*, acetaminophen), hyaluronic acid, a steroid, an antibiotic (*e.g.*, penicillins and/or streptomycins), glycoproteins (*e.g.*, lipids), growth factors (*e.g.*, fibroblast growth factor (FGF), an epidermal growth factor (RGF), a platelet derived growth factor (PGDF)), or a combination of any two or more thereof. In any embodiment herein, the biocompatible dye may include, but is not limited to, E124, fluorescein isothiocyanate (FITC), 4',6-diamidino-2-phenylindole (DAPI), methylene blue, erythrosine B, ponceau S, alura red, SYBR green, alcian blue, brilliant blue G, calcein blue, cardio green, crystal violet, nile blue, india ink, brilliant blue, indigo carmine, sudan III, methyl green, oil red, pyronin Y, tattoo ink, purpurin, phloxine B, picric acid, carbon nanotubes, a fuchsin, resazurin, a trichrome, or a combination of any two or more thereof.

The Inner Core

[0039] In any embodiment disclosed herein, the inner core may include a wound-facing side.

[0040] The biopolymer of the inner core may be a collagen, an oxidized cellulose, and oxidized regenerated cellulose (ORC), a polysaccharide, chitosan, gelatin, hyaluronic acid, or a combination of any two or more thereof. The inner core may include about 10 wt.% to about 100 wt.% of the biopolymer; thus, the inner core may include the biopolymer at an amount (based on the weight of the inner core) of about 10 wt.%, about 15 wt.%, about 20 wt.%, about 25 wt.%, about 30 wt.%, about 35 wt.%, about 40 wt.%, about 45 wt.%, about 50 wt.%, about 55 wt.%, about 60 wt.%, about 65 wt.%, about 70 wt.%, about 75 wt.%, about 80 wt.%, about 85 wt.%, about 90 wt.%, about 95 wt.%, about 99 wt.%, about 100 wt.%, or any range including and/or in between any two of these values. In any embodiment herein, the inner core may include less than about 0.01 wt.% of crosslinked biopolymer.

[0041] In any embodiment disclosed herein, the inner core may include one or more additional materials. Suitable additional materials may include, but are not limited to, biocompatible dyes, non—steroidal anti-inflammatory drug (*e.g.*, acetaminophen), hyaluronic acid, a steroid, an antibiotic (*e.g.*, penicillins and/or streptomycins), glycoproteins (*e.g.*, lipids), growth factors (*e.g.*, fibroblast growth factor (FGF), an epidermal growth factor (RGF), a platelet derived growth factor (PGDF)), or a combination of any two or more

thereof. In any embodiment herein, the biocompatible dye may include, but is not limited to, E124, fluorescein isothiocyanate (FITC), 4',6-diamidino-2-phenylindole (DAPI), methylene blue, erythrosine B, ponceau S, alura red, SYBR green, alcian blue, brilliant blue G, calcein blue, cardio green, crystal violet, nile blue, india ink, brilliant blue, indigo carmine, sudan III, methyl green, oil red, pyronin Y, tattoo ink, purpurin, phloxine B, picric acid, carbon nanotubes, a fuchsin, resazurin, a trichrome, or a combination of any two or more thereof.

[0042] In any embodiment herein, the inner core may further include powders, porous matrices, or combinations thereof. Such powders in any embodiment herein, for example, may include freeze-dried collagen/ORC in powder form. Such porous matrix materials may include a freeze-dried collagen/ORC matrix.

Features of the Outer Layer and/or Inner Core

[0043] In any embodiment disclosed herein, the collagen of the outer layer and/or the inner core may include a mammalian collagen, such as a bovine collagen, a human collagen, or a combination thereof. The collagen of any embodiment herein may be a Type I collagen, a Type II collagen, a Type III collagen, may be obtained from any natural source, may be chemically-modified collagen (*e.g.*, an atelocollagen obtained by removing the immunogenic telopeptides from natural collagen), or may be a combination of any two or more thereof. For example, the collagen may include collagen obtained from bovine corium that has been rendered largely free of non-collagenous components, for example, including fat, non-collagenous proteins, polysaccharides, and other carbohydrates, such as by procedures described in U.S. Pat. Nos. 4,614,794 and 4,320,201, each of which is incorporated herein by reference. The bovine collagen may include one or both of bovine collagen type I and bovine collagen type III. In any embodiment disclosed herein, the outer layer and/or inner core may include a weight ratio of human collagen type I to human collagen type III of about 100:0, about 90:10, about 80:20, about 70:30, about 60:40, about 50:50, about 40:60, about 30:70, about 20:80, about 10:90, about 0:100, or any range including and/or in between any two of these values. The ratio by weight of human collagen type I to human collagen type III may be greater than about 50:50, or greater than about 70:30. The collagen of any embodiment herein may include a weight ratio of type I bovine collagen to type III bovine collagen of about 95:5, about 85:15, about 75:25, about 65:35, about 55:45, about 50:50, about 45:55, about 65:35, about 75:25, about 85:15, about 95:5, or any range including and/or in between

any two of these values. The ratio by weight of the type I bovine collagen to type III bovine collagen may be about 85:15.

[0044] The amount of collagen included in the outer layer and/or the inner core of any embodiment herein may be about 30 wt.% to 100 wt.%. Thus, the amount of collagen may be about 30 wt.%, about 32 wt.%, about 34 wt.%, about 36 wt.%, about 38 wt.%, about 40 wt.%, about 42 wt.%, about 44 wt.%, about 46 wt.%, about 48 wt.%, about 50 wt.%, about 52 wt.%, about 54 wt.%, about 56 wt.%, about 58 wt.%, about 60 wt.%, about 62 wt.%, about 64 wt.%, about 66 wt.%, about 68 wt.%, about 70 wt.%, about 72 wt.%, about 74 wt.%, about 76 wt.%, about 78 wt.%, about 80 wt.%, about 82 wt.%, about 84 wt.%, about 86 wt.%, about 88 wt.%, about 90 wt.%, about 92 wt.%, about 94 wt.%, about 95 wt.%, about 96 wt.%, about 97 wt.%, about 98 wt.%, about 99 wt.%, or any range including and/or in between any two of these values.

[0045] The collagen included in the outer layer and/or the inner core of any embodiment herein may have a weight-average molecular weight of about 5,000, about 6,000, about 7,000, about 8,000, about 9,000, about 10,000, about 12,000, about 14,000, about 16,000, about 18,000, about 20,000, about 22,000, about 24,000, about 26,000, about 28,000, about 30,000, about 32,000, about 34,000, about 36,000, about 38,000, about 40,000, about 45,000, about 50,000, about 55,000, about 60,000, about 65,000, about 70,000, about 75,000, about 80,000, about 85,000, about 90,000, about 95,000, about 100,000, or any range including and/or in between any two of these values.

