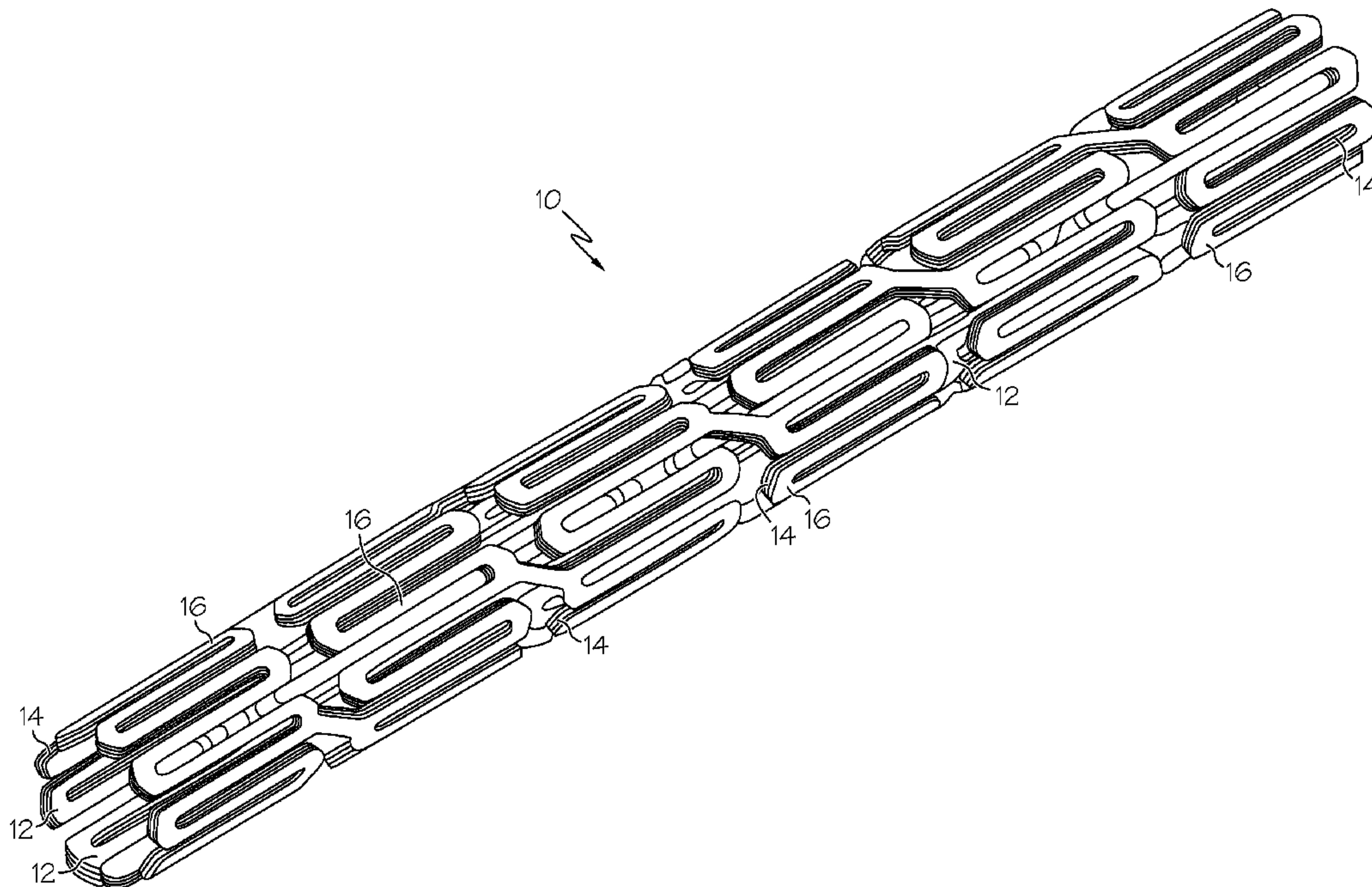




(86) Date de dépôt PCT/PCT Filing Date: 2013/08/28
(87) Date publication PCT/PCT Publication Date: 2014/03/20
(45) Date de délivrance/Issue Date: 2018/06/12
(85) Entrée phase nationale/National Entry: 2014/10/09
(86) N° demande PCT/PCT Application No.: US 2013/057049
(87) N° publication PCT/PCT Publication No.: 2014/042875
(30) Priorité/Priority: 2012/09/12 (US61/700,008)

(51) Cl.Int./Int.Cl. *A61L 31/10* (2006.01),
A61L 31/14 (2006.01)
(72) Inventeurs/Inventors:
HINGSTON, JOHN, US;
JORDAN, GARY, US;
BERTOLINO, WILLIAM, US;
NORTON, PAUL K., US;
WEINER, JASON, US
(73) Propriétaire/Owner:
BOSTON SCIENTIFIC SCIMED, INC., US
(74) Agent: SMART & BIGGAR

(54) Titre : REVETEMENT ADHESIF ANTI-MIGRATION POUR ENDOPROTHESE VASCULAIRE
(54) Title: ADHESIVE STENT COATING FOR ANTI-MIGRATION



(57) Abrégé/Abstract:

A stent, the stent comprising a first coating composition comprising at least one bioadhesive and a second coating composition disposed over the first coating composition, the second coating composition comprising at least one biodegradable polymer.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
20 March 2014 (20.03.2014)

(10) International Publication Number
WO 2014/042875 A1

- (51) **International Patent Classification:**
A61L 31/10 (2006.01) *A61L 31/14* (2006.01)
- (21) **International Application Number:**
PCT/US2013/057049
- (22) **International Filing Date:**
28 August 2013 (28.08.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/700,008 12 September 2012 (12.09.2012) US
- (71) **Applicant:** BOSTON SCIENTIFIC SCIMED, INC.
[US/US]; One Scimed Place, Maple Grove, Minnesota 55311 (US).
- (72) **Inventors:** HINGSTON, John; 7 Baldwin Ave., Framingham, Massachusetts 01701 (US). JORDAN, Gary; 9 Parker Circle, Litchfield, New Hampshire 03052 (US). BERTOLINO, William; 19 Hadley Rd., Framingham, Massachusetts 01701 (US). NORTON, Paul, K.; 758 Lancaster Ave., Lunenburg, Massachusetts 01462 (US). WEINER, Jason; 15 Fay Mountain Rd., Grafton, Massachusetts 01519 (US).
- (74) **Agent:** RYAN-LINDQUIST, Lisa; Vidas, Arrett & Steinkraus, Suite 400, 6640 Shady Oak Road, Eden Prairie, Minnesota 55344 (US).

- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) **Title:** ADHESIVE STENT COATING FOR ANTI-MIGRATION

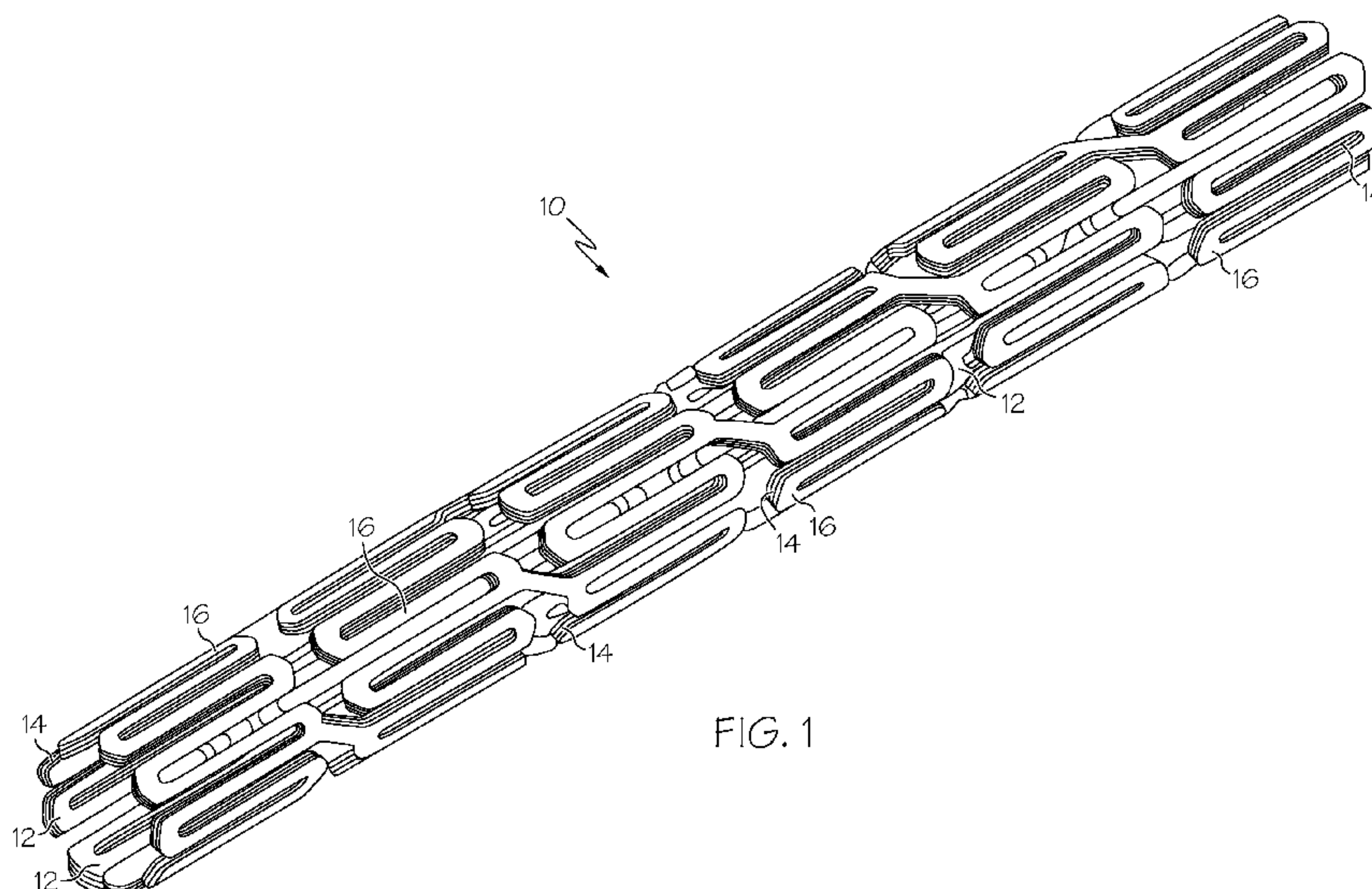


FIG. 1

(57) **Abstract:** A stent, the stent comprising a first coating composition comprising at least one bioadhesive and a second coating composition disposed over the first coating composition, the second coating composition comprising at least one biodegradable polymer.



