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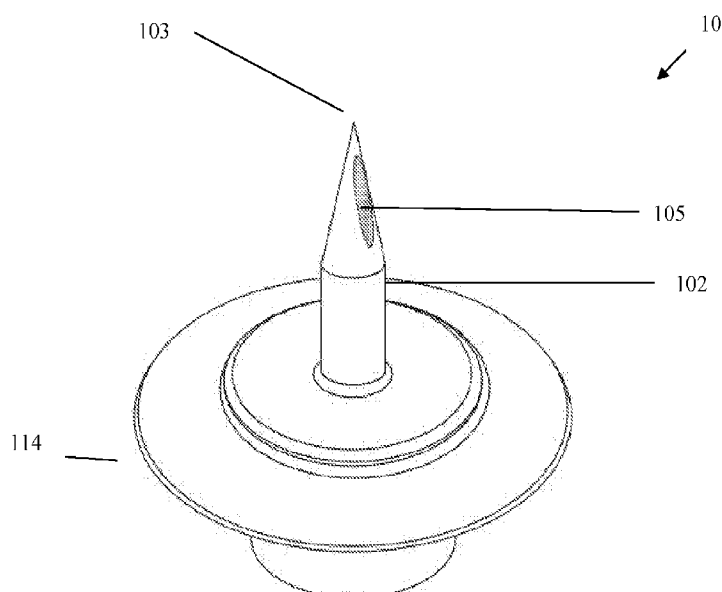
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(54) Title: ULTRA-SHARP MICRONEEDLE

FIGURE 2



(57) Abstract: A microneedle having a body including a base, shaft and pointed tip, and at least one lumen disposed within the shaft. The lumen having an opening that is offset from the tip and open to the exterior of the microneedle.

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ULTRA-SHARP MICRONEEDLE**RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Application Serial Nos. 62/834,807, filed April 16, 2019 and 62/965,701, filed January 24, 2020, the contents of each of which are incorporated herein by reference thereto.

FIELD

[0002] The disclosed subject matter describes an apparatus for controlled precision of perforating a thin membrane and delivery or aspiration of fluid. More particularly, the subject matter described is an ultra-sharp microneedle configured to produce a controlled and precisely shaped and sized perforation in a thin membrane, for example, of the inner ear. Further, the needle apparatus may be configured for safe, controlled, local injection delivery to or aspiration of fluid across the thin membrane.

GOVERNMENT FUNDING

[0003] This invention was made with Government Support Under Contracts No. R01-DC014547-03 and grant number 753600XOTO Otolaryngology GG011895 01 70003 AKL2144, awarded by the National Institute Institutes of Health. The government may have certain rights in the subject matter of this disclosure.

BACKGROUND

[0004] Symptoms such as hearing loss, tinnitus, and vertigo – which can have debilitating effects on one's quality of life –are quite prevalent in the general population. These

symptoms, either alone or in combination, can be reflective of underlying otologic disorders that necessitate specific medical or surgical intervention. Despite previous research and innovation, effective treatments for common inner ear illnesses such as sudden or progressive sensorineural hearing loss (SNHL) and Ménière's disease have remained particularly elusive, in part due to the anatomic inaccessibility of the cochlea. Protected by one of the hardest bones in body, the cochlea is nearly an impenetrable structure frustrating both bacteria and clinician trying to gain access to it. As a result, a means for reliable delivery of agents into the inner ear for therapeutic purposes remains a formidable challenge.

[0005] Various methods of intracochlear delivery have been developed to access this elusive anatomical space, but these methods all involve breaching the inner ear and consequently risk hearing impairment from traumatic disruption of the cochlea. Thus, despite extensive research and promising new technologies, a safe, reliable method for intracochlear delivery remains to be developed. Likewise, the challenge of delivering large quantities of medication or sampling of large volumes of biological fluids remains.

[0006] Due to pharmaceutical limitations, such as solubility and dosage, it is of great interest to displace large amounts of liquids in the cochlea. Since the cochlea is small in scale, it becomes difficult to inject "large" amounts since an amount equal to what has been introduced needs to flow out. If the outflow happens slowly, this can increase intracochlear pressure, possibly causing harm to the delicate structures of the inner ear. Hence, it is important that this process is facilitated in a controlled way. For example, it would be useful to be able to inject a liquid therapeutic agent into the inner ear while simultaneously withdrawing an equal amount of liquid from the inner ear.

[0007] In order to acquire samples for diagnostic purposes, volumes of greater than 1 μL are typically necessary for analysis. Volumes of this size are quite significant with regards to the total size of the cochlea, and can create problems if not replaced, especially with volumes over 3 μL . This can be crucial for some potential diagnostic tests which require large amounts of biofluids to be processed. Artificial perilymph is known to be a good substitute for perilymph, and can be created easily. It would be useful to be able to withdraw a sample of perilymph from a subject's inner ear while simultaneously replacing it with an equal volume of artificial perilymph.

SUMMARY

[0008] An ultra-sharp microneedle is provided. The microneedle is sized for use in the eye, ear and central nervous system. In some applications, the microneedle has multi-lumen for simultaneous delivery and sampling into a fixed volume of biological tissue.

[0009] The microneedle generally includes a base disposed at a proximal end of the microneedle body and a tip disposed at the distal end of the microneedle body. A cylindrical shaft having a longitudinal body is disposed between the base and the tip. In some embodiments, the base, shaft and tip may be integral. The base can have a cylindrical shape configured to mount onto a medical instrument, such as a syringe. For example, the microneedle may be mounted on a 30 gauge syringe. The base has a width greater than the width of the tip, and in some embodiments is also greater than the shaft. In other words, for a cylindrical base and shaft, the diameter of the base is greater than the diameter of the shaft. Further the base is sized to mount and securely engage an instrument such as a driver or syringe. In this regard, mounting on a hollow or solid material of any cross-sectional shape may be achieved. Likewise, the mount

may also consist of one or more lumen that would allow the delivery or aspiration of varying amounts of material through each lumen.

[0010] The at least one lumen defines a channel that provides fluid communication and passage through at least the shaft of the needle. The lumen is disposed within at least the shaft cylindrical body of the microneedle. An opening is defined at the distal end of the lumen body and also at a loci of the shaft body to communicate to the exterior of the microneedle. The opening is offset from a central longitudinal axis of the tip. The central longitudinal axis of the tip may also be the central longitudinal axis of the shaft. In this regard, the opening would also be offset from the shaft central axis.

[0011] The at least one lumen has a body may extend through the base to the shaft of the microneedle. Thus, the lumen may terminate prior to or proximate the tip of the microneedle.

[0012] The tip includes a sharp, pointed apex. The tip may have 500-nm curvature of radius. The shaft may have a total length of about 350 micrometers. The maximum tip diameter may be about 10-20 microns. In some embodiments, there is one sole lumen, in other embodiments, there are at least a first and second lumen.

[0013] The shaft in some embodiments has a tapered longitudinal, cylindrical body configured with a taper along a portion of its length.

[0014] In a second embodiment, the a microneedle comprising a base, a shaft, a sharp tip and two or more lumens wherein a first lumen provides fluid communication and passage from a first portion of the base of the microneedle to a first locus proximate to the tip of the microneedle and a second lumen provides fluid communication and passage from a second portion of the base of the microneedle to a second locus on the shaft of the microneedle. The first locus and the

second locus are diametrically opposed on the microneedle, e.g., shaft. The microneedle may have a maximum tip diameter of about 10-20 microns.