[0046] As discussed above, the outer layer and/or the inner core may include ORC. ORC may be produced by the oxidation of cellulose, for example with dinitrogen tetroxide and/or as described in U.S. Pat. No. 3,122,479 (incorporated herein by reference). Not intending to be bound by theory, it is believed that this process may convert primary alcohol groups on the saccharide residues of the cellulose to carboxylic acid groups, for example, forming uronic acid residues within the cellulose chain. The oxidation may not proceed with complete selectivity, and as a result hydroxyl groups on carbons 2 and 3 of the saccharide residue may be converted to the keto form. These ketone units may introduce an alkali labile link, which at pH 7 or higher initiates the decomposition of the polymer *via* formation of a lactone and sugar ring cleavage. As a result, oxidized regenerated cellulose is biodegradable and bioresorbable under physiological conditions. ORC is available with a variety of degrees of oxidation and hence rates of degradation. The ORC may include particles, fibers, or both; in

any embodiment disclosed herein, the ORC may be in the form of particles, such as fiber particles or powder particles. In embodiments that include ORC fibers, the ORC fibers may have a volume fraction such that at least 80% of the fibers have lengths in the range from about 5 μm to about 1000 μm, or from about 250 μm to about 450 μm.

[0047] The outer layer and/or the inner core of any embodiment herein may include about 30 wt.% to about 70 wt.% ORC (for the outer layer, this may be crosslinked ORC) with a weight-average molecular weight of about 50,000 to about 1,000,000. Thus, the ORC of any embodiment disclosed herein may be included in an amount of about 30 wt.%, about 32 wt.%, about 34 wt.%, about 36 wt.%, about 38 wt.%, about 40 wt.%, about 42 wt.%, about 44 wt.%, about 46 wt.%, about 48 wt.%, about 50 wt.%, about 52 wt.%, about 54 wt.%, about 56 wt.%, about 58 wt.%, about 60 wt.%, about 62 wt.%, about 64 wt.%, about 66 wt.%, about 68 wt.%, about 70 wt.%, or any range including and/or in between any two of these values. The ORC may have a weight-average molecular weight of about 50,000, about 100,000, about 150,000, about 200,000, about 250,000, about 300,000, about 350,000, about 400,000, about 450,000, about 500,000, about 550,000, about 600,000, about 650,000, about 700,000, about 750,000, about 800,000, about 850,000, about 900,000, about 950,000, about 1,000,000, or any range including and/or in between any two of these values.

[0048] In any embodiment herein including one or more of collagen and chitosan along with ORC in the outer layer and/or the inner core, a weight ratio of the one or more of collagen and chitosan to ORC may be about 60:40 to about 40:60 in the outer layer and/or the inner core. The weight ratio of the one or more of collagen and chitosan to ORC may be about 60:40, about 59:41, about 58:42, about 57:43, about 56:44, about 55:45, about 54:46, about 53:47, about 52:48, about 51:49, about 50:50, about 49:51, about 48:52, about 47:53, about 46:54, about 45:55, about 44:56, about 43:57, about 42:58, about 41:59, about 40:60, or any range including and/or in between any two of these values.

[0049] In any embodiment disclosed herein, the outer layer and/or the inner core may include about 0.001 wt.% to about 5 wt.% of an antimicrobial agent. Thus, the total amount of antimicrobial agent(s) in the outer layer and/or the inner core may independently for each be about 0.001 wt.%, about 0.002 wt.%, about 0.003 wt.%, about 0.004 wt.%, about 0.005 wt.%, about 0.006 wt.%, about 0.007 wt.%, about 0.008 wt.%, about 0.009 wt.%, about 0.01 wt.%, about 0.02 wt.%, about 0.03 wt.%, about 0.04 wt.%, about 0.05 wt.%, about 0.06 wt.%, about 0.07 wt.%, about 0.08 wt.%, about 0.09 wt.%, about 0.1 wt.%, about 0.2 wt.%, about 0.3 wt.%, about 0.4 wt.%, about 0.5 wt.%, about 0.6 wt.%, about 0.7 wt.%, about 0.8 wt.%,

about 0.9 wt.%, about 1 wt.%, about 2 wt.%, about 3 wt.%, about 4 wt.%, about 5 wt.%, or any range including and/or in between any two of these values. The antimicrobial agent may include a penicillin, a streptomycin, ionic silver (or a source for ionic silver), chlorhexidine, a poly(hexamethylene biguanide) (PHMB), iodine, or a combination of any two or more thereof. Suitable sources of ionic silver may include ionic silver in a variety of forms including as pharmaceutically acceptable salts, where representative examples include but are not limited to silver oxide, silver chromate, silver allantoinate, silver borate, silver glycerolate, silver nitrate, silver acetate, silver chloride, silver sulfate, silver lactate, silver bromide, silver iodide, silver carbonate, silver citrate, silver laurate, silver deoxycholate, silver salicylate, silver *p*-aminobenzoate, silver *p*-aminosalicylate, or a combination of any two or more thereof. In addition, while ionic silver (or a source thereof) may initially be incorporated into the outer layer and/or inner core as a silver salt, at least a portion (if not substantially all) of the ionic silver may be complexed to, *e.g.*, ORC, in the outer layer and/or the inner core.

[0050] The outer layer and inner core may contain varying concentration of any of the above referenced materials (*e.g.*, biopolymers, plasticizers, antimicrobial agents, and/or additional materials as described herein in any embodiment). For example, in any embodiment, the outer layer may include about 50 wt.% to about 100 wt.% gelatin and the inner core may include intact collagen, such that the inner core has a higher concentration of collagen than the outer layer. In any embodiment herein, both the outer layer and inner core may include one or more antimicrobial agents as described herein, where the outer layer may include a higher concentration of antimicrobial agents than the inner core. In any embodiment herein, both the outer layer and inner core may include one or more antimicrobial agents as described herein, where the outer layer may include a lower concentration of antimicrobial agents than the inner core.

The Wound Insert

[0051] As provided previously, the present disclosure provides a wound insert that includes an outer layer and an inner core. The outer layer may include a outward-facing side and an inner-core facing side. In any embodiment disclosed herein, an exterior surface of the inner core may be adjoined with the inner core-facing side of the outer layer.

[0052] In any embodiment disclosed herein, the wound insert of the present technology may be in the shape of a cylinder, a sphere, a cube, a cuboid, a hexagonal prism, a cone, a square-based pyramid, triangular-based pyramid, or a triangular prism. For example, the wound insert of the present technology may be in the shape of a cylinder, a cylinder with at least one rounded edge, cuboid, or a cuboid with at least one rounded edge. In any embodiment herein, the wound insert may be in the shape of a cylinder, wherein the cylindrical wound insert further comprises a hemispherical compartment on each end of the wound insert (*see* FIGs. 1A-1B). In any embodiment herein, the wound insert may be in the shape of a cuboid with one or more rounded edges, wherein the cuboid wound insert further comprises a cubed compartment on each end of the wound insert (*see* FIGs. 2A-2B).

[0053] In any embodiment disclosed herein, the length of the wound insert of the present technology compared to the width may be from about 15:1 to about 15:6. For example, in any embodiment herein, the length to width ratio may be about 15:1, about 15:2, about 15:3, about 15:4, about 15:5, about 15:6, or any range including and/or in between any two of the preceding values. In any embodiment disclosed herein, the width to height ratio of the wound insert according to the present technology may be about 3:2 to 2:3. For example, in any embodiment herein, the width to height ratio may be about 3:2, about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, about 2:3, or any range including and/or in between any two of the preceding values.