WO 2014/042875 A1

ADHESIVE STENT COATING FOR ANTI-MIGRATION

BACKGROUND OF THE INVENTION

[0001] The present invention relates generally to a coated medical device and more particularly to a coated stent. Stents, grafts, stent-grafts, vena cava filters and similar implantable medical devices, collectively referred to hereinafter as stents, are radially expandable endoprotheses which are typically implants capable of being implanted transluminally and enlarged radially after being introduced percutaneously. Stents may be implanted in a variety of body lumens or vessels such as within the vascular system, esophagus, gastrointestinal tract, large and small intestine, biliary ducts, pancreas ducts, pulmonary and urinary tracts, etc. Stents may be used to reinforce body vessels and to prevent restenosis following angioplasty in the vascular system. Stents may also be used to open strictures. They may be self-expanding, mechanically expandable or hybrid expandable.

[0002] Stents are typically tubular members that are radially expandable from a reduced diameter configuration for delivery through a patient's body lumen to an expanded configuration once deployed at the treatment site.

[0003] Stents may be constructed from a variety of materials such as stainless steel, Elgiloy®, nickel, titanium, nitinol, shape memory polymers, other polymeric materials, etc. For metallic stents, a stent may be typically formed from a tubular member, either extruded or formed from a sheet, in which a pattern is subsequently formed by etching or cutting material from the tubular member.

[0004] Polymeric stents formed from a variety of thermoplastic polymer materials may be formed by weaving or braiding fibers or filaments.

[0005] Stents may further be provided with a cover, such as a silicone cover to prevent tissue ingrowth.

[0006] Desirable stent properties include sufficient flexibility to be able to conform to the tortuous body lumen during delivery, yet sufficiently rigid to resist migration once deployed at the treatment site.

[0007] In some stents, the compressible and flexible properties that assist in stent delivery may also result in a stent that has a tendency to migrate from its originally deployed position. Stent covering may contribute to migration as well. Stent migration affects many endoscopic stents including esophageal, pancreatic and biliary stents. Risk factors associated with stent migration are discussed in *Incidence and risk factors for biliary and pancreatic stent migration*, Johanson JF, Schmah. MJ, Geenen JE. *Gastrointest Endosc.* 1992 May-Jun;38(3):341-6.

[0008] It is thus desirable to provide a stent configuration that resists migration following deployment.

[0009] Commonly assigned US Patent Publication No. 20090098176, the entire content of which is incorporated by reference herein, discloses medical devices with triggerable bioadhesives.

SUMMARY OF THE INVENTION

[0010] In one aspect, the present invention relates to a stent including a first coating composition comprising at least one bioadhesive and a second coating composition disposed over the first coating composition, the second coating composition comprising at least one biodegradable polymer.

[0011] In another aspect, the present invention relates to a method of making a stent including the steps of providing a stent having an inner surface and an outer surface, applying a bioadhesive at least to a portion of said outer surface of said stent and applying a biodegradable coating over said bioadhesive.

[0012] These and other aspects, embodiments and advantages of the present disclosure will become immediately apparent to those of ordinary skill in the art upon review of the Detailed Description and Claims to follow.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of a stent 10 according to the invention in an unexpanded state.

FIG. 2 is a perspective view of a stent 10 according to the invention in an expanded state.

FIG. 3 is a partial enlarged view of a stent according to the invention.

FIG. 4 is a partial enlarged view of an alternative embodiment of a stent according to the invention.

FIG. 5 is a perspective view of an exemplary stent on which the coatings may be employed.

FIG. 6 is a side view of an embodiment of a stent according to the invention.

FIG. 7 is a cross-sectional view taken at section 7 in FIG. 6.

FIG. 8 is a side view of a stent according to the invention.

FIG. 9 is a cross-sectional view taken at section 9 in FIG. 8.

DETAILED DESCRIPTION OF THE INVENTION

[0013] While embodiments of the present invention may take many forms, there are described in detail herein, specific embodiments of the present disclosure. This description is an exemplification of the principles of the present disclosure and is not intended to limit the disclosure to the particular embodiments illustrated herein.

[0014] Turning now to the drawings, FIG. 1 is a perspective view of a stent 10 according to the invention in an unexpanded state. Stent 10 is shown having a stent wall 12, a bioadhesive layer 14 and an outer biodegradable layer 16.

[0015] FIG. 2 is a perspective view of a stent 10 according to the invention in an expanded state having a stent wall 12, a bioadhesive layer 14 and an outer biodegradable layer 16.

[0016] FIG. 3 is partial enlarged view of a stent 10 having a stent wall 12, a bioadhesive layer 14 and an outer biodegradable layer 16.

[0017] FIG. 4 is a partial enlarged view of a stent 10 having a stent wall 12 and disposed on the stent wall 12 is a bioadhesive layer 14 and an outer biodegradable layer 16. In this

embodiment, stent 10 is shown also having a silicone covering 18 disposed on the inner surface of the stent wall 12 beneath.

[0018] FIG. 5 is a perspective view of an endoscopic stent 10 on which the coatings may be employed. Stent 10 may be coiled or patterned as a braided or woven open network or fibers or filaments as disclosed, for example, in commonly assigned US Patent Publication No. 2012/0128793.

[0019] In one embodiment, stent 10 has a braided construction 20 and a flared proximal end 22. In this embodiment, stent 10 is an esophageal stent. Stent 10 may be formed of any suitable stent material including metallic and non-metallic materials as well as shape memory materials. Examples of suitable materials include, but are not limited to, shape memory alloys such as Nitinol®, other metallic materials such as stainless steel, tantalum, titanium, nickel-chrome, or cobalt-chromium alloys such as those sold under the tradename of Elgiloy®.

[0020] Thermoplastic polymer materials which may be employed in forming the device include both elastomeric and non-elastomeric materials, examples of which include, but are not limited to, polyolefins such as metallocene catalyzed polyethylenes, polypropylenes, and polybutylenes and copolymers thereof; vinyl aromatic polymers such as polystyrene; vinyl aromatic copolymers such as styrene-isobutylene copolymers and butadiene-styrene copolymers; ethylenic copolymers such as ethylene vinyl acetate (EVA), ethylene-methacrylic acid and ethylene-acrylic acid copolymers where some of the acid groups have been neutralized with either zinc or sodium ions (commonly known as ionomers); polyacetals; chloropolymers such as polyvinylchloride (PVC); fluoropolymers such as polytetrafluoroethylene (PTFE); polyesters such as polyethyleneterephthalate (PET);

polyester-ethers; polyamides such as nylon 6 and nylon 6,6; polyamide ethers; polyethers; elastomers such as elastomeric polyurethanes and polyurethane copolymers; polycarbonates; and mixtures and block or random copolymers of any of the foregoing.

[0021] Stent 10 may also optionally be formed at least partially, or entirely of a biodegradable or bioabsorbable polymer material. Examples include, but are not limited to, poly(alpha-hydroxy acid) polymers and copolymers, such as polymers and copolymers of glycolide including polyglycolide (PGA), poly(glycolide-co-lactide)(PGLA), and poly(glycolide-co-trimethylene carbonate(PGA/TMC; polymers and copolymers of polylactide (PLA) including poly-L-lactide (PLLA), poly-D-lactide (PDLA), poly-DL-lactide (PDLLA), poly(lactide-co-tetramethylene glycolide), poly(lactide-co-trimethylene carbonate), poly(lactide-co-delta-valerolactone), poly(lactide-co-epsilon-caprolactone), poly(glycine-co-DL-lactide) and poly(lactide-co-ethylene oxide); polydioxanone polymers such as asymmetrically 3,6-substituted poly-1,4-dioxane-2,5-diones; poly(beta-hydroxybutyrate) (PHBA) and copolymers of the same such as poly(beta-hydroxybutyrate-co-beta-hydroxyvalerate); polygluconate; poly(beta-hydroxypropionate) (PHPA); poly(beta-dioxanone)(PDS); poly(delta-valerolactone); poly(epsilon-caprolactone); methylmethacrylate-N-vinylpyrrolidone copolymers; polyester amides; polyesters of oxalic acid; polydihydropyranes; poly(alkyl-2-cyanoacrylate); polyvinyl alcohol (PVA); polypeptides; poly(beta-maleic acid) (PMLA); poly(beta-alkanoic acid); poly(ethylene oxide) (PEO); polyanhydrides, polyphosphoester, and chitin polymers. See, for example, commonly assigned US Patent Publication No. 20120123521. This patent also illustrates various stent designs which can be employed herein.

[0022] Turning now to the drawings, FIG. 6 is a side view of one embodiment of a stent on which the coatings according to the invention be employed. In this embodiment, stent 10 is a self-expanding stent formed of a shape memory metal such as Nitinol® having a silicone covering. The stent has a braided wire construction. In this embodiment, stent 10 is shown having a silicone covering 18. Stent 10 is disposed on silicone covering 18 and is partially embedded therein.

[0023] Stent 10 may be fully, substantially or partially covered or lined with a polymeric covering 18. The stent 10 may also be embedded in the polymer material. The covering may be in the form of a tubular structure. Nonlimiting examples of useful polymeric materials include polyesters, polypropylenes, polyethylenes, polyurethanes, polynaphthalenes, polytetrafluoroethylenes, expanded polytetrafluoroethylene, silicone, copolymers thereof and mixtures or combinations thereof. Desirably, the polymeric covering 18 is silicone. The polymeric material or silicone 18 may be disposed on the external surfaces of the stent 10, or disposed on the internal surfaces of the stent 10, as depicted in FIGS. 4, 6 and 7, or combinations thereof.

[0024] Stents of this type are described in commonly assigned US Patent Publication Nos. 2006/0276887 and 2008/0009934.

[0025] Stent 10 further includes a bioadhesive layer 14 and an outer biodegradable layer 16.