[0015] In some embodiments, the microneedle shaft is configured with a taper along a portion of its length. The taper comprises a gradual taper having a gradual decrease in diameter along the length of the microneedle. The taper may comprise a stepped taper with abrupt changes in diameter that serve as reinforcing ribs or ledges.

[0016] The microneedle distal portion comprises a narrow sharp tip, the proximal end may comprise a wide base and a shaft between the tip and the base. The base of the distal portion may comprise one or more projections or barbs that engage the distal side of the membrane after penetration through the membrane and is held in place thereby. The base may be configured to physically engage a driver device capable of creating temporary perforations in an anatomic membrane. The may be configured to penetrate an anatomic membrane and simultaneously inject a first liquid into the distal side of the membrane and withdraw a second liquid from the distal side of the membrane. The anatomic membrane may be a membrane of the inner ear.

[0017] In some embodiments, one lumen is an aspirating lumen which is connected to a suction device, such as a vacuum source, to suction a fluid from the distal side of the membrane. The same or a second lumen may an injection lumen which is connected to an injection device, such as a syringe, to inject a fluid into the distal side of the membrane.

[0018] In another aspect, a medical device comprises the microneedle described in any of the embodiments above, wherein the base the microneedle is physically engaged with a driver device capable of creating temporary perforations in an anatomic membrane and simultaneously inject a first liquid into the distal side of the membrane and withdraw a second liquid from the distal side of the membrane. The membrane may be the round window membrane of an inner ear.

[0019] The microneedle and the driver comprise separate components that are engaged to each other to define a modular system. The medical device may further comprise an indicator to indicate when the membrane is fully penetrated by the microneedle.

[0020] In another aspect, a method of delivering a therapeutic agent through an anatomic membrane is provided. The method includes positioning a microneedle proximate the membrane wherein the microneedle is configured to penetrate the membrane. Perforating the anterior side of the membrane, dispensing a therapeutic agent at the perforation from a first lumen and withdrawing an amount of fluid from the posterior side of the membrane, wherein the amount of fluid withdrawn is substantially equivalent to the amount of the therapeutic agent injected. The withdrawal and aspiration steps can occur simultaneously.

[0021] In some embodiments, the method delivers a therapeutic agent into the cochlea and comprises positioning at least one microneedle proximate the round window membrane. The microneedle is configured to penetrate the round window membrane, and the method includes perforating the round window membrane, dispensing a therapeutic agent at said perforation(s), and withdrawing perilymph from the inner ear.

[0022] In some embodiments, the microneedle can sample microliter amounts of perilymph fluid, such as aspirating 1 microliter of perilymph fluid. Advantageously, the sampling does not cause lasting damage to hearing and heals within hours, such as 72 hours after perforation. Perforations with the microneedle described herein may also result in no hearing loss.

[0023] In another aspect, a method of sampling a bodily fluid through an anatomic membrane. The method comprises positioning a microneedle proximate the membrane wherein the microneedle is configured to penetrate the membrane, perforating the membrane, sampling the bodily fluid at said perforation via a first lumen by withdrawing an amount of fluid from the posterior side of the membrane, and dispensing a second fluid into the posterior side of the membrane that is substantially equivalent or equivalent to the amount of bodily fluid withdrawn via a second lumen.

[0024] In one embodiment, the method is for sampling a subject's perilymph from the cochlea and comprises positioning at least one microneedle proximate the round window membrane wherein the microneedle is configured to penetrate the round window membrane; perforating the round window membrane; withdrawing perilymph from the inner ear via a first lumen; and dispensing artificial perilymph into the distal side of the membrane that is substantially equivalent or equivalent to the amount of the subject's perilymph withdrawn via a second lumen.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] A detailed description of various aspects, features, and embodiments of the subject matter described herein is provided with reference to the accompanying drawings, which are briefly described below. The drawings are illustrative and are not necessarily drawn to scale, with some components and features being exaggerated for clarity. The drawings illustrate various aspects and features of the present subject matter and may illustrate one or more embodiment(s) or example(s) of the present subject matter in whole or in part.

[0026] FIGURE 1 is a schematic illustration of a microneedle in accordance with the disclosed subject matter.

[0027] FIGURE 2 is another schematic illustration of the microneedle of FIGURE 1.

[0028] FIGURE 3 is another schematic illustration of an offset lumen within the shaft of the microneedle of FIGURE 1

[0029] FIGURE 4 shows perspective views of another embodiment of a microneedle in accordance with the disclosed subject matter.

[0030] FIGURES 5A – 5D show schematic views of a microneedle in accordance with the disclosed subject matter.

[0031] FIGURES 6A and 6B shows top and cross-section schematic views of a microneedle according to an embodiment of this disclosure.

[0032] FIGURE 7A–7D show schematic views of a mold for fabricating a microneedle by two- photon templated electrodeposition according to an embodiment of this disclosure.

[0033] FIGURE 8 shows top and cross-section schematic views of a microneedle mold according to an embodiment of this disclosure, similar to the embodiment shown in FIGURES 7A–7D.

[0034] FIGURE 9 shows a view of an array of microneedles on a unitary base according to an embodiment of this disclosure.

DETAILED DESCRIPTION

[0035] Reference has been made in detail to select embodiments of the disclosed subject matter, examples of which are illustrated in the accompanying drawings. The method and corresponding steps of the disclosed subject matter will be described in conjunction with the detailed description of the system.

[0036] In one aspect, a microneedle for controlled precision of perforating a thin membrane and delivery or aspiration of fluid is provided. The microneedle may be configured to produce a controlled and precisely shaped and sized perforation in a thin membrane, for example, of the inner ear. The microneedle may achieve a safe, reliable method for intracochlear delivery.

[0037] Referring to FIGURE 1, in one embodiment the microneedle 10 generally comprises a base 101, shaft 102 and ultra-sharp, pointed tip 103. A lumen 104 having a longitudinal body is disposed within the shaft 102. The lumen 104 defines a channel for fluid communication and passageway from a first portion of the microneedle to a first opening 105 defined at the distal end of the lumen and a locus of the shaft 102, said opening 105 proximate to the end of tip 103. In this regard, first opening 105 is offset from a center longitudinal axis 110 of the shaft 102 and tip 103. Referring to FIGURES 2 and 3, in some embodiments, first opening 105 may have a diameter of about 30 micrometers, and first opening 105 is offset from the center longitudinal axis 110 of the shaft and/or tip apex by about 25 micrometers.

[0038] Referring to FIGURE 1, the base includes a first section defined by a cylindrical body 112 and skirt 114. Skirt 114 may function as a stop in certain applications. In some embodiments, base 101 further includes leg members 116, as shown in FIGURE 3.

[0039] Referring to FIGURE 3, the shaft 102 has a length extending from the base 101 to the tip 103. The first section is defined by a cylindrical, hollow body having a substantially uniform diameter. The second section is defined by a conical, shaped body defined by a taper along a portion of its length terminating at a sharp or pointed tip. In some embodiments, the tip is closed, i.e., does not have a port or opening. In some embodiments depending on the application, the microneedle may have a maximum tip diameter of about 10-20 microns. Lumen 104 extends from shaft 102 through to or through at least a portion of base 101, and has a second opening (not shown) disposed in base 101.

[0040] Base 101 is configured to mount to a commercially available standard blunt syringe. In this regard, second opening of lumen is in fluid communication with syringe and provides a channel for passage of therapeutic agent from syringe through lumen 102 to opening 105 and exterior of microneedle 10. Introduction of the lumen 104 through substantially the entire the microneedle body enables direct injection of fluids, such as therapeutics agents, from inside the syringe, and/or allows sampling of fluids from body, such as the inner ear, into the syringe structure.