[0054] In any embodiment disclosed herein, the length of the wound insert of the present technology may be about 1 cm to about 10 cm. Thus, the length of the wound insert may be about 1 cm, about 1.1 cm, about 1.2 cm, about 1.3 cm, about 1.4 cm, about 1.5 cm, about 1.6 cm, about 1.7 cm, about 1.8 cm, about 1.9 cm, about 2.0 cm, about 2.2 cm, about 2.4 cm, about 2.6 cm, about 2.8 cm, about 3.0 cm, about 3.2 cm, about 3.4 cm, about 3.6 cm, about 3.8 cm, about 4.0 cm, about 4.2 cm, about 4.4 cm, about 4.6 cm, about 4.8 cm, about 5.0 cm, about 5.5 cm, about 6.0 cm, about 6.5 cm, about 7.0 cm, about 7.5 cm, about 8.0 cm, about 8.5 cm, about 9.0 cm, about 9.5 cm, about 10.0 cm, or any range including and/or in between any two of these values.

[0055] In any embodiment disclosed herein, the width and/or height of the wound insert of the present technology may be about 0.1 cm to about 3 cm. Thus, the width and/or height of the wound insert may be about 0.1 cm, about 0.2 cm, about 0.3 cm, about 0.4 cm, about 0.5 cm, about 0.6 cm, about 0.7 cm, about 0.8 cm, about 0.9 cm, about 1.0 cm, about 1.1 cm,

about 1.2 cm, about 1.3 cm, about 1.4 cm, about 1.5 cm, about 1.6 cm, about 1.7 cm, about 1.8 cm, about 1.9 cm, about 2.0 cm, about 2.1 cm, about 2.2 cm, about 2.3 cm, about 2.4 cm, about 2.5 cm, about 2.6 cm, about 2.7 cm, about 2.8 cm, about 2.9 cm, about 3.0 cm, or any range including and/or in between any two of these values.

[0056] In any embodiment disclosed herein, the wound insert of the present technology may comprise perforations to facilitate tissue integration. The perforations of the wound insert may be about 0.1 μM to about 100 μM in width and/or height. The perforations of the wound insert may be about 0.1 μM to about 100 μM deep. The perforations of the wound insert may be through the entire thickness of the outer layer. FIG. 3 provides an illustrative side view illustration of a wound insert 300 that includes an outer layer 301, an inner core 302, and a plurality of perforations 303.

[0057] In any embodiment disclosed herein, the wound insert of the present technology may comprise through-holes through the entire width, height, and/or length of the wound insert, such as for beneficial use of the wound insert in negative pressure therapy. The through-holes of the wound insert may be about 2 mm to about 8 mm in width and/or height. Thus, the through-holes of the wound insert may be about 2 mm, about 2.2 mm, about 2.4 mm, about 2.6 mm, about 2.8 mm, about 3 mm, about 3.2 mm, about 3.4 mm, about 3.6 mm, about 3.8 mm, about 4 mm, about 4.2 mm, about 4.4 mm, about 4.6 mm, about 4.8 mm, about 5 mm, about 5.5 mm, about 6 mm, about 6.5 mm, about 7 mm, about 7.5 mm, about 8 mm, or any range including and/or in between any two of these values. FIG. 4 provides an illustrative side view illustration of a wound insert 400 that includes an outer layer 401, inner core 402, and a plurality of through-holes 403.

[0058] In any embodiment disclosed herein, the wound insert of the present disclosure may be sterile and packaged in a microorganism-impermeable container.

Negative-Pressure Therapy

[0059] The wound insert of any embodiment described herein may be employed in therapy in which a wound is treated with reduced pressure. Treatment of a wound with reduced pressure may be commonly referred to as "negative-pressure therapy," but is also known by other names, including "negative-pressure wound therapy," "reduced-pressure therapy," "vacuum therapy," "vacuum-assisted closure," and "topical negative-pressure," for example. Negative-pressure therapy may provide a number of benefits, including migration of

epithelial and subcutaneous tissues, improved blood flow, and/or micro-deformation of tissue at a wound site. Together, these benefits may increase development of granulation tissue and reduce healing times.

[0060] Generally, the system may be configured to provide negative-pressure to a wound in accordance with this specification. In any embodiment herein, the system may generally include a negative-pressure supply, and may include or be configured to be coupled to a distribution component. In general, a distribution component may refer to any complementary or ancillary component configured to be fluidly coupled to a negative-pressure supply in a fluid path between a negative-pressure supply and a wound.

[0061] In any embodiment herein, the wound insert may be configured to distribute negative pressure. Additionally or alternatively, the fluid path(s) may be reversed or a secondary fluid path may be provided to facilitate movement of fluid across a wound. Additionally or alternatively, the fluid pathways of the through-holes may be interconnected to improve distribution or collection of fluids.

[0062] The fluid mechanics associated with using a negative-pressure source to reduce pressure in another component or location, such as within a sealed therapeutic environment, can be mathematically complex. However, the basic principles of fluid mechanics applicable to negative-pressure therapy are generally well-known to those skilled in the art. The process of reducing pressure may be described generally and illustratively herein as "delivering," "distributing," or "generating" negative pressure, for example.

[0063] In general, a fluid, such as wound fluid (for example, wound exudates and other fluids), flows toward lower pressure along a fluid path. Thus, the term "downstream" typically implies something in a fluid path relatively closer to a source of negative pressure or further away from a source of positive pressure. Conversely, the term "upstream" implies something relatively further away from a source of negative pressure or closer to a source of positive pressure. This orientation is generally presumed for purposes of describing various features and components herein. However, the fluid path may also be reversed in some applications (such as by substituting a positive-pressure source for a negative-pressure source) and this descriptive convention should not be construed as a limiting convention.

[0064] "Negative pressure" may generally refer to a pressure less than a local ambient pressure, such as the ambient pressure in a local environment external to a sealed therapeutic

environment provided by the wound insert. In many cases, the local ambient pressure may also be the atmospheric pressure proximate to or about a wound. Alternatively or additionally, the pressure may be less than a hydrostatic pressure associated with the tissue at the wound. While the amount and nature of negative pressure applied to a wound may vary according to therapeutic requirements, the pressure is generally a low vacuum, also commonly referred to as a rough vacuum, between -5 mm Hg (-667 Pa) and -500 mm Hg (-66.7 kPa), gauge pressure. Common therapeutic ranges are between -50 mm Hg (-6.7 kPa) and -300 mm Hg (-39.9 kPa), gauge pressure.