[0026] FIG. 7 is an enlarged partial cross-sectional view taken at section 6 in FIG. 6 illustrating the tacky polymeric coating on a covered stent 10 according to the invention.

[0027] In one embodiment, the stent is a polymeric self-expanding stent formed from polyethylene terephthalate (PET) filaments having a silicone covering. These types of stents

are commercially available from Boston Scientific Inc. located in Natick, MA under the tradename of Polyflex®.

[0028] Another example of a covered stent is a self-expanding nitinol stent formed of braided or woven wires and having a silicone covering. These types of stents are commercially available from Boston Scientific Inc. located in Natick, MA under the tradename of WallFlex®.

[0029] Another example of a covered stent is a self-expanding nitinol stent formed of braided or woven wires and having a polyurethane covering. These types of stents are commercially available from Boston Scientific Inc. located in Natick, MA under the tradename of Ultraflex®.

[0030] FIG. 8 is a side view illustrating covered stents of this type. Stent 10 has a stent wall 12, a silicone covering 18 disposed on the outer surface of stent wall 12, a tacky adhesive coating 14 and a biodegradable coating 16. FIG. 9 is a cross-sectional view of stent 10 taken at section 9 in FIG. 8.

[0031] Other suitable covering materials can be employed as well. Examples include, but are not limited to, polyethylene, polypropylene, polyvinyl chloride, polytetrafluoroethylene, including expanded polytetrafluoroethylene (ePTFE), fluorinated ethylene propylene, fluorinated ethylene propylene, polyvinyl acetate, polystyrene, poly(ethylene terephthalate), naphthalene, dicarboxylate derivatives, such as polyethylene naphthalate, polybutylene naphthalate, polytrimethylene naphthalate and trimethylenediol naphthalate, polyurethane, polyurea, silicone rubbers, polyamides, polyimides, polycarbonates, polyaldehydes, polyether ether ketone, natural rubbers, polyester copolymers, styrene-butadiene copolymers, polyethers, such as fully or partially halogenated polyethers, and copolymers

and combinations thereof. See, for example, commonly assigned US Patent No. 8,114,147, the entire content of which is incorporated by reference herein.

[0032] These type of stents are loaded into a catheter delivery system and are maintained therein in an unexpanded state for delivery through a patient's body lumen. Once at the treatment site, and are expanded or deployed at the treatment site.

[0033] The bioadhesive layer can encapsulate the entire stent, can be disposed only over a portion of the outer surface of the stent or be disposed on the entirety of the outer surface of the stent. The biodegradable layer may be disposed over the bioadhesive layer.

[0034] Any suitable bioadhesive can be employed herein. Bioadhesion refers to the ability of certain materials such as polymers, macromolecules and hydrocolloids to adhere to biological or body tissue.

[0035] The bioadhesive material employed herein and can include natural polymeric materials, as well as synthetic materials, and synthetic materials formed from biological monomers such as sugars. Bioadhesives can also be obtained from the secretions of microbes or by marine molluscs and crustaceans. Bioadhesives are designed to adhere to biological tissue.

[0036] Examples of bioadhesives include, but are not limited to, mucoadhesives, amino adhesives, adhesive surface proteins (MSCRAMMS), adhesively modified biodegradable polymers such as Fatty Ester Modified PLA/PLGA, polymer materials, hydrogels, minigel particles, and so forth, each discussed in detail below, as well as mixtures thereof.

[0037] Amino acids find use in embodiments of the present disclosure. Amino acids can be both utilized to facilitate release from the delivery vehicle as well as to gain adhesion to the lesion site. Zwitterionic amino acids can be employed either as a layer or as a component

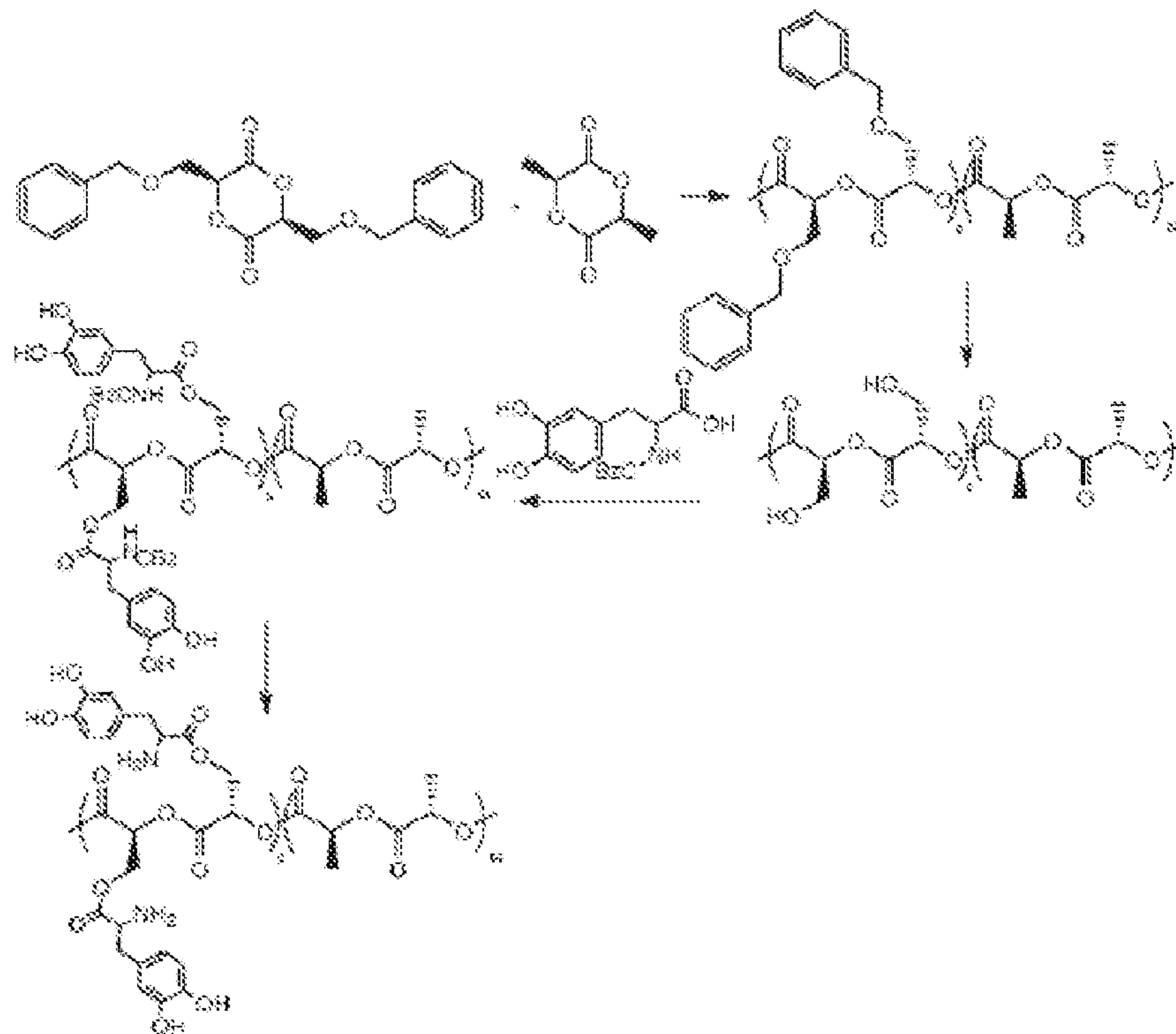
within the HA/active agent layer. The zwitterionic amino acid can be oriented so that the hydrophobic side of the zwitterionic amino acid selectively facilitates adhesion to the lipophilic lesion. One example of a useful compound is amino acid 3,4-L-dihydroxyphenylalanine (L-DOPA), a tyrosine derivative found in high concentrations in the “glue” proteins of mussels.

[0038] Protein adhesions called MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) can also be employed as a bioadhesive in the second coating composition. MSCRAMMS are naturally produced by pathogens to initiate adhesion to the host extra cellular matrix to initiate infection. These adhesive surface proteins can be isolated or synthesized and utilized either as a separate layer or in the HA/active agent composition to facilitate adhesion the lesion site.

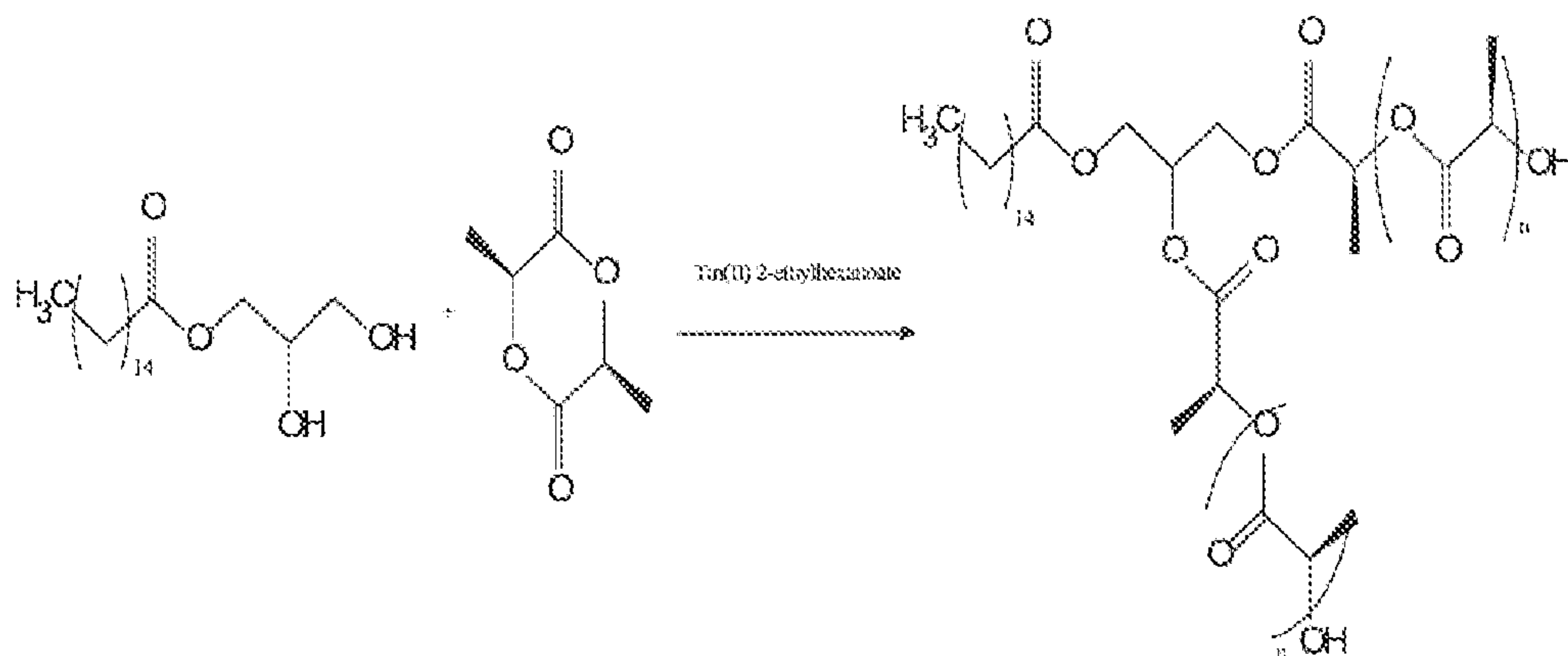
[0039] In some embodiments, the bioadhesive may include a catechol moiety. Examples include, but are not limited to, L-DOPA, D-DOPA, dopamine or carbidopa.