[0041] In some embodiments, the outer diameter of shaft 102 is 100 micrometers and the inner diameter is 35 micrometers, the height of the microneedle from proximal end of base 101 to distal end of tip 103, or alternatively, from proximal end of shaft 102 to distal end of tip 103 is not greater than 350 micrometers. Thus, the microneedle may be configured to penetrate a thin membrane with tip 103 and is suitably sized to fit within small spaces of the anatomy, such as

the cochlear, or other sites, for local delivery of therapeutic agent or aspirate fluid, such as perilymph fluid from the inner ear. In some embodiments, the ultra-sharp microneedle has a 500-nm tip radius of curvature.

[0042] In another aspect, a dual-lumen microneedle is provided. The multi-lumen structure enables, for example, a sample of perilymph from a subject's inner ear to be withdrawn, while simultaneously replacing it with an equal volume of artificial perilymph. Thus, this application, which should not be construed to limit the microneedle to this application, permits acquisition of samples from the cochlea for diagnostic purposes, for example in volumes of greater than 1 μL , for example 3 μL or more, while simultaneously replacing the withdrawn biofluid with an equal or substantially equal volume of fluid, such as artificial biofluid. Thus, increased intracochlear pressure, and harm to the delicate structures of the inner ear may be minimized, inhibited or prevented.

[0043] Referring to FIGURE 4, in another aspect, a multi-lumen microneedle 10' having a first lumen 104a' and a second lumen 104b' disposed within shaft 102' of the microneedle is provided. The first lumen 104a' has a first opening 105a' and second opening 106a' and defines a first channel therebetween. The first channel defined by first lumen provides fluid communication and passageway from a first portion of the microneedle to first opening 105a' defined at the distal end of the lumen 105a' and at a first locus of shaft 102' proximate the tip 103'. As shown the shaft may be hollow as depicted in FIGURE 1 -3 or only partially hollow, for example, hollow portions created by the one or more lumen, as depicted in FIGURE 4. The one or more lumen may extend through the shaft or the entire microneedle including base 101. Each individual lumen could run to near the tip of the microneedle, or it could run only a portion of the way up the shaft as described.

[0044] Opening 105a' is offset from the center longitudinal axis 110' of the shaft 102' and tip 103'. The second lumen 104b' defines a second channel for fluid communication and passageway from a second portion of the microneedle to opening 105b' defined at the distal end of the lumen 104b' and at a second locus of shaft 102' proximate tip 103. In one embodiment, first opening 105a' associated with lumen 104a' is disposed at a first locus that is diametrically opposed to the disposition of the second opening 105b' of second lumen 104b' at the second locus. Lumen 104b' further includes opening 106b' extending through base 101', for example, through the skirt 114' to the exterior of the microneedle 10'. In this regard, lumen 104b' may withdraw fluid from a subject after penetration with microneedle 10' and dispel said withdrawn fluid to the exterior of the subject and microneedle 10'.

[0045] FIGURE 5A–5D show schematic views of a microneedle according to an embodiment of this disclosure, similar to the embodiment shown in FIGURE 4, wherein solid lines denote visible aspects of the microneedle and dashed lines denote invisible aspects of the microneedle, for example portions of the microneedle on the interior of the microneedle. Referring to FIGURE 5A a first lumen 104a' provides fluid communication and passage from a first portion of the base of the microneedle to a first locus proximate to the tip of the microneedle and a second lumen provides fluid communication from a second portion of the base of the microneedle to a second locus on the shaft of the microneedle. FIGURE 2B shows a top schematic view of the microneedle. FIGURE 5C shows a side schematic view of the microneedle, viewed along line 5C shown in FIGURE 5B. FIGURE 5D shows a side schematic view of the microneedle, viewed along line 5D shown in FIGURE 5B.

[0046] FIGURE 6 shows top and cross-section schematic views of a microneedle according to an embodiment of this disclosure, similar to the embodiment shown in FIGURE 1.

The upper image shows a top schematic view of the microneedle, wherein solid lines denote visible aspects of the microneedle and dashed lines denote invisible aspects of the microneedle, for example portions of the microneedle on the interior of the microneedle. The bottom image shows a cross-section view of the microneedle wherein the structure of the microneedle has been cut away along line A–A shown in the upper image. Solid (i.e. polymerized) portions of the microneedle are shown as hashed areas. The lumens are shown as non-hashed.

[0047] Microneedles according to embodiments of this disclosure may have the following dimensions.

Microneedle portion	Range	Example
Tip radius of curvature	less than 3 μm	1.5 μm
Shaft diameter	75 to 150 μm	100 μm
Base diameter	300 to 450 μm	405 μm
Needle height	300 to 500 μm	430 μm
Total structural height	400 to 650 μm	585 μm

[0048] In another aspect, a method of delivering a therapeutic agent through an anatomic membrane is provided. The method comprises positioning the microneedle, described herein, proximate the membrane wherein the microneedle is configured to penetrate the membrane; perforating the membrane; dispensing a therapeutic agent at said perforation from a first lumen; and withdrawing an amount of fluid from the distal side of the membrane that is equivalent to the amount of the therapeutic agent injected. For example, the method may deliver a therapeutic agent into the cochlea and comprises positioning at least one microneedle proximate the round window membrane wherein the microneedle is configured to penetrate the round window

membrane; perforating the round window membrane; dispensing a therapeutic agent at said perforation(s); and withdrawing perilymph from the inner ear.

[0049] In another aspect, thus, a method of sampling a bodily fluid through an anatomic membrane. The method comprises positioning a microneedle proximate the membrane wherein the microneedle is configured to penetrate the membrane; perforating the membrane; sampling the bodily fluid at said perforation via a first lumen by withdrawing an amount of fluid from the distal side of the membrane; and dispensing a second fluid into the distal side of the membrane that is equivalent to the amount of bodily fluid withdrawn via a second lumen.

[0050] In one embodiment, the method is for sampling a subject's perilymph from the cochlea and comprises positioning at least one microneedle proximate the round window membrane wherein the microneedle is configured to penetrate the round window membrane; perforating the round window membrane; withdrawing perilymph from the inner ear via a first lumen; and dispensing artificial perilymph into the distal side of the membrane that is equivalent to the amount of the subject's perilymph withdrawn via a second lumen.

[0051] Since the cochlea has a fixed volume, fluid could be aspirated from the lumen exiting near the base of the microneedle at the same time a therapeutic is injected out of the lumen exiting near the tip. Alternatively if the goal is aspiration without injection of a therapeutic, aspiration could occur from one of the lumina while artificial perilymph (or another "inert" substance) is injected through the other. This method could maintain the same volume of fluid within the cochlea thus minimizing pressure changes within the cochlea during such interventions. Or, the aspiration and injection flow rates and tidal volumes could be prescribed not to be the same to introduce purposely a change in pressure in the closed volume. Of course these same principles would apply if more than two lumina are in the microneedle.

[0052] The microneedles described herein may be fabricated using Two Photon Polymerization Lithography (2PP) techniques. (Nanoscribe, GmbH) (Material used: IP-S photoresist by Nanoscribe GmbH). Two-Photon Polymerization (2PP) is a new technology suited for the fabrication of nearly arbitrary 3D micro- and macro-structures. Many items can be produced by either subtracting materials, such as machining or carving, or by adding materials, for example 3D printing. With two-photon polymerization, a photosensitive material is provided and very short pulses of laser light are used to build structures within that material. Once the structure is done, the non-polymerized material is removed, by for example washing the workpiece with a suitable solvent. Using this method, complex shapes can be created that would be impossible with routine 3D printing.