[0065] Additionally or alternatively, in any embodiment herein, a negative-pressure supply may be a reservoir of air at a negative pressure, or may be a manual or electrically-powered device that can reduce the pressure in a sealed volume, such as a vacuum pump, a suction pump, a wall suction port available at many healthcare facilities, or a micro-pump, for example. A negative-pressure supply may be housed within or used in conjunction with other components, such as sensors, processing units, alarm indicators, memory, databases, software, display devices, or user interfaces that further facilitate therapy. A negative-pressure source may be combined with a controller and other components into a therapy unit. A negative-pressure supply may also have one or more supply ports configured to facilitate coupling and de-coupling of the negative-pressure supply to one or more distribution components.

[0066] In any embodiment herein, components may be fluidly coupled to each other to provide a path for transferring fluids (*i.e.*, liquid and/or gas) between the components. For example, components may be fluidly coupled through a fluid conductor, such as a tube. As used herein, the term "fluid conductor" may include a tube, pipe, hose, conduit, or other structure with one or more lumina or open passages adapted to convey a fluid between two ends thereof. Typically, a fluid conductor may be an elongated, cylindrical structure with some flexibility, but the geometry and rigidity may vary. Additionally or alternatively, in any embodiment herein, the negative-pressure source may be operatively coupled to the wound insert *via* an interface.

Treatment Methods of the Present Technology

[0067] In an aspect, methods for treating a wound in a subject in need thereof are provided, wherein the method includes administering a wound insert of any embodiment disclosed

herein to the wound. The wound may be a tunneling wound, a dermal wound, a diabetic wound, an acute wound, a chronic wound, or a combination of any two or more thereof. Exemplary chronic wounds include, but are not limited to, infectious wounds, venous ulcers, decubitus ulcers, or diabetic ulcers. In any embodiment herein, the wound is a tunneling wound. The method may include administering two or more wound inserts to the wound.

[0068] The wound insert may be administered directly to the wound. Any method known to those in the art for administering a wound insert to a tunneling wound, a dermal wound, a diabetic wound, an acute wound, or a chronic wound disclosed herein may be employed. Suitable methods include *in vitro* or *in vivo* methods. *In vivo* methods typically include the administration of one or more wound inserts to a subject in need thereof, suitably a human. When used *in vivo* for therapy, the one or more wound inserts described herein are administered to the subject in effective amounts (*i.e.*, amounts that have desired therapeutic effect). The dose and dosage regimen will depend upon the state of the wound of the subject and the characteristics of the particular wound insert used.

[0069] The effective amount may be determined during pre-clinical trials and clinical trials by methods familiar to physicians and clinicians. An effective amount of one or more wound inserts useful in the methods may be administered to a subject in need thereof by any number of well-known methods for administering wound inserts.

[0070] In any embodiment disclosed herein, the wound inserts may be administered daily for 1 hour or more, for 2 hours or more, for 3 hours or more, for 4 hours or more, for 5 hours or more, for 6 hours or more, or for 12 hours or more. In any embodiment disclosed herein, the wound inserts may be administered one, two, three, four, or five times per day. In any embodiment disclosed herein, the wound inserts may be administered daily for one, two, three, four, or five weeks. In any embodiment disclosed herein, the wound inserts may be administered daily for less than 6 weeks. In any embodiment disclosed herein, the wound inserts may be administered daily for 6 weeks or more. In any embodiment disclosed herein, the wound inserts may be administered daily for 12 weeks or more. In any embodiment disclosed herein, the wound inserts may be administered every day, every other day, every third day, every fourth day, every fifth day, or every sixth day. In any embodiment disclosed herein, the wound inserts may be administered weekly, bi-weekly, tri-weekly, or monthly. In any embodiment disclosed herein, the wound inserts may be administered for a chronic wound as appropriate.

[0071] In any embodiment herein, the method may include employing the wound insert in the context of a negative-pressure therapy, where the negative-pressure therapy may include positioning the wound insert in and/or proximate to the wound. The negative-pressure therapy may further include sealing the wound insert to tissue surrounding the wound to form a sealed space. For example, the wound insert may be positioned in and/or proximate to the wound and sealed to an attachment surface near the wound, for example, to undamaged epidermis peripheral to a wound.

[0072] The negative-pressure therapy method in any embodiment herein may further include fluidly coupling a negative-pressure source to the sealed space and operating the negative-pressure source to generate a negative pressure in the sealed space. For example, the negative-pressure source may be coupled to the wound insert such that the negative-pressure source may be used to reduce the pressure in the sealed space. For example, negative pressure applied across the wound, for example, via the wound insert may be effective to induce macrostrain and microstrain at the wound site, as well as remove exudates and other fluids from the wound.

Methods of Manufacturing a Wound Insert of the Present Technology

[0073] In a further related aspect, a method of manufacturing a wound insert of any embodiment of the present technology is provided, where the method includes: fabricating an outer layer of the wound insert from a first slurry comprising one or more biopolymers, wherein the outer layer is in a shape having a hollow center; photo-crosslinking and/or reagent-crosslinking the outer layer to obtain one or more photocrosslinked and/or reagent-crosslinked biopolymers; drying the outer layer of the wound insert; depositing a second slurry into the hollow center of the outer layer to form an inner core of the wound insert; and removing residual moisture from the inner core, where the shape of the outer layer may be a cylinder, a sphere, a cube, a cuboid, a hexagonal prism, a cone, a square-based pyramid, triangular-based pyramid, or a triangular prism; the second slurry includes a biopolymer; the outer layer exhibits a modulus of elasticity from about 0.5 MPa to about 5.0 MPa; and the inner core exhibits a lower modulus of elasticity than the outer layer.

[0074] In any embodiment herein, the fabricating may include extrusion of the first slurry to fabricate the outer layer. For example, in any embodiment herein, the first slurry may be extruded via a die having a hollow center to obtain a shape (*e.g.*, a tube structure). As

disclosed herein, the outer layer shape (*i.e.*, tube structure) may be a cylinder, a sphere, a cube, a cuboid, a hexagonal prism, a cone, a square-based pyramid, triangular-based pyramid, or a triangular prism.

[0075] In any embodiment herein, the first slurry may have a pH from about 3 to 7. For example, in any embodiment herein, the first slurry may have a pH of about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, or any range including and/or in between any two or more of the preceding values. In any embodiment herein, the pH of the first slurry may be from about 4.5 to about 5.5.

[0076] In any embodiment disclosed herein, the first slurry may further include at least one plasticizer as described herein in any embodiment. The at least one plasticizer may be included in the amount of about 2 wt.% to about 30 wt.% within the first slurry. Thus, the at least one plasticizer may be included in the amount of about 2 wt.%, about 3 wt.%, about 4 wt.%, about 5 wt.%, about 6 wt.%, about 7 wt.%, about 8 wt.%, about 9 wt.%, about 10 wt.%, about 11 wt.%, about 12 wt.%, about 13 wt.%, about 14 wt.%, about 15 wt.%, about 16 wt.%, about 17 wt.%, about 18 wt.%, about 19 wt.%, about 20 wt.%, about 21 wt.%, about 22 wt.%, about 23 wt.%, about 24 wt.%, about 25 wt.%, about 26 wt.%, about 27 wt.%, about 28 wt.%, about 29 wt.%, about 30 wt.%, or any range including and/or in between any two of these values.