[0040] One example of this type of adhesively modified polymer is able polymers include, but are not limited to, L-DOPA (L-3,4-dihydroxyphenylalanine) modified PLA(poly(lactic acid)) or PLGA poly(lactide-co-glycolide)

[0041] In some embodiments, the bioadhesive may include a catechol moiety. Examples include, but are not limited to, L-DOPA, D-DOPA, dopamine or carbidopa. One example of this type of adhesively modified polymer is L-DOPA (L-3,4-dihydroxyphenylalanine) modified PLA(poly(lactic acid)) or PLGA (poly(lactide-co-glycolide)) having the following general structure:



[0042] Another example of an adhesively modified biodegradable polymer is a fatty ester modified PLA/PLGA, having the following structure:



[0043] In the above embodiment, other examples of suitable adhesive moieties include, but are not limited to, monopalmitate (shown above), monostearin, glycerol, α,α' -dilaurin or iso-stearyl alcohol.

[0044] Another particular class of bioadhesives is the mucoadhesives. The term "*mucoadhesive*" denotes a compound which exhibits an affinity for a mucosa surface. Mucoadhesive polymers are typically polymers having hydrogen bonding groups. See <http://en.wikipedia.org/wiki/Bioadhesive#Mucoadhesion>. "Mucoadhesion is the ability of materials to adhere to mucosal membranes in the human body and provide a temporary retention". "Excellent mucoadhesive properties are typical for hydrophilic polymers possessing charged groups and/or non-ionic functional groups capable of forming hydrogen bonds with mucosal surfaces." [*Macromol Biosci. 2011 Jan 14; 1J(6):748-64. doi: 10.1002/mabi.201000388.Epub 2010 Dec 27*].

[0045] Examples of suitable mucoadhesives include, but are not limited to, polysaccharides including, for example, dextran, dextrane, dextrin, pectin, amylopectin, sorbitol, sucrose, xylitol, anionic hydrated polysaccharides such as gellan, curdlan, XM-6 and xanthan gum (Xantural® available from CPKelco, A Huber Company, in Atlanta, GA); agar; gums, including, for example, guar gum or locust bean gum; salts of alginic acid such as sodium alginate or magnesium alginate, and hydrated gels thereof; cellulose such as methylcellulose, sodium carboxy methylcellulose, hydroxypropylcellulose (Klucel™ available from Ashland in Covington, KY); chitosan, proteins such as gelatin; carbohydrates such as starch; and so forth.

[0046] Polysaccharides useful herein also include Aloe vera polysaccharides.

[0047] Hydrogels find utility herein and include, but are not limited to, polyvinylpyrrolidone (PVP), polyacrylate, chitosan, polyalkylene glycols such as polyethylene glycol (PEG), polyethylene glycol/dextran aldehyde, polyalkylene oxides such as polyethylene oxide and polypropylene oxide, polyvinyl esters such as polyvinyl acetate,

polyhydroxyethyl methacrylate, polyvinyl alcohol and polyvinyl ether, polyanions having a high charge density such as crosslinked or non-crosslinked homopolymers and copolymers of (meth)acrylic acid such as Noveon AA-1 Polycarbophil which is an acrylic acid polymer crosslinked with divinyl glycol, copolymers of acrylic acid such as acrylic acid-co-acrylamide copolymers (P(AA-co-AM)), and derivatives of polyacrylic acid such as salts and esters thereof, for example, Carbopol® polymers which are homo- and copolymers of acrylic acid crosslinked with a polyalkenyl polyether available from Lubrizol in Wickliffe, OH; polymers and copolymers of (meth)acrylic esters; and so forth. Derivatives of many of these polymers may also be employed herein. See for example U.S. Patent No. 6391033.

[0048] Hydrogels are disclosed in commonly assigned US Patent Application No. 5,693,034 to Buscemi et al.

[0049] For a discussion of polyacrylic acid mucoadhesion see *Mechanisms of Mucoadhesion of Poly(acrylic Acid) Hydrogels*, by Haesun Park and Joseph R. Robinson, *Pharmaceutical research*, 1987, Vol 4, No 6, 457-464.

[0050] Another bioadhesive is poly(NIPAM) (poly(N-isopropylacrylamide) minigel particles. This polymer has the property of being in a liquid state at room temperature and an adhesive at body temperature. See “*Preparation and Swelling Properties of Poly(NIPAM) “Minigel” Particles Prepared by Inverse Suspension Polymerization*”, Dowding, John et al., *Journal of Colloid and Interface Science* 221, 268-272 (2000), available online at <http://www.idealibrary.com>.

[0051] For better retention to a medical device surface, several techniques may be employed. Suitably, the minigel particles are crosslinked or mixed with a higher molecular weight polymer to allow enough time for retention of the minigel to the medical device during delivery, or uncrosslinked minigel particles can be employed in a crosslinked polymer network.

[0052] For example, an uncrosslinked minigel such as poly(N-isopropylacrylamide) may be employed with the reaction product of a vinyl polymer. See commonly assigned US Patent No. 5,693,034.

[0053] Poly(N-isopropylacrylamide) may also be blended with a higher molecular weight polymer such as a higher molecular weight hydrogel polymer. Examples of hydrogels that may be blended with poly(n-isopropylacrylamide) include, but are not limited to, polyvinylpyrrolidone, polyacrylamides, polyethylene oxide, polyacrylic acid, poly (sodium-4-styrenesulfonate), poly(3-hydroxybutyric acid), and 2-hydroxyethyl methacrylate.

[0054] These bioadhesives are disclosed in commonly assigned copending US Patent Publication No. 2012-0095396, filed August 16, 2011 and claiming the benefit of US Provisional Patent Application No. 61/394104 filed October 18, 2010.

[0055] Another mucoadhesive, xyloglucan, is disclosed in US Patent Publication No. 20120088726. Glycerol, which can be employed in combination with any of the above mucoadhesives, has been found to increase the mucoadhesiveness of xyloglucan.

[0056] Other bioadhesives are also disclosed in US Patent Publication No. 2010/00316712, and in Tao et al., "Bioadhesive poly(methyl methacrylate) microdevices for controlled drug delivery", Journal of Controlled Release, 88, (2003), 215-228; Sekiyama et al., "Novel Sutureless Transplantation of Bioadhesive-Coated, Freeze-Dried Amniotic Membrane for

Ocular Surface Reconstruction”, Investigative Ophthalmology & Visual Science, April 2007, Vol. 48, No. 4, 1528-1534; and Lim et al., “The adhesive properties of coacervated recombinant hybrid mussel adhesive proteins”, Biomaterials, 31, (2010), 3715-3722.

[0057] These lists are intended for illustrative purposes only, and not as a limitation on the scope of the present invention.

[0058] Any biodegradable material can be employed herein that does not form an adhesive layer. These biodegradable materials break down and lose their integrity *in vivo*. Examples of suitable biodegradable polymers include, but are not limited to, poly(amides) such as poly(amino acids) and poly(peptides), poly(esters) such as polylactide including poly(DL-lactide) and polyglycolide, and copolymers thereof such as polylactide-co-glycolide including poly(DL-lactide-co-glycolide), poly(L-lactide-co-glycolide), poly(caprolactone) and polylactide-co-caprolactone including poly(DL-lactide-co-caprolactone and poly(L-lactide-co-caprolactone), poly(anhydrides), poly(orthoesters), poly(carbonates) including tyrosine derived polycarbonates, polyhydroxyvalerate, polyhydroxybutyrate, polyhydroxybutyrate-co-valerate, and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), copolymers and mixtures thereof.

[0059] Biodegradable metallic elements can also be employed herein. Examples include, but are not limited to, iron (Fe) and magnesium (Mg) and alloys thereof. Examples of

suitable biodegradable metal alloys include, but are not limited to, Fe₃₀Mn (Mn=manganese) and Fe₃₀Mn₆Si (Si= silicon).

[0060] These lists are intended for illustrative purposes only, and not as a limitation on the scope of the present invention.

[0061] Some of the bioadhesives may form a permanent coating on the stent while others will form a temporary coating on the stent. In cases wherein it is desirable to remove the stent after treatment, it may be desirable to select a temporary bioadhesive.

[0062] For example, hydrogels and proteins, carbohydrates, glycoproteins and mucopolysaccharides which can be used for form hydrogels, may be used where temporary adhesion is desirable.

[0063] Permanent bioadhesives can be crosslinked materials that are generated via a “mix to activate” process.

[0064] L-DOPA, discussed above, can be used to form a covalently crosslinked permanent bioadhesive on the surface of the medical device.

[0065] While it is preferable to employ a biodegradable coating layer over the bioadhesive layer, for some bioadhesives it may be possible to employ them without the biodegradable coating layer.

[0066] Therapeutic agents may be incorporated in the bioadhesive coating layer, the biodegradable coating layer, or both.