[0053] In contrast to conventional 3D printing, 2PP is not limited to a layer-wise fabrication of the desired structure. In fact, it is an inherently 3D process technology. 2PP technology is based on a process where light triggers a chemical reaction, leading to polymerization of a photosensitive material. Polymerization is a process in which monomers or weakly cross-linked polymers (liquid or solid) interconnect and form three-dimensional network of highly cross-linked polymer (solid). Photoinitiators, molecules which have low photo dissociation energy, are often added in order to increase the material photosensitivity. Absorption of a photon in the photoreactive material leads to a bond cleavage (photo dissociation) and formation of highly reactive radicals. Absorption of a UV photon breaks C-C bond and results in the formation of two radicals, which react with the monomer, e.g. methyl methacrylate, and initiate radical polymerization. The reaction is terminated when two radicals react with each other.

[0054] 2PP is made possible by tightly focusing femto-second laser pulses into a transparent photopolymer. The femtosecond laser radiation induces a highly localized chemical reaction leading to polymerization of the photosensitive material. The photon-polymerization triggered by the laser pulses is strongly confined to the focal volume as the underlying process. Two- Photon Absorption (TPA) can only occur if the intensity is sufficiently large. As a consequence, the site of the reaction i.e. the solidification of the material is located in the tiny focal volume.

[0055] For 3D fabrication, the focal volume is scanned in 3D space followed by a solvent wash to separate the rest of the (nonpolymerized) photopolymer from the solidified 3D structure. In addition to being a true 3D process, 2PP is not limited to the optical diffraction limit as the photon-polymerization is a threshold process. By adjusting the photon dose only slightly beyond the polymerization threshold, feature sizes in the order of 100 nm can be achieved.

[0056] Freeform microlenses and microoptics used in 2PP allow for the fabrication of more complex topographies, particularly non-spherical or free-form designs. The photosensitive material is typically supported on a substrate such as silicon, borosilicate glass or fused silica, and the substrate may be transparent or opaque. Following creation of the microneedle(s) by 2PP and removing the nonpolymerized material, the microneedle(s) can be separated from the substrate. In some embodiments, the microneedle can be separated from the substrate by leaving a portion of the photopolymer adjacent to the substrate nonpolymerized, which is then removed by the solvent wash. Alternatively, portions of the microneedle, such as a portion of the base, may comprise a substrate that the polymerized microneedle remains adhered to after fabrication. Because the fabrication process may take a significant amount of time, such as hours

or even days, it is desirable to perform the 2PP process in a way that can make more than one microneedle at a time.

[0057] It may also be possible to create similar microneedles using two-photon templated electrodeposition, which means the microneedles will then be fully metallic. This fabrication process directly links three-dimensional (3D) modeling and simulation with microscale printing and replication. The process involves micromolds fabricated by 3D stereolithography directly from CAD drawings, which are then used to provide shaped metal microneedles using electrodeposition techniques. Alternatively, the molds may be prepared by 2PP.

[0058] FIGURE 7A shows a perspective schematic view of mold 700 for manufacturing a plurality of microneedles. As illustrated, in one embodiment, the mold comprises multiple cavities 701 -709 arranged in a 3 by 3 array (for example but not limitation) for preparing microneedles according to this disclosure. The microneedles in this embodiment are similar in design to the microneedles shown in FIGURES 1 through 6. The microneedles manufactured in mold 700 are metallic. A first lumen provides fluid communication from a first portion of the base of the microneedle to a first locus proximate to the tip of the microneedle and a second lumen provides fluid communication from a second portion of the base of the microneedle to a second locus on the shaft of the microneedle. FIGURE 7B shows a top schematic view of the microneedle mold. FIGURE 7C shows a side schematic view of the microneedle mold, viewed along line 7C shown in FIGURE 7B. FIGURE 7D shows a side schematic view of the microneedle, viewed along line 7D shown in FIGURE 7B.

[0059] FIGURE 8 shows top and cross-section schematic views of a microneedle mold according to an embodiment of this disclosure, similar to the embodiment shown in FIGURE 8A-8D. The upper image shows a top schematic view of the microneedle mold, wherein solid

lines denote visible aspects of the microneedle mold and dashed lines denote invisible aspects of the microneedle, for example portions of the microneedle cavities on the interior of the microneedle mold. The bottom image shows a cross-section view of the microneedle mold wherein the structure of the microneedle mold has been cut away along line B–B shown in the upper image. The manufacturing process can be summarized as described below.

[0060] High precision 3D molds can be manufactured via two-photon lithography or two-photon polymerization. The fabrication method starts with manufacturing of the molds on a conductive substrate. We have shown that microneedles with 0.5 micrometer radius of curvature tips can be manufactured. Using the same order of magnitude feature sizes, the molds are made in the negative image of the desired needles by curing photoresist using two-photon lithography. The uncured photoresist is then stripped away by means of chemical treatment to leave cavities or voids in the mold. The substrate would then be left bare only at locations where the tips of the microneedles will be.

[0061] The substrate needs to have a conductive surface to enable electrodeposition of metal. Every part of the conductive surface, except for the bare parts inside the patterned molds will need to be masked before being submerged into the electrolyte for electrodeposition. The mold- substrate assembly would then be submerged into an electrolyte and electrochemical deposition of metal would occur, filling the cavities or voids inside the molds, taking the shape prescribed by the voids.

[0062] After submersion, electrodeposition is conducted by flowing current or applying voltage to the system, growing the needles, such as by tip-first, into the voids of the molds. The current density may be controlled by predicting the necessary current through mathematical models or keeping a constant voltage throughout the process.

[0063] Electrochemical deposition of metal into the mold can be accomplished using a rotating disk electrode. The bulk of the microneedle can be made by electrodeposition of a metal such as copper.

[0064] After the molds are filled with metal, the molds can be stripped away by means of heat treatment or chemical treatment. The metal needles may be released as a final step by electropolishing or etching the underlying layer of material. Because copper is not biocompatible, the microneedles are treated to put conformal layers of 1.5 microns of nickel and 100nm of immersion gold to ensure biocompatibility. Conformal coating can be verified via energy-dispersive X-ray spectroscopy.

[0065] Hence, full metal needles will be manufactured in the shape of the voids inside the 3D lithographed molds, and this process in itself provides design freedom that is well suited and sometimes critical for a variety of applications.

[0066] In some embodiments, the microneedle(s) may be prepared in an array comprising a plurality of microneedles on a conductive substrate.

[0067] The microneedles of this disclosure may be used singly or as part of an array of a plurality microneedles 900 on a unitary base such as shown in FIGURE 9. In the embodiment of FIGURE 9, seven microneedles are shown but any number of microneedles may be used such as from 2 to 10 or more. The unitary base may include a portion in fluid communication with the injection lumens of the plurality of the microneedles and a reservoir holding a therapeutic agent or replacement fluid, such as artificial perilymph for inner ear applications, depending on whether the microneedles are used for delivery of a therapeutic agent or for sampling a subject's bodily fluid. A second portion of the unitary base may be in fluid communication with the

aspiration lumens of the plurality of the microneedles and a vacuum source and a receptacle for collecting fluids aspirated from the distal side of the membrane.

[0068] Various materials may be used to manufacture the microneedle. For example, in some embodiments, the microneedles are composed of only metallic material. For example, the microneedle may be fabricated from copper and may have a coating, such as but not limited to metals, ceramics, polymers, organics, etc. In one embodiment, the coating is gold. The coatings could consist of multiple layers and multiple materials and material classes.