[0077] In any embodiment herein, the first slurry and/or second slurry correspond to the resultant outer layer and/or inner core, respectively. In any embodiment herein, the first slurry and/or second slurry may include one or more biopolymers including, but not limited to, a collagen, an oxidized cellulose, an oxidized regenerated cellulose (ORC), a polysaccharide, a chitosan, a gelatin, hyaluronic acid, or a combination of any two or more thereof. In any embodiment disclosed herein, the collagen of the first slurry and/or the second slurry may include a mammalian collagen, such as a bovine collagen, a human collagen, or a combination thereof as described herein in any embodiment.

[0078] The amount of collagen included in the first slurry and/or the second slurry of any embodiment herein may be about 30 wt.% to 100 wt.% as described herein in any embodiment. Thus, the amount of collagen may be about 30 wt.%, about 32 wt.%, about 34 wt.%, about 36 wt.%, about 38 wt.%, about 40 wt.%, about 42 wt.%, about 44 wt.%, about 46 wt.%, about 48 wt.%, about 50 wt.%, about 52 wt.%, about 54 wt.%, about 56 wt.%, about 58 wt.%, about 60 wt.%, about 62 wt.%, about 64 wt.%, about 66 wt.%, about 68 wt.%, about 70

wt.%, about 72 wt.%, about 74 wt.%, about 76 wt.%, about 78 wt.%, about 80 wt.%, about 82 wt.%, about 84 wt.%, about 86 wt.%, about 88 wt.%, about 90 wt.%, about 92 wt.%, about 94 wt.%, about 95 wt.%, about 96 wt.%, about 97 wt.%, about 98 wt.%, about 99 wt.%, or any range including and/or in between any two of these values.

[0079] The collagen included in the first slurry and/or second slurry of any embodiment herein may have a weight-average molecular weight of about 5,000, about 6,000, about 7,000, about 8,000, about 9,000, about 10,000, about 12,000, about 14,000, about 16,000, about 18,000, about 20,000, about 22,000, about 24,000, about 26,000, about 28,000, about 30,000, about 32,000, about 34,000, about 36,000, about 38,000, about 40,000, about 45,000, about 50,000, about 55,000, about 60,000, about 65,000, about 70,000, about 75,000, about 80,000, about 85,000, about 90,000, about 95,000, about 100,000, or any range including and/or in between any two of these values.

[0080] As discussed above, the first slurry and/or second slurry may include ORC as described herein in any embodiment. The first slurry and/or the second slurry of any embodiment herein may include about 30 wt.% to about 70 wt.% ORC (for the outer layer, this may be crosslinked ORC) with a weight-average molecular weight of about 50,000 to about 1,000,000. Thus, the ORC of any embodiment disclosed herein may be included in an amount of about 30 wt.%, about 32 wt.%, about 34 wt.%, about 36 wt.%, about 38 wt.%, about 40 wt.%, about 42 wt.%, about 44 wt.%, about 46 wt.%, about 48 wt.%, about 50 wt.%, about 52 wt.%, about 54 wt.%, about 56 wt.%, about 58 wt.%, about 60 wt.%, about 62 wt.%, about 64 wt.%, about 66 wt.%, about 68 wt.%, about 70 wt.%, or any range including and/or in between any two of these values. The ORC may have a weight-average molecular weight of about 50,000, about 100,000, about 150,000, about 200,000, about 250,000, about 300,000, about 350,000, about 400,000, about 450,000, about 500,000, about 550,000, about 600,000, about 650,000, about 700,000, about 750,000, about 800,000, about 850,000, about 900,000, about 950,000, about 1,000,000, or any range including and/or in between any two of these values.

[0081] In any embodiment herein including one or more of collagen and chitosan along with ORC in the first slurry and/or second slurry, a weight ratio of the one or more of collagen and chitosan to ORC may be about 60:40 to about 40:60 in the first slurry and/or the second slurry. The weight ratio of the one or more of collagen and chitosan to ORC may be about 60:40, about 59:41, about 58:42, about 57:43, about 56:44, about 55:45, about 54:46,

about 53:47, about 52:48, about 51:49, about 50:50, about 49:51, about 48:52, about 47:53, about 46:54, about 45:55, about 44:56, about 43:57, about 42:58, about 41:59, about 40:60, or any range including and/or in between any two of these values.

[0082] In any embodiment disclosed herein, the first slurry and/or second slurry may include about 0.001 wt.% to about 5 wt.% of an antimicrobial agent as described herein in any embodiment. Thus, the total amount of antimicrobial agent(s) in the outer layer and/or the inner core may independently for each be about 0.001 wt.%, about 0.002 wt.%, about 0.003 wt.%, about 0.004 wt.%, about 0.005 wt.%, about 0.006 wt.%, about 0.007 wt.%, about 0.008 wt.%, about 0.009 wt.%, about 0.01 wt.%, about 0.02 wt.%, about 0.03 wt.%, about 0.04 wt.%, about 0.05 wt.%, about 0.06 wt.%, about 0.07 wt.%, about 0.08 wt.%, about 0.09 wt.%, about 0.1 wt.%, about 0.2 wt.%, about 0.3 wt.%, about 0.4 wt.%, about 0.5 wt.%, about 0.6 wt.%, about 0.7 wt.%, about 0.8 wt.%, about 0.9 wt.%, about 1 wt.%, about 2 wt.%, about 3 wt.%, about 4 wt.%, about 5 wt.%, or any range including and/or in between any two of these values.

[0083] Following fabrication of the outer layer, the method may further include treating the outer layer with a weak basic gas. For example, in any embodiment herein, the weak gas may be ammonia.

[0084] As disclosed above, the method includes photocrosslinking and/or reagent-crosslinking the outer layer to obtain one or more crosslinked biopolymers. Photo-crosslinking may be carried out by exposing the outer layer to light with a wavelength from about 360 nm to about 370 nm. The total radiant power of all wavelengths of light used to crosslink the one or more biopolymers of the outer layer may be from about 10 mW/cm^2 to about 1000 mW/cm^2. Thus, the total radiant power of all wavelengths of light used to crosslink the biopolymer of the outer layer may be from about 10 mW/cm^2, about 15 mW/cm^2, about 20 mW/cm^2, about 25 mW/cm^2, about 30 mW/cm^2, about 35 mW/cm^2, about 40 mW/cm^2, about 45 mW/cm^2, about 50 mW/cm^2, about 55 mW/cm^2, about 60 mW/cm^2, about 65 mW/cm^2, about 70 mW/cm^2, about 75 mW/cm^2, about 80 mW/cm^2, about 85 mW/cm^2, about 90 mW/cm^2, about 95 mW/cm^2, about 100 mW/cm^2, about 110 mW/cm^2, about 120 mW/cm^2, about 130 mW/cm^2, about 140 mW/cm^2, about 150 mW/cm^2, about 160 mW/cm^2, about 170 mW/cm^2, about 180 mW/cm^2, about 190 mW/cm^2, about 200 mW/cm^2, about 210 mW/cm^2, about 220 mW/cm^2, about 230 mW/cm^2, about 240 mW/cm^2, about 250 mW/cm^2, about 260 mW/cm^2, about 270 mW/cm^2, about 280 mW/cm^2, about 290 mW/cm^2,