[0067] Various therapeutic agents may be employed herein depending on the condition which is being treated. As used herein, the terms, “therapeutic agent”, “drug”, “pharmaceutically active agent”, “pharmaceutically active material”, “beneficial agent”, “bioactive agent”, and other related terms may be used interchangeably herein and include

genetic therapeutic agents, non-genetic therapeutic agents and cells. A drug may be used singly or in combination with other drugs. Drugs include genetic materials, non-genetic materials, and cells.

[0068] A therapeutic agent may be a drug or other pharmaceutical product such as non-genetic agents, genetic agents, cellular material, etc. Some examples of suitable non-genetic therapeutic agents include but are not limited to: antithrombogenic agents such as heparin, heparin derivatives, vascular cell growth promoters, growth factor inhibitors, etc. Where an agent includes a genetic therapeutic agent, such a genetic agent may include but is not limited to: DNA, RNA and their respective derivatives and/or components; hedgehog proteins, etc. Where a therapeutic agent includes cellular material, the cellular material may include but is not limited to: cells of human origin and/or non-human origin as well as their respective components and/or derivatives thereof.

[0069] Other active agents include, but are not limited to, antineoplastic, antiproliferative, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antiproliferative, antibiotic, antioxidant, and antiallergic substances as well as combinations thereof.

[0070] Examples of antineoplastic/antiproliferative/antimitotic agents include, but are not limited to, paclitaxel (e.g., TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), the olimus family of drugs including sirolimus (rapamycin), biolimus (derivative of sirolimus), everolimus (derivative of sirolimus), zotarolimus (derivative of sirolimus) and tacrolimus, methotrexate, azathioprine, vincristine, vinblastine, 5-fluorouracil, doxorubicin hydrochloride, mitomycin, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors. While the preventative and treatment properties of the foregoing therapeutic substances or agents are well-known to those of ordinary skill

in the art, the substances or agents are provided by way of example and are not meant to be limiting. Other therapeutic substances are equally applicable for use with the disclosed methods and compositions. See commonly assigned U.S. Patent Application Nos. 2010/0087783, 2010/0069838, 2008/0071358 and 2008/0071350. See also commonly assigned U.S. Patent Application Nos. 2004/0215169 and 2009/0098176, and U.S. Patent No. 6,805,898.

[0071] Derivatives of many of the above mentioned compounds also exist which are employed as therapeutic agents and of course mixtures of therapeutic agents may also be employed.

[0072] For application, the therapeutic agent can be dissolved in a solvent or a cosolvent blend along with the bioadhesive or biodegradable polymer material.

[0073] Suitable solvents include, but are not limited to, dimethyl formamide (DMF), butyl acetate, ethyl acetate, tetrahydrofuran (THF), dichloromethane (DCM), acetone, acetonitrile, dimethyl sulfoxide (DMSO), butyl acetate, etc.

[0074] The stents according to the invention are manufactured using any conventional method which may first involve extrusion of a tubular member or folding of a sheet of a suitable material and the cutting a stent pattern therein such as with laser cutting, etching or the like. Braided stents also find utility herein.

[0075] The stent may be coated with the bioadhesive material by first dissolving the material in a suitable solvent or cosolvent blend and then coating the stent by spraying, dipping, painting or the like.

[0076] Suitable polar solvents include, but are not limited to, alcohols including methanol, ethanol and isopropanol, and water.

[0077] Other suitable solvents include tetrahydrofuran, chloroform, toluene, acetone, isooctane, 1,1,1-trichloroethane, or a mixture thereof. Acetone can be employed with either polar or non-polar systems and is readily blended with both types of solvents.

[0078] The stent is then coated with the outer biodegradable layer by dissolving the material in a suitable solvent and then coating by spraying, brushing, painting or the like.

[0079] Examples of specific coating techniques that can be employed herein include, but are not limited to, Drop-on-Demand coating techniques, MicroPen coating techniques and M³D direct-write coating technologies.

[0080] The bioadhesive can be applied to the stent so as to encapsulate the entire stent, to coat only the outside surface/diameter of the stent or coat specific regions of the stent, for example, the stent flares.

[0081] In one embodiment, the stent is provided with cavities/holes/well/pockets wherein the bioadhesive is disposed in the cavities and the biodegradable coating is applied over the top thereof to seal the bioadhesive in the cavities.

[0082] Alternatively, the stent may be coated with a silicone coating prior to application of the bioadhesive.

[0083] The stent is then loaded into the stent delivery system using conventional stent loading techniques.

[0084] The adhesive layer provides adhesion between the stent and the lumen and/or lesion. The outer biodegradable polymer layer prevents self-adhesion of the bioadhesively coated stent during handling, storage and delivery *in situ*.

[0085] The outer biodegradable polymer layer also allows the stent to be loaded into a delivery system in any conventional manner.

[0086] Once the stent is deployed in the patient's body, the biodegradable polymer layer erodes, exposing the bioadhesive layer which provides adhesion of the stent at the desired treatment site thus preventing undesirable stent migration.

[0087] The coatings can be employed on any stent including, but not limited to, endoscopic, pulmonary and vascular stents. Examples of endoscopic stents include, but are not limited to, esophageal, pancreatic, gastrointestinal and biliary stents. A specific example of a stent on which the coatings of the invention can be employed is on the Polyflex® esophageal stent available from Boston Scientific. Polyflex® stents are described in commonly assigned US Patent Publication No. 2009/00082840. Methods of loading the stents into a delivery device are also disclosed therein.

[0088] The invention may also be employed on urethral, ureteral and tracheal stents.

[0089] The above lists are intended for illustrative purposes only, and not as a limitation on the scope of the present invention.

[0090] The description provided herein is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of certain embodiments. The methods, compositions and devices described herein can comprise any feature described herein either alone or in combination with any other feature(s) described herein. Indeed, various modifications, in addition to those shown and described herein, will become apparent to those skilled in the art from the foregoing description and accompanying drawings using no more than routine experimentation. Such modifications and equivalents are intended to fall within the scope of the appended claims.

[0091] Citation or discussion of a reference herein shall not be construed as an admission that such is prior art.

**THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE
PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:**

1. A stent comprising:
 - 5 a stent body having a proximal end portion, a distal end portion, and a length extending therebetween, the stent body having an inner surface and an outer surface;
a first coating composition comprising at least one bioadhesive disposed on at least a portion of the outer surface of the stent body;
a second coating composition disposed over the first coating composition, the
10 second coating composition comprising at least one biodegradable material; and
a silicone coating disposed on said stent body, said silicone coating being located radially inward relative to said first coating composition comprising said at least one bioadhesive.
- 15 2. The stent of claim 1, wherein said at least one bioadhesive is a mucoadhesive.
3. The stent of claim 2, wherein said mucoadhesive comprises at least one member selected from the group consisting of homopolymers and copolymers of acrylic acid and crosslinked acrylic acid, polysaccharides, cellulose and mixtures thereof.
20
4. The stent of claim 2, wherein said mucoadhesive comprises a hydrogel.
5. The stent of claim 1, wherein said at least one biodegradable material is a polymer comprising at least one member selected from the group consisting of
25 polylactide and polylactide-co-glycolide.

6. The stent of claim 1, wherein said at least one biodegradable material comprises a biodegradable metallic element.
7. The stent of claim 6, wherein said biodegradable metallic element comprises at least one of iron and magnesium and alloys thereof.
8. The stent of claim 1, wherein said stent is a member selected from the group consisting of esophageal stents, pancreatic stents, biliary stents, duodenal stents, colonic stents and airway stents.
9. The stent of claim 1, wherein at least one of said proximal end portion and said distal end portion comprises a flare.
10. The stent of claim 9, wherein said distal end portion comprises said flare.
11. The stent of claim 9, wherein said at least one bioadhesive is applied to said flare.
12. The stent of claim 1, wherein said silicone coating is disposed on the inner surface of the stent body.
13. The stent of claim 1, wherein said stent body is encapsulated by said at least one bioadhesive.

14. The stent of claim 1, wherein said at least one bioadhesive is disposed on the entirety of the outer surface of the stent body.
15. The stent of claim 1, wherein said at least one bioadhesive is crosslinked.
- 5
16. The stent of claim 1, wherein said at least one bioadhesive is temporary.
17. A method of making a stent comprising the steps of:
- providing a stent having an inner surface and an outer surface;
- 10 applying a silicone coating on at least one of said inner surface and said outer surface;
- applying a bioadhesive at least to a portion of a radially outer surface of said silicone coating; and
- applying a biodegradable coating over the entirety of said bioadhesive.
- 15
18. The method of claim 17, comprising applying said silicone coating to said inner surface of said stent prior to applying said bioadhesive.
19. A stent comprising:
- 20 a stent body;
- a silicone coating disposed on said stent body;
- a first coating composition comprising at least one mucosal bioadhesive located radially outward from the silicone coating; and
- a second coating composition disposed over the first coating composition, the
- 25 second coating composition comprising at least one biodegradable material, the second

coating composition forming a substantially continuous layer over the entirety of the first coating composition.