[0069] Although the microneedle is described for the use the thin membrane of the inner ear, this application should not be construed as limiting. The microneedles described and embodied herein may be used for other applications. Further, the microneedle may be modified to suit a plethora of needs, for sampling or delivering across different physiological structures. One of ordinary skill in the art would also appreciate that the selection of materials to fabricate the microneedle may be modified to create more rigid structures to penetrate other membrane and anatomies.

[0070] While the disclosed subject matter is described herein in terms of certain non-limiting exemplary embodiments, those skilled in the art will recognize that various modifications and improvements may be made to the disclosed subject matter without departing from the scope thereof. Moreover, although individual features of one embodiment of the disclosed subject matter may be discussed herein or shown in the drawings of the one embodiment and not in other embodiments, it should be apparent that individual features of one embodiment may be combined with one or more features of another embodiment or features from a plurality of embodiments. In addition to the specific embodiments claimed below, the disclosed subject matter is also directed to other embodiments having any other possible

combination of the dependent features claimed below and those disclosed above. As such, the particular features presented in the dependent claims and disclosed above can be combined with each other in other manners within the scope of the disclosed subject matter such that the disclosed subject matter should be recognized as also specifically directed to other embodiments having any other possible combinations. Thus, the foregoing description of non-limiting example embodiments of the disclosed subject matter has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the disclosed subject matter to those embodiments disclosed herein.

[0071] It will be apparent to those skilled in the art that various modifications and variations can be made in the method and system of the disclosed subject matter without departing from the spirit or scope of the disclosed subject matter. While the disclosures herein are described for accessing the cochlea, the issue of localized drug delivery across anatomic barriers to enclosed spaces extends beyond the field of otolaryngology.

CLAIMS

What is claimed:

1. A microneedle comprising:

a base disposed at a proximal end of the microneedle body and a tip disposed at the distal end of the microneedle body, a shaft having a longitudinal body disposed between the base and the tip, wherein the base has a width greater than the width of the tip,

at least one lumen defining a channel providing fluid communication and passage disposed within at least the shaft of the microneedle body, and

an opening defined at the distal end of the lumen and at a loci of the shaft, wherein the opening is off-set from the central longitudinal axis of the tip.

2. The microneedle of claim 1, wherein the at least one lumen has a body extending through the base to the shaft of the microneedle.
3. The microneedle of claims 1 or 2, wherein the at least one lumen has a body that terminates proximate to the tip.
4. The microneedle of claims 1 or 2 or 3, wherein the base is configured to mount a medical instrument.
5. The microneedle of claim 4, wherein the medical instrument is a syringe.
6. The microneedle of claims 1, 2, 3, or 4, wherein the base has a width greater than the shaft.
7. The microneedle of any of the preceding claims, wherein the base, shaft and tip are integral to form microneedle body.

8. The microneedle of any of the preceding claims, wherein the tip includes a sharp, pointed apex.
9. The microneedle of any of the preceding claims, wherein the offset is about ____.
10. The microneedle of any of the preceding claims, wherein the tip has a 500 nm radius of curvature.
11. The microneedle of any of the preceding claims, wherein the shaft is about 350 micrometers.
12. The microneedle of any of the preceding claims, wherein the at least one lumen is only one sole lumen.
13. The microneedle any of the preceding claims, wherein the at least one lumen is two separate lumen.
14. The microneedle of any of the preceding claims, wherein the maximum tip diameter is about 10-20 microns.
15. The microneedle of any of the preceding claims, wherein the shaft has a tapered longitudinal, cylindrical body configured with a taper along a portion of its length.
16. A microneedle comprising a base, a shaft, a sharp tip and two or more lumens wherein a first lumen provides fluid communication and passage from a first portion of the base of the microneedle to a first locus proximate to the tip of the microneedle and a second lumen provides fluid communication and passage from a second portion of the base of the microneedle to a second locus on the shaft of the microneedle.
17. The microneedle of claim 16 wherein the first locus and the second locus are diametrically opposed on the microneedle.

18. The microneedle of claim 16 or 17 wherein the microneedle has a maximum tip diameter of about 10-20 microns.
19. The microneedle of claim 16-18 wherein the microneedle is configured with a taper along a portion of its length.
20. The microneedle of claim 19 wherein the taper comprises a gradual taper having a gradual decrease in diameter along the length of the microneedle.
21. The microneedle of claim 19 wherein the taper comprises a stepped taper with abrupt changes in diameter that serve as reinforcing ribs or ledges.
22. The microneedle of any of the preceding claims 16-21, wherein a distal portion comprises a narrow sharp tip, the proximal end comprises a wide base and a shaft between the tip and the base.
23. The microneedle of claim 22 wherein the base of the distal portion may comprise one or more projections or barbs that engage the distal side of the membrane after penetration through the membrane and is held in place thereby.
24. The microneedle of claim any of the preceding claims 16-24, wherein the base is of the microneedle is configured to physically engage a driver device capable of creating temporary perforations in an anatomic membrane.
25. The microneedle of claim any of the preceding claims 16-24, configured to penetrate an anatomic membrane and simultaneously inject a first liquid into the distal side of the membrane and withdraw a second liquid from the distal side of the membrane.
26. The microneedle of claim 25 wherein the anatomic membrane is a membrane of the inner ear.
27. The microneedle of claim 25 wherein one lumen is an aspirating lumen which is connected to a suction device, such as a vacuum source, to suction a fluid from the posterior side of the membrane.

28. The microneedle of claim any of the preceding claims 16-27, wherein one lumen is an injection lumen which is connected to an injection device, such as a syringe, to inject a fluid into the posterior side of the membrane.
29. A medical device comprising a microneedle of any of any of the preceding claims 16-28, wherein the base the microneedle is physically engaged with a driver device capable of creating temporary perforations in an anatomic membrane and simultaneously inject a first liquid into the posterior side of the membrane and withdraw a second liquid from the posterior side of the membrane.
30. The medical device of claim 29 wherein the membrane is the round window membrane of an inner ear.
31. The medical device of claim 29 wherein the microneedle and the driver comprise separate components that are engaged to each other to define a modular system.
32. The medical device of claim 29 further comprising an indicator to indicate when the membrane is fully penetrated by the microneedle.