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[0085] Reagent-crosslinking may be carried out by cross-linking compounds, where part of the cross-linking compound is incorporated into the biopolymer to generate reagent-crosslinked biopolymers as described herein. Exemplary reagent-crosslinked biopolymers are biopolymers crosslinked by one or more of disuccinimidyl suberate (DSS), disuccinimidyl tartrate (DST), dithiobis succinimidyl propionate (DSP), bismaleimidoethane (BMOE), dithiobismaleimidoethane (DTME), *m*-maleimidobenzoyl-*N*-hydroxysuccinimide ester (MBS), *N*-γ-maleimidobutyryl-oxysuccinimide ester (GMBS), *N*-ε-maleimidocaproyloxy-succinimide ester (EMCS), and *N*-ε-maleimidocaproyl-oxysulfosuccinimide ester (sulfo-EMCS). Other exemplary reagent-crosslinked biopolymers are biopolymers crosslinked in the presence of light (*e.g.*, 250-350 nm light) with *N*-((2-pyridyldithio)ethyl)-4-azidosalicylamide and/or *N*-5-azido-2-nitrobenzyloxysuccinimide – thus, light may be used to initiate the crosslinking reaction of the cross-linking compound with a biopolymer.

[0086] The drying may be carried out at a temperature from about 20 °C to about 80 °C. Suitable drying temperatures in any embodiment herein may include, but are not limited to, about 20 °C, about 25 °C, about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, about 60 °C, about 65 °C, about 70 °C, about 75 °C, about 80 °C, or any range including and/or in between any two of the preceding values. The drying may be carried out for a duration of about 2 hours to about 24 hours. For example, in any embodiment herein, the drying may be carried out for about 2 hours, about 3 hours, about 4 hour, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about

23 hours, about 24 hours, or any range including and/or in between any two of the preceding values.

[0087] In any embodiment herein, depositing the second slurry may include injecting or extruding the second slurry within the outer layer's hollow center to form the inner core. Following deposition of the second slurry to form the inner core, the method includes removing residual water from the inner core. For example, in any embodiment herein, removing the residual moisture from the inner core may include freeze-drying the inner core. In any embodiment herein, the inner core may retain 0% to about 5% of residual moisture. Suitable amounts of residual moisture may include, but are not limited to, about 0.05%, about 0.1%, about 0.5%, about 1%, about 2%, about 3%, about 4%, about 5%, or any range including and/or in between any two of the preceding values.

[0088] In any embodiment herein, the method may include shaping (*e.g.*, hemispherical, cubed, or other suitable shape) excess outer layer to form a fully or partially closed end of the wound insert (*see* FIGS. 1A and 2A).

[0089] In a related aspect, the present disclosure provides a wound insert prepared according to the method of manufacturing said wound insert as described herein in any embodiment.

Kits Comprising the Wound Insert of the Present Technology

[0090] In a further related aspect, the present disclosure provides kits that include a wound insert of any embodiment disclosed herein and instructions for use. The kits of the present technology may also include methods for treating a wound in a subject in need thereof. The kit may optionally comprise components such as antiseptic wipes, ointment, adhesive tape, tweezers, scissors, *etc*.

[0091] The examples herein are provided to illustrate advantages of the present technology and to further assist a person of ordinary skill in the art with preparing or using the compositions and systems of the present technology. The examples should in no way be construed as limiting the scope of the present technology, as defined by the appended claims. The examples can include or incorporate any of the variations, aspects, or embodiments of the present technology described above. The variations, aspects, or embodiments described

above may also further each include or incorporate the variations of any or all other variations, aspects or embodiments of the present technology.

EQUIVALENTS

[0092] While certain embodiments have been illustrated and described, a person with ordinary skill in the art, after reading the foregoing specification, can effect changes, substitutions of equivalents and other types of alterations to the compositions, systems, and methods of the present technology. Each aspect and embodiment described above can also have included or incorporated therewith such variations or aspects as disclosed in regard to any or all of the other aspects and embodiments.

[0093] The present technology is also not to be limited in terms of the particular aspects and embodiments described herein, which are intended as single illustrations of individual aspects of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. It is to be understood that this present technology is not limited to particular methods, reagents, compounds, compositions, labeled compounds or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to be limiting. Thus, it is intended that the specification be considered as exemplary only with the breadth, scope and spirit of the present technology indicated only by the appended claims, definitions therein and any equivalents thereof.

[0094] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase “consisting essentially

of" will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase "consisting of" excludes any element not specified.

[0095] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0096] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "down to," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. As will also be understood by one skilled in the art all language such as "greater than," "less than," and the like, refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

[0097] All publications, patent applications, issued patents, and other documents (for example, journals, articles and/or textbooks) referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety to the extent they are not inconsistent with the explicit teachings of this specification. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[0098] Other embodiments are set forth in the following claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A wound insert comprising:
   an outer layer comprising one or more of a photocrosslinked and a reagent-crosslinked biopolymer; and
   an inner core comprising a biopolymer; and
   wherein
      the outer layer exhibits a modulus of elasticity from about 0.5 MPa to about 5.0 MPa; and
      the inner core exhibits a lower modulus of elasticity than the outer layer.

2. The wound insert of claim 1, wherein the wound insert further comprises a suture thread connected to and extending from the outer layer.

3. The wound insert of claim 2, wherein the suture thread is bioresorbable suture thread.

4. The wound insert of claim 2 or claim 3, wherein the suture thread is bioresorbable suture thread comprising a poly(glycolic acid), a poliglycaprone, a polydioxanone, a collagen, or a combination of any two or more thereof.

5. The wound insert of any one of claims 1-4, wherein the wound insert is in a shape comprising a cylinder, a cylinder with at least one rounded edge, a cuboid, or a cuboid with at least one rounded edge.

6. The wound insert of any one of claims 1-5, wherein the wound insert is in a shape comprising a cylinder with hemispherical shaped ends.

7. The wound insert of any one of claims 1-6, wherein the width and/or height of the wound insert is about 0.1 cm to about 3 cm.

8. The wound insert of any one of claims 1-7, wherein the width and/or height of the wound insert is about 0.5 cm to about 1.5 cm.

9. The wound insert of any one of claims 1-8, wherein the length of the wound insert is about 1 cm to about 10 cm.

10. The wound insert of any one of claims 1-9, wherein the length of the wound insert is about 2 cm to about 5 cm.

11. The wound insert of any one of claims 1-10, wherein the thickness of the outer layer is about 20 μm to about 300 μm.

12. The wound insert of any one of claims 1-11, wherein the thickness of the outer layer is about 40 μm to about 120 μm.

13. The wound insert of any one of claims 1-12, wherein the wound insert comprises perforations in at least the outer layer.

14. The wound insert of any one of claims 1-13, wherein the wound insert comprises through-holes through the entire insert.