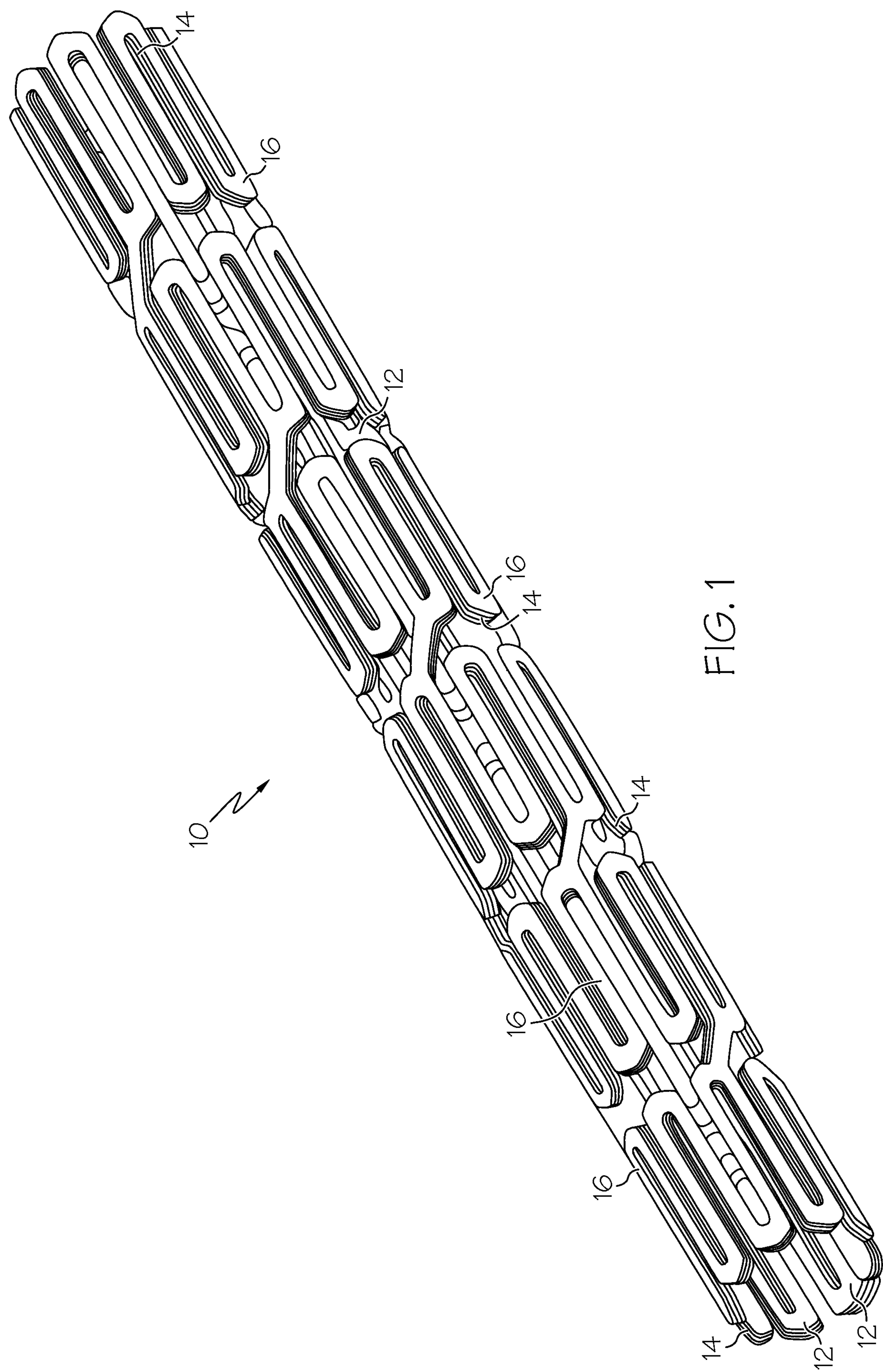


FIG. 1

2 / 9

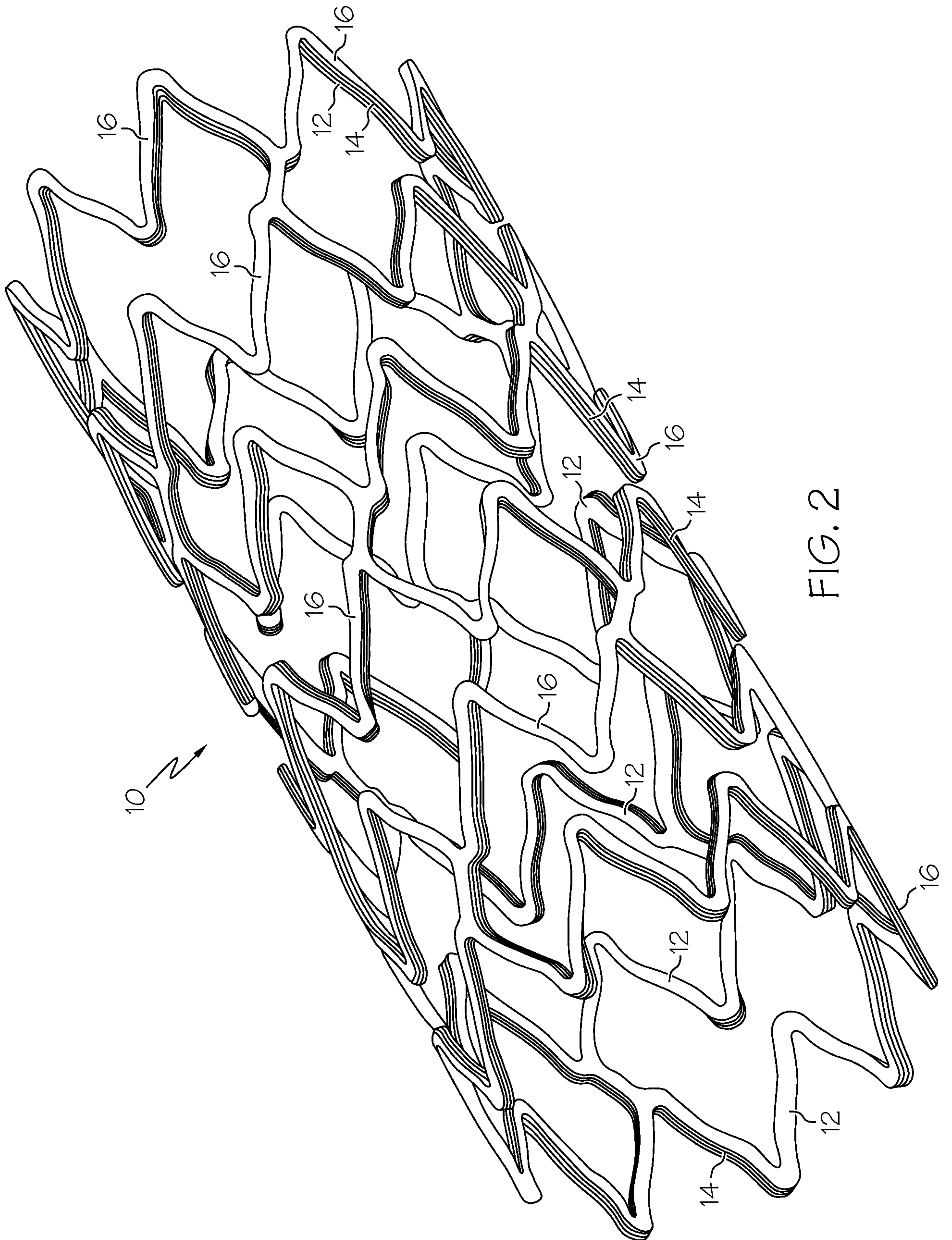


FIG. 2

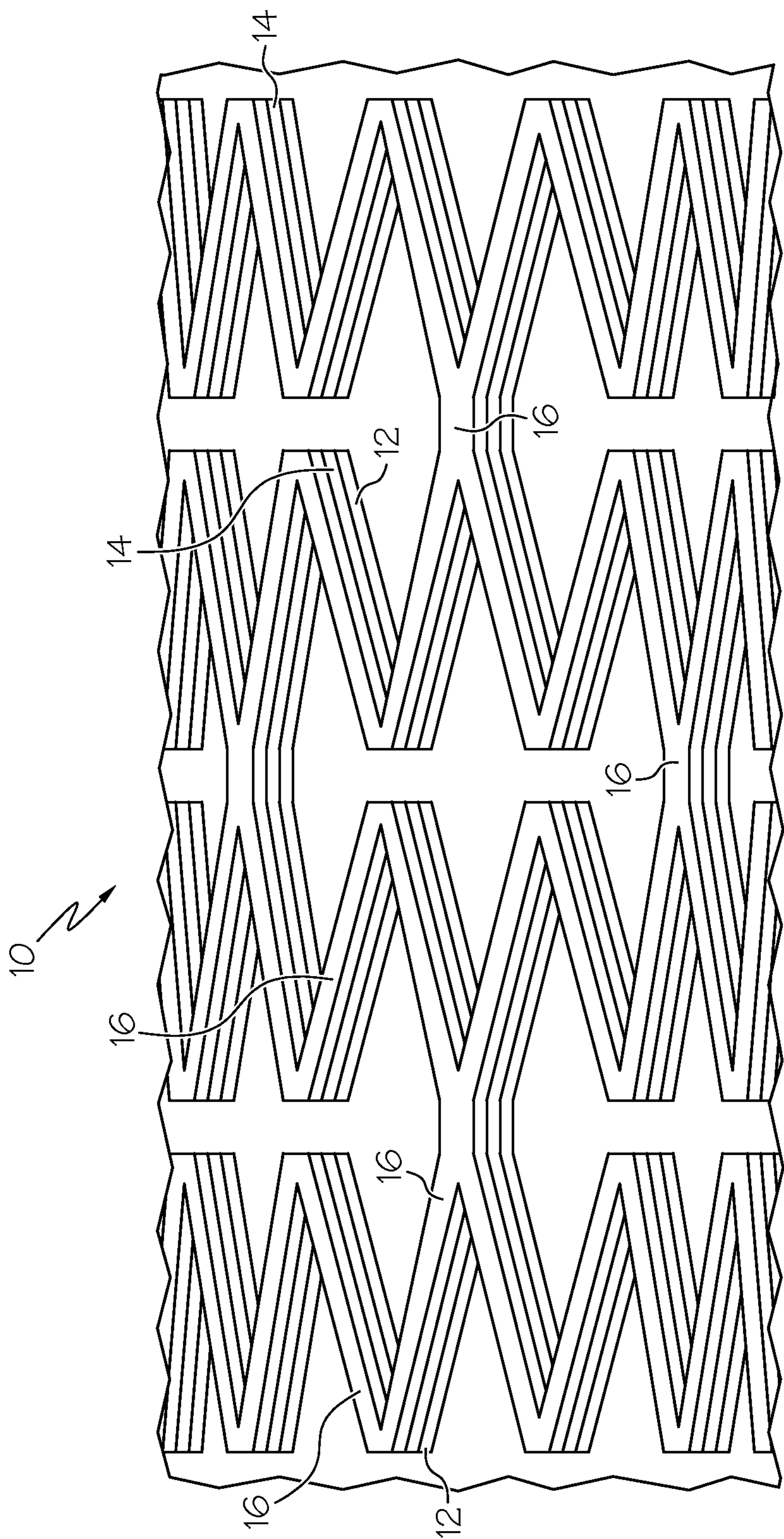


FIG. 3