FIGURE 1

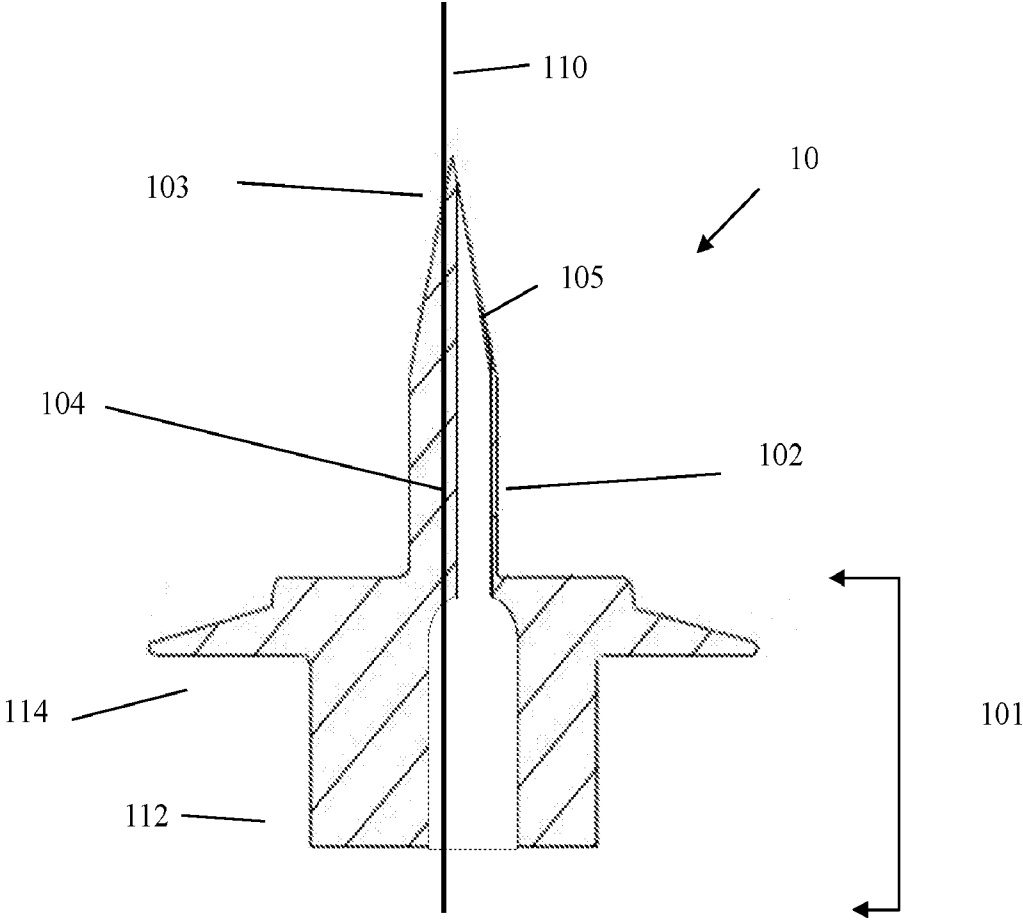


FIGURE 2

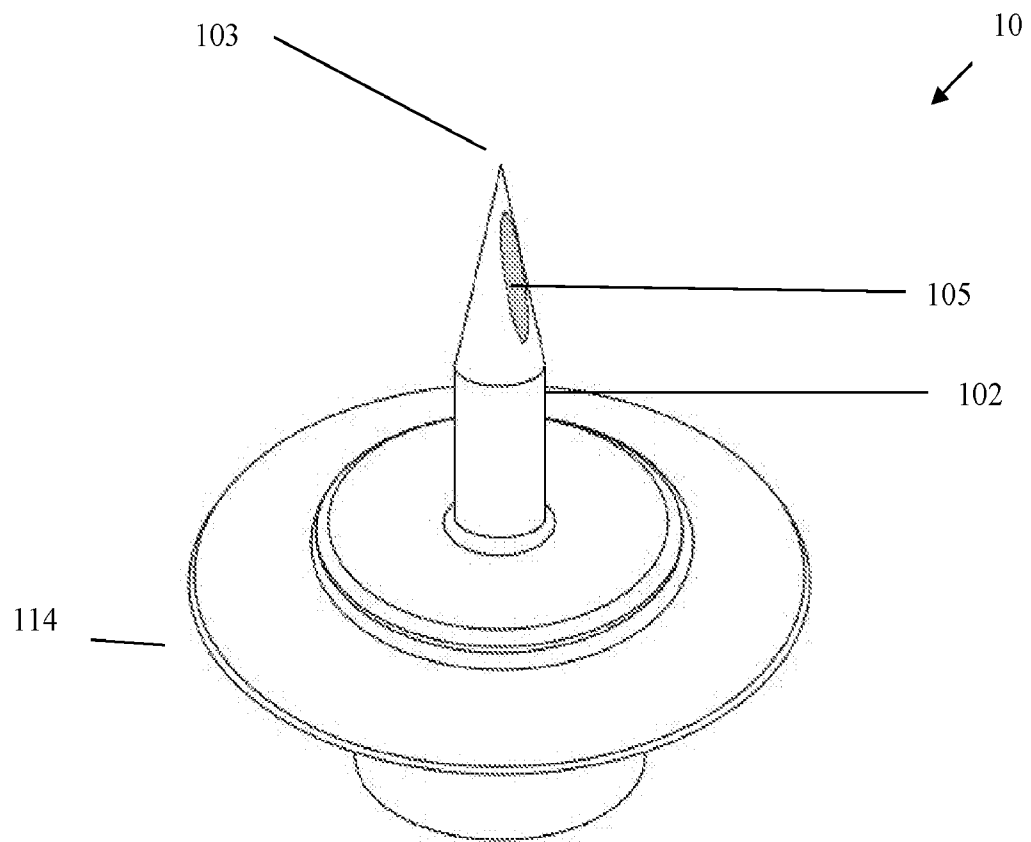


FIGURE 3

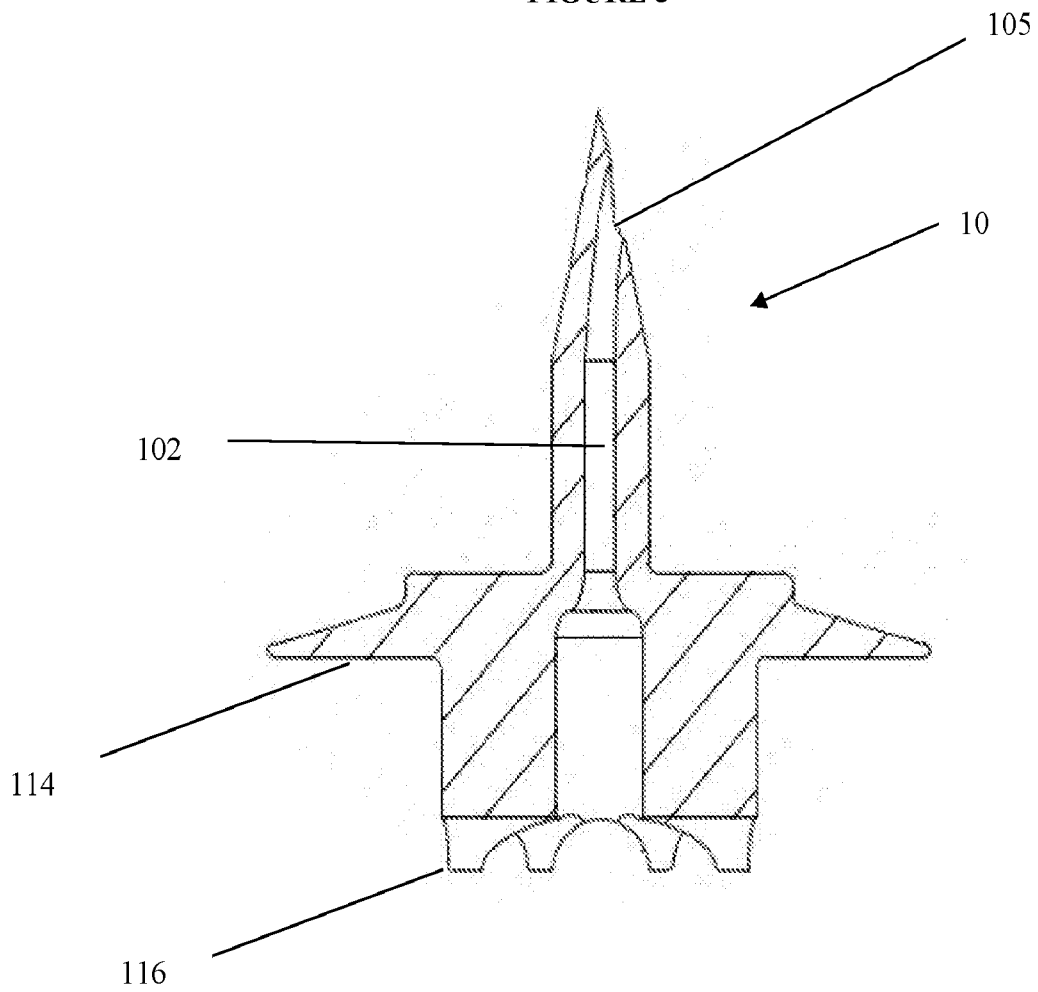