15. The wound insert of claim 14, wherein the through-holes have a width and/or height of about 2 mm to about 8 mm.

16. The wound insert of any one of claims 1-15, wherein the one or more of the photocrosslinked and the reagent-crosslinked biopolymer of the outer layer comprises a collagen, an oxidized cellulose, an oxidized regenerated cellulose (ORC), a polysaccharide, a chitosan, a gelatin, hyaluronic acid, or a combination of any two or more thereof.

17. The wound insert of any one of claims 1-16, wherein the photocrosslinked and the reagent-crosslinked biopolymer of the outer layer comprises collagen and ORC.

18. The wound insert of any one of claims 1-16, wherein the photocrosslinked and the reagent-crosslinked biopolymer of the outer layer comprises collagen, ORC, and gelatin.

19. The wound insert of any one of claims 1-18, wherein the outer layer comprises about 0.01 wt.% to about 100 wt.% of the one or more of the photocrosslinked and the reagent-crosslinked biopolymer.

20. The wound insert of any one of claims 1-19, wherein the outer layer comprises photocrosslinked biopolymer.

21. The wound insert of any one of claims 1-20, wherein the outer layer comprises at least one plasticizer.

22. The wound insert of any one of claims 1-21, wherein the outer layer comprises about 2 wt.% to about 30 wt.% at least one plasticizer.

23. The wound insert of claim 21 or claim 22, wherein the at least one plasticizer comprises an acetylated monoglyceride, an alkyl citrate, methyl ricinoleate, glycerol, or a combination of any two or more thereof.

24. The wound insert of claim 23, wherein the alkyl citrate is triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate, trioctyl citrate, acetyl trioctyl citrate, trihexyl citrate, acetyl trihexyl citrate, butyryl trihexyl citrate, trimethyl citrate, or a combination of any two or more thereof.

25. The wound insert of any one of claims 1-24, wherein the outer layer comprises collagen, ORC, and glycerol.

26. The wound insert of any one of claims 1-25, wherein the outer layer comprises collagen, ORC, gelatin, and glycerol.

27. The wound insert of any one of claims 1-26, wherein the outer layer comprises 0.001 wt.% to about 5 wt.% of an antimicrobial agent.

28. The wound insert of any one of claims 1-27, wherein the outer layer comprises 0.001 wt.% to about 5 wt.% ionic silver.

29. The wound insert of any one of claims 1-28, wherein the biopolymer of the inner core comprises a collagen, an oxidized cellulose, an oxidized regenerated cellulose (ORC), a polysaccharide, a chitosan, a gelatin, hyaluronic acid, or a combination of any two or more thereof.

30. The wound insert of any one of claims 1-29, wherein the inner core comprises one or more of collagen and chitosan along with ORC, wherein a weight ratio of the one or more of collagen and chitosan to ORC is about 60:40 to about 40:60.

31. The wound insert of any one of claims 1-30, wherein the inner core comprises about 10 wt.% to about 100 wt.% of the biopolymer.

32. The wound insert of any one of claims 1-31, wherein the inner core comprises 0.001 wt.% to about 5 wt.% of an antimicrobial agent.

33. The wound insert of any one of claims 1-32, wherein the inner core comprises 0.001 wt.% to about 5 wt.% of a source for ionic silver.

34. A method for treating a wound in a subject in need thereof, the method comprising administering to the wound a wound insert of any one of claims 1-33.

35. The method of claim 34, wherein the wound is a tunneling wound, a dermal wound, a diabetic wound, an acute wound, a chronic wound, or a combination of any two or more thereof.

36. The method of claim 34 or claim 35, wherein the wound is a tunneling wound.

37. The method of any one of claims 34-36, wherein the wound insert is administered directly to the wound.

38. The method of any one of claims 34-37, further comprising providing negative pressure to the wound.

39. The method of any one of claims 34-38, further comprising removing the wound insert, wherein the wound insert is removed by pulling the suture thread away from the wound.

40. A method of manufacturing a wound insert comprising:

fabricating an outer layer of the wound insert from a first slurry comprising one or more biopolymers, wherein the outer layer is in a shape having a hollow center;

photo-crosslinking or reagent-crosslinking the outer layer to obtain one or more photocrosslinked and reagent-crosslinked biopolymers;

drying the outer layer of the wound insert;

depositing a second slurry into the hollow center of the outer layer to form an inner core of the wound insert; and

removing residual moisture from the inner core;

wherein:

the shape of the outer layer comprises a cylinder, a sphere, a cube, a cuboid, a hexagonal prism, a cone, a square-based pyramid, triangular-based pyramid, or a triangular prism;

the second slurry comprises a biopolymer;

the outer layer exhibits a modulus of elasticity from about 0.5 MPa to about 5.0 MPa; and

the inner core exhibits a lower modulus of elasticity than the outer layer.

41. The method of claim 40, wherein the first slurry has a pH from about 3 to 7.

42. The method of claim 40 or claim 41, wherein the first slurry has a pH from about 4.5 to about 5.5.

43. The method of any one of claims 40-42, wherein the first slurry comprises one or more biopolymers comprising a collagen, an oxidized cellulose, an oxidized regenerated cellulose (ORC), a polysaccharide, a chitosan, a gelatin, hyaluronic acid, or a combination of any two or more thereof.

44. The method of any one of claims 40-43, wherein the first slurry further comprises at least one plasticizer.

45. The method of any one of claims 40-44, wherein the first slurry comprises about 2 wt.% to about 30 wt.% of at least one plasticizer.

46. The method of claim 44 or claim 45, wherein the at least one plasticizer comprises an acetylated monoglyceride, an alkyl citrate, methyl ricinoleate, glycerol, or a combination of any two or more thereof.

47. The method of any one of claims 40-46, wherein the fabricating comprises extruding the first slurry to fabricate the outer layer.

48. The method of any one of claims 40-47, further comprising treating the outer layer with a weak basic gas.

49. The method of claim 48, wherein the weak basic gas is ammonia.

50. The method of any one of claims 40-49, wherein the biopolymer of the second slurry comprises a collagen, an oxidized cellulose, an oxidized regenerated cellulose (ORC), a polysaccharide, a chitosan, a gelatin, hyaluronic acid, or a combination of any two or more thereof.

51. The method of any one of claims 40-50, wherein the second slurry comprises one or more of collagen and chitosan along with ORC, wherein a weight ratio of the one or more of collagen and chitosan to ORC is about 60:40 to about 40:60.

52. The method of any one of claims 40-51, wherein the second slurry comprises about 10 wt.% to about 100 wt.% of the biopolymer.

53. The method of any one of claims 40-52, wherein the second slurry comprises 0.001 wt.% to about 5 wt.% of an antimicrobial agent.

54. The method of any one of claims 40-53, wherein the second slurry further comprises 0.001 wt.% to about 5 wt.% of a source for ionic silver.

55. The method of any one claims 40-54, wherein removing residual water from the inner core comprises freeze drying the inner core.