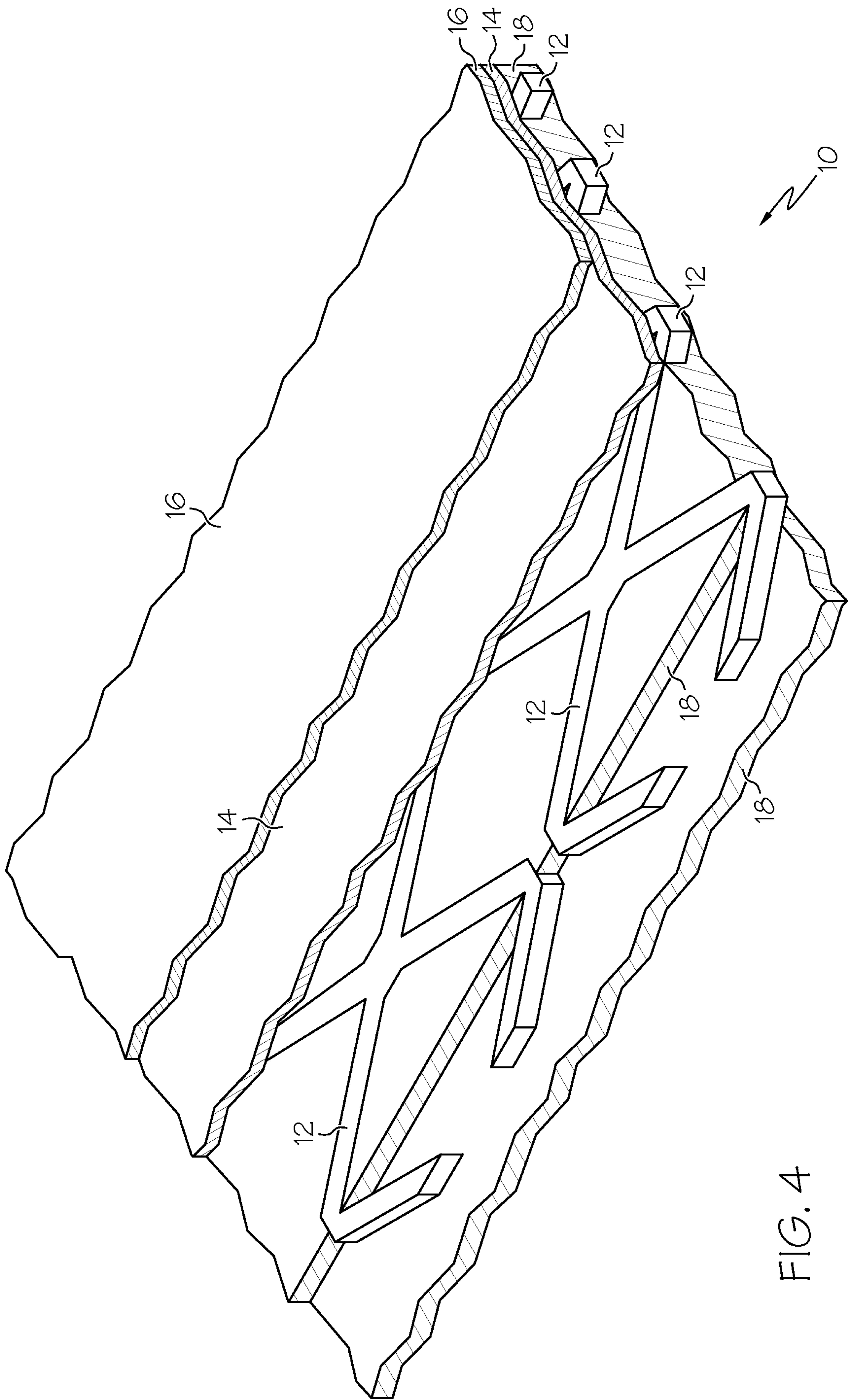


FIG. 4

5 / 9

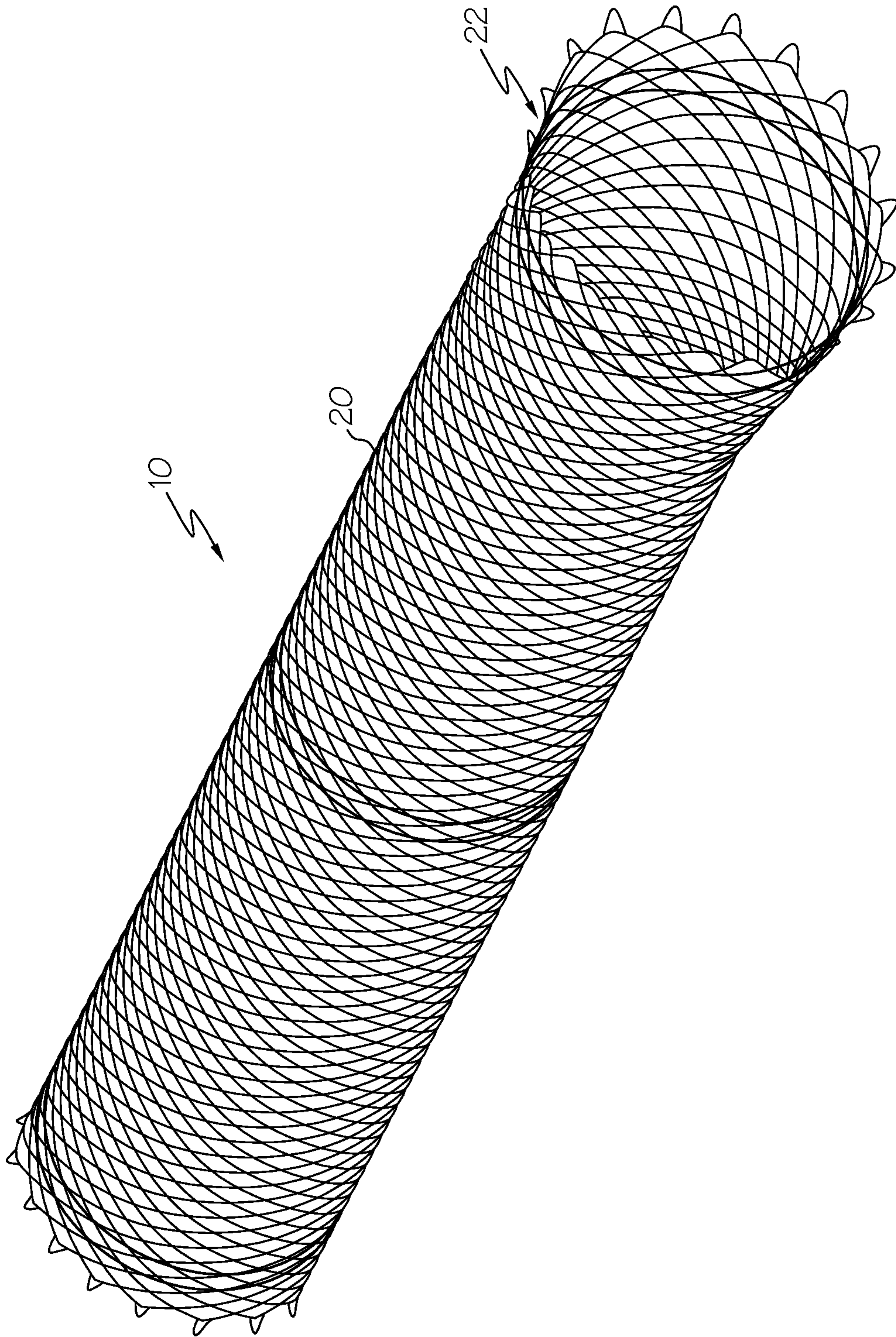


FIG. 5

6 / 9

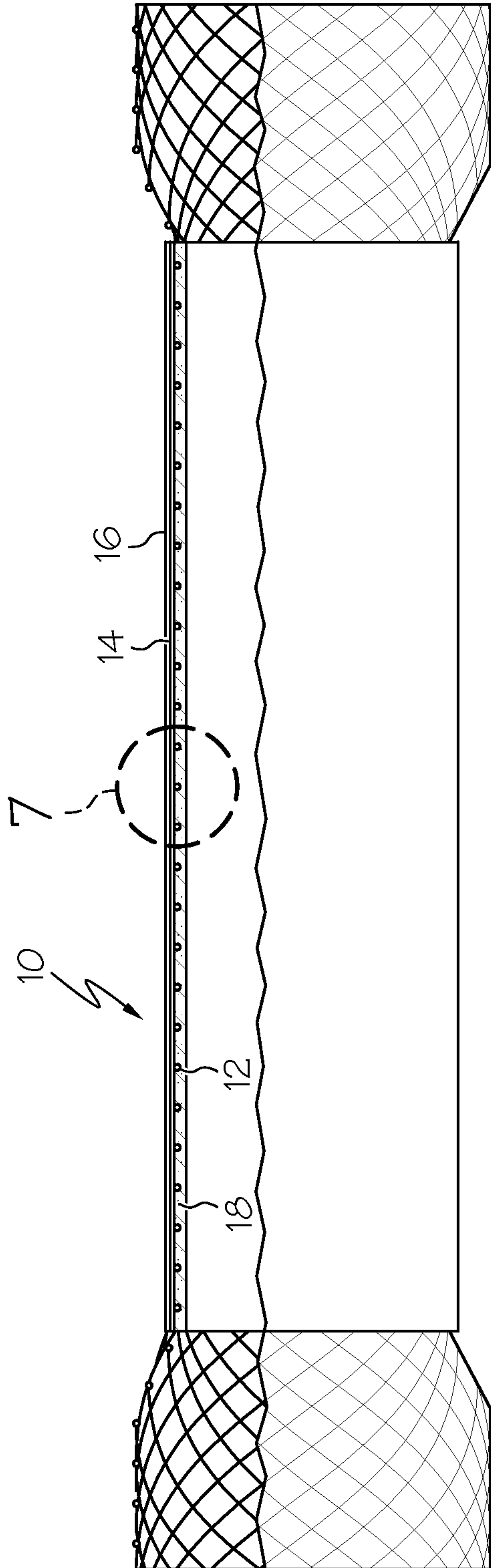