FIGURE 4

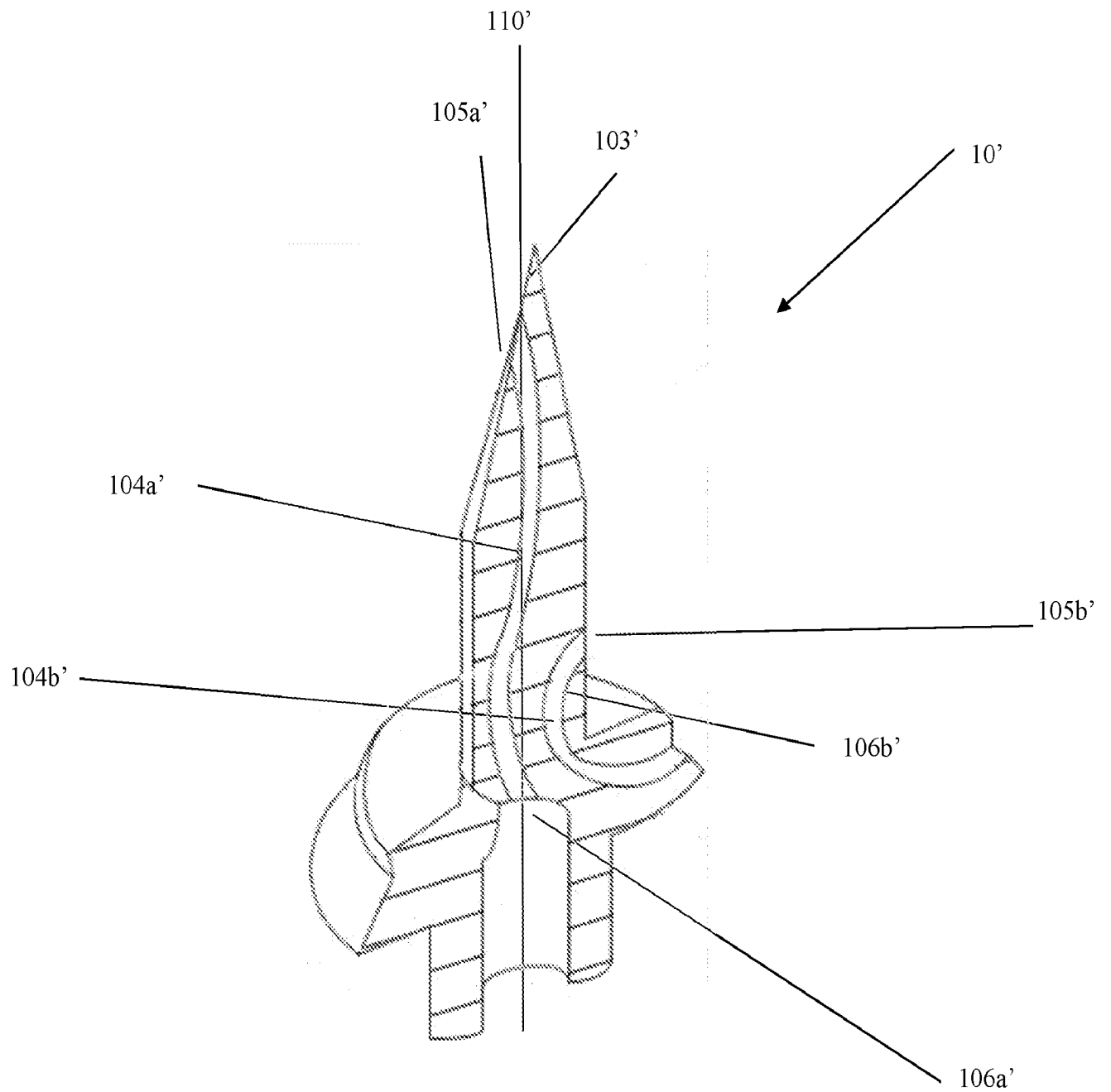


FIGURE 5A

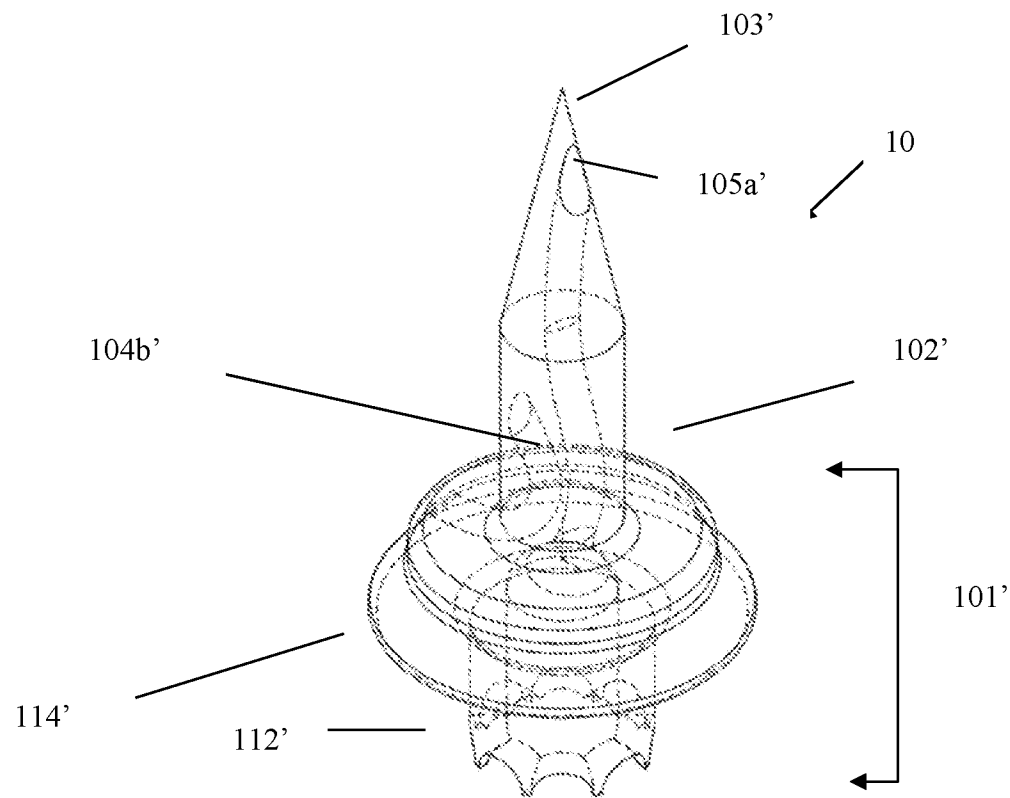


FIGURE 5B