56. A wound insert prepared according to the method of any one of claims 40-55.

57. A kit comprising the wound insert of any one of claims 1-33, and instructions for use.

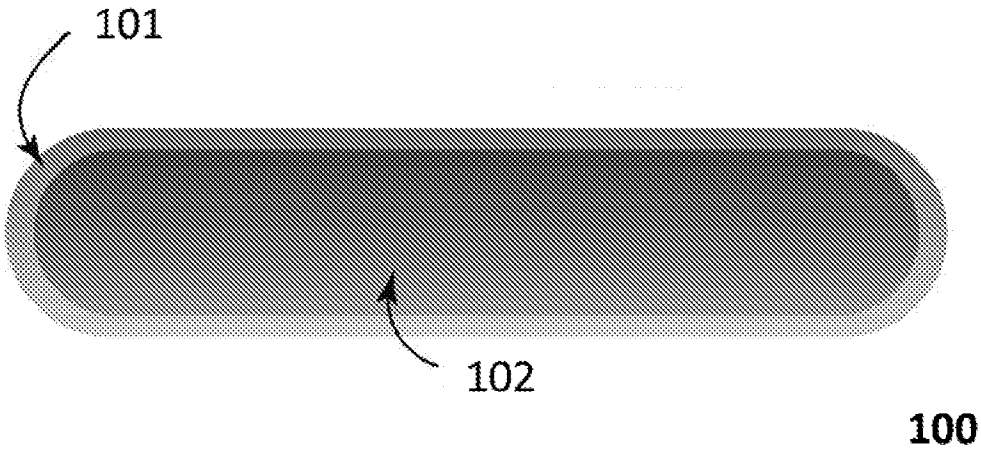


FIG. 1A

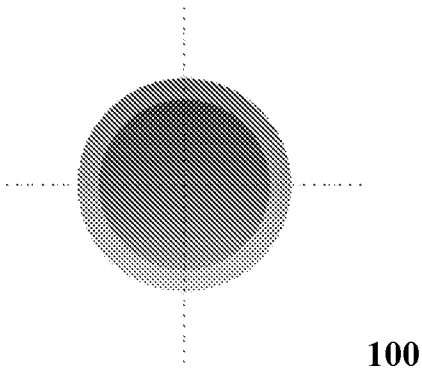


FIG. 1B

FIG. 2A

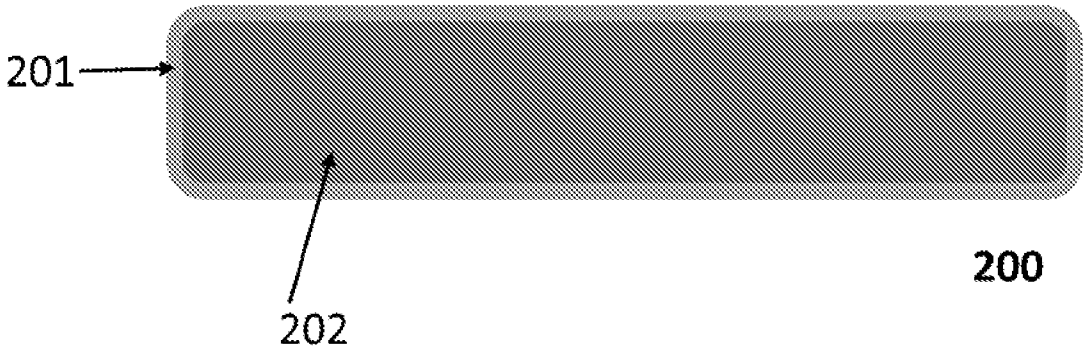


FIG. 2B

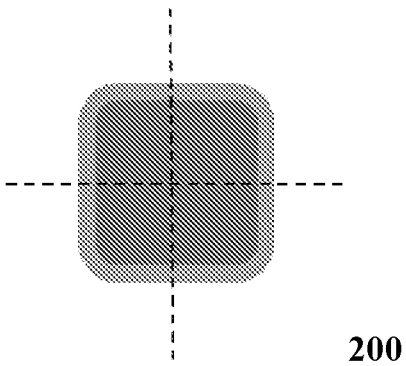


FIG. 3

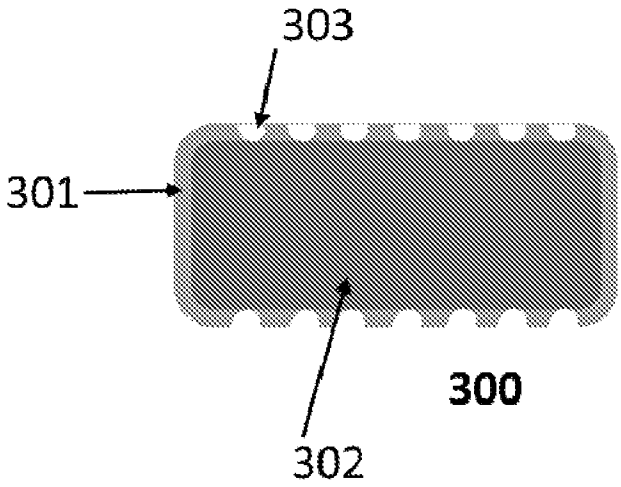
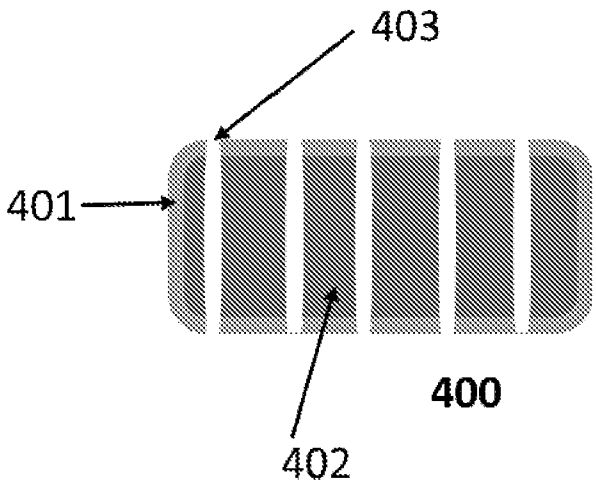


FIG. 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/039576

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F13/00 A61L15/22 A61L15/28 A61L15/32 A61L15/42
A61L15/46 A61L15/64 A61L27/20 A61L27/24 A61L27/26
A61L27/50 A61L27/54 A61L27/58 A61M27/00

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)
A61F A61M A61L

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 254 105 A (HAAGA JOHN R [US]) 19 October 1993 (1993-10-19)	1-39,56, 57
A	column 3, line 12 - column 4, line 3 column 4, lines 41-68 column 7, line 8 - column 8, line 17 claims	40-55

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2020	02/10/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Van den Bulcke, H

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/039576

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 2001/046518 A1 (SAWHNEY AMARPREET S [US]) 29 November 2001 (2001-11-29) page 3, paragraph 28-37 page 6, paragraph 66-70 page 7, paragraph 89 - page 9, paragraph 107 examples 1,7	1-57
A	WO 2018/035063 A1 (KCI USA INC [US]; SYSTAGENIX WOUND MAN IP CO BV [GB]) 22 February 2018 (2018-02-22) claims	1-57

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International application No
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