FIG. 6

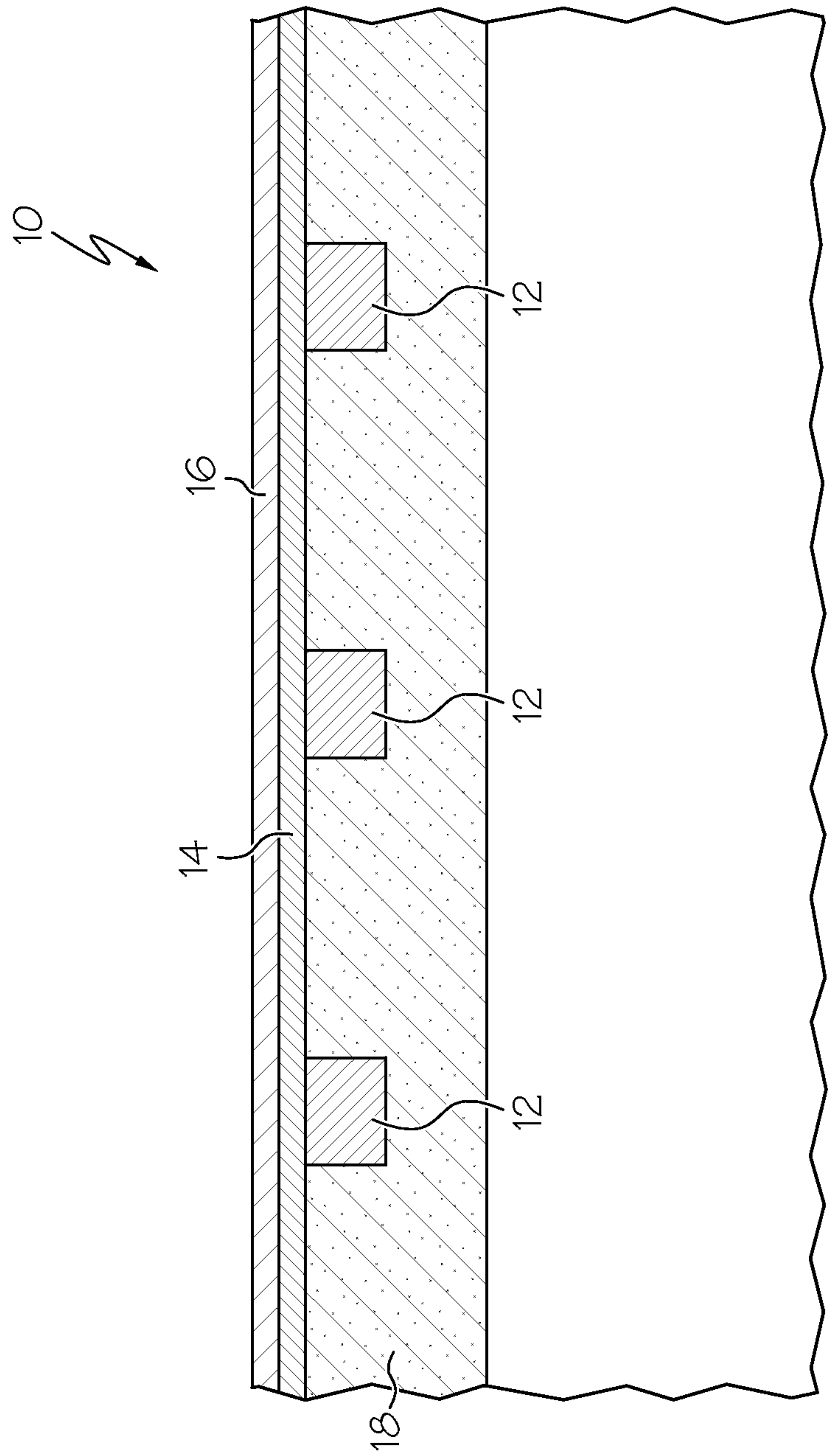


FIG. 7

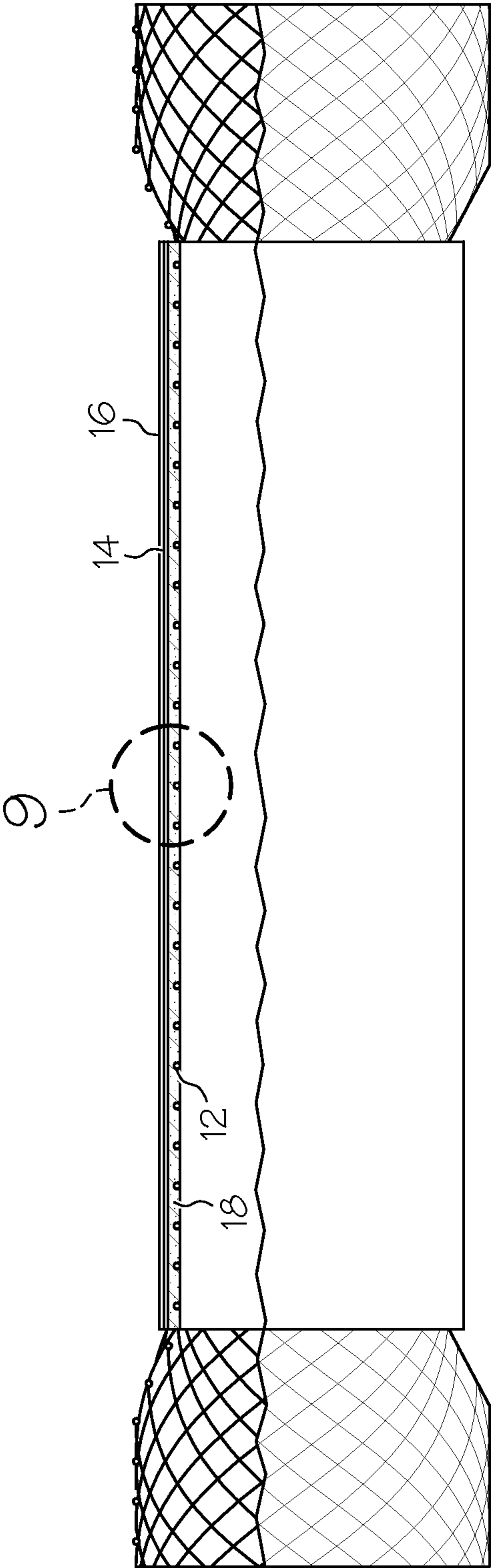


FIG. 8

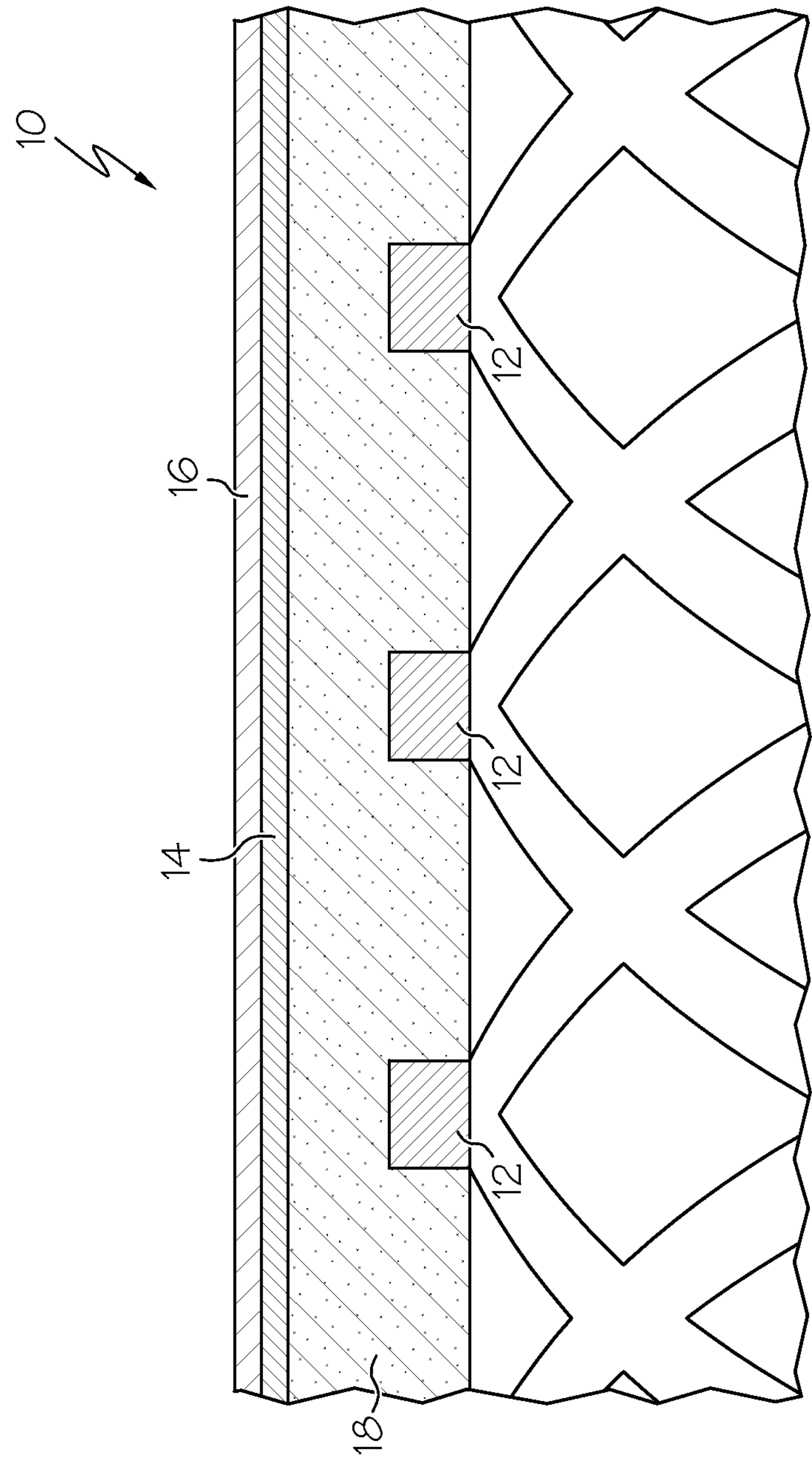


FIG. 9