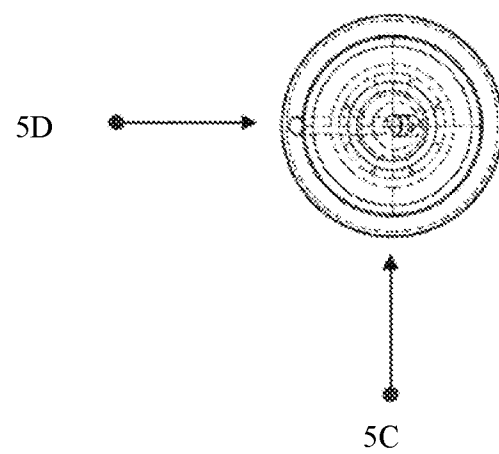


FIGURE 5C

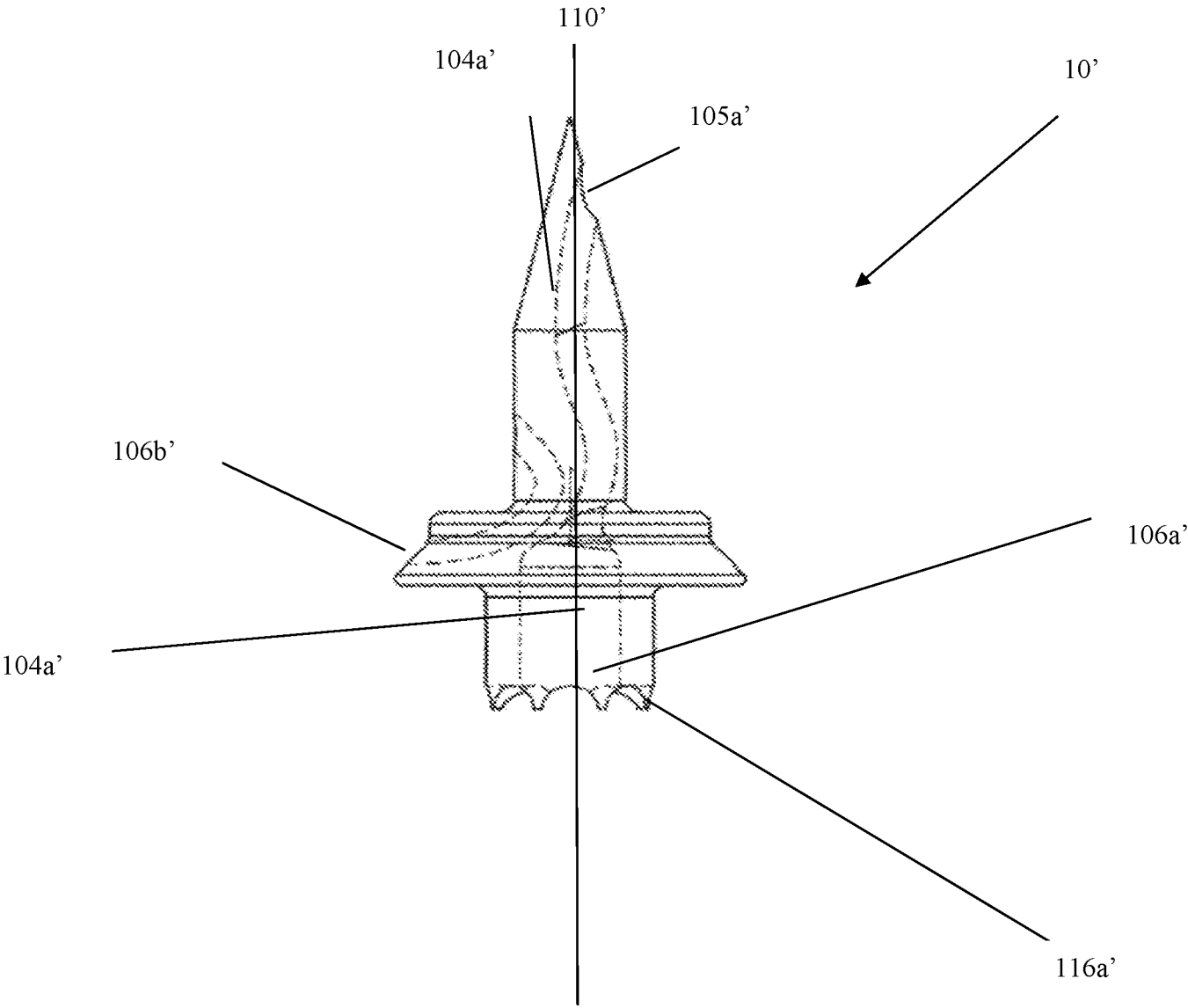


FIGURE 5D

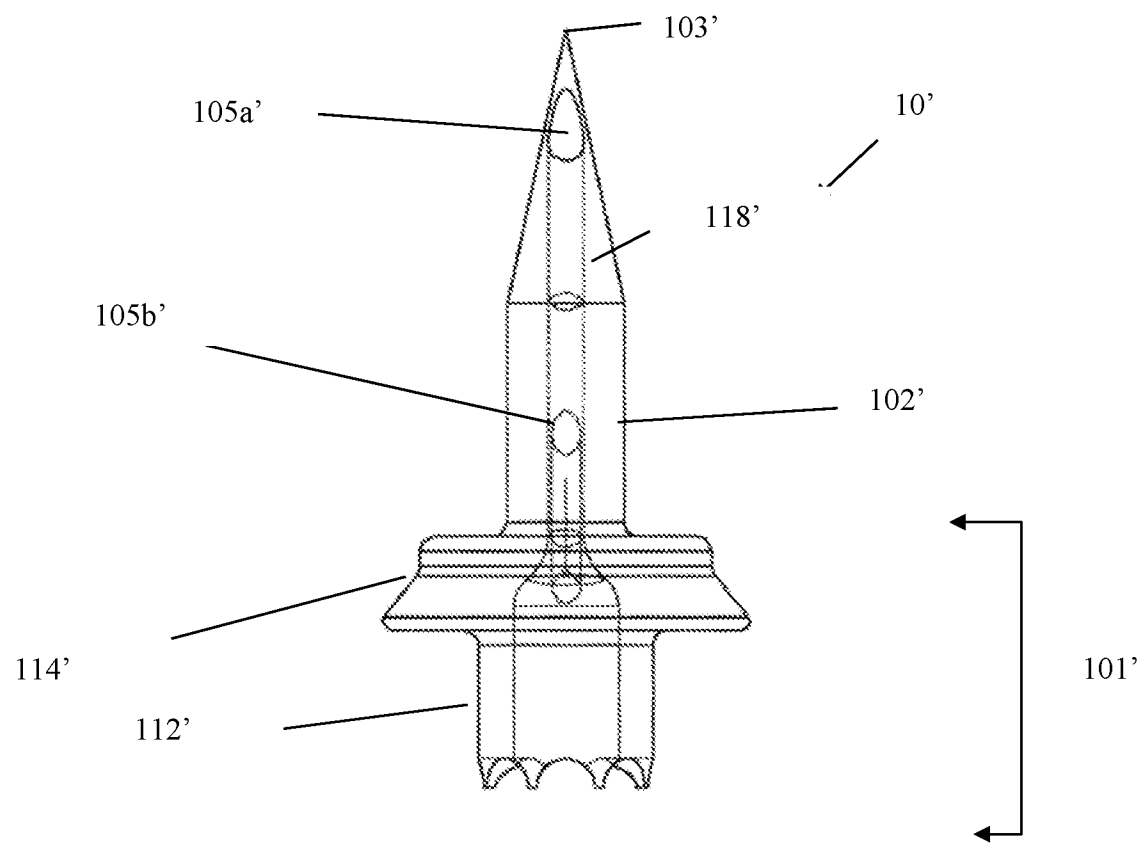


FIGURE 6A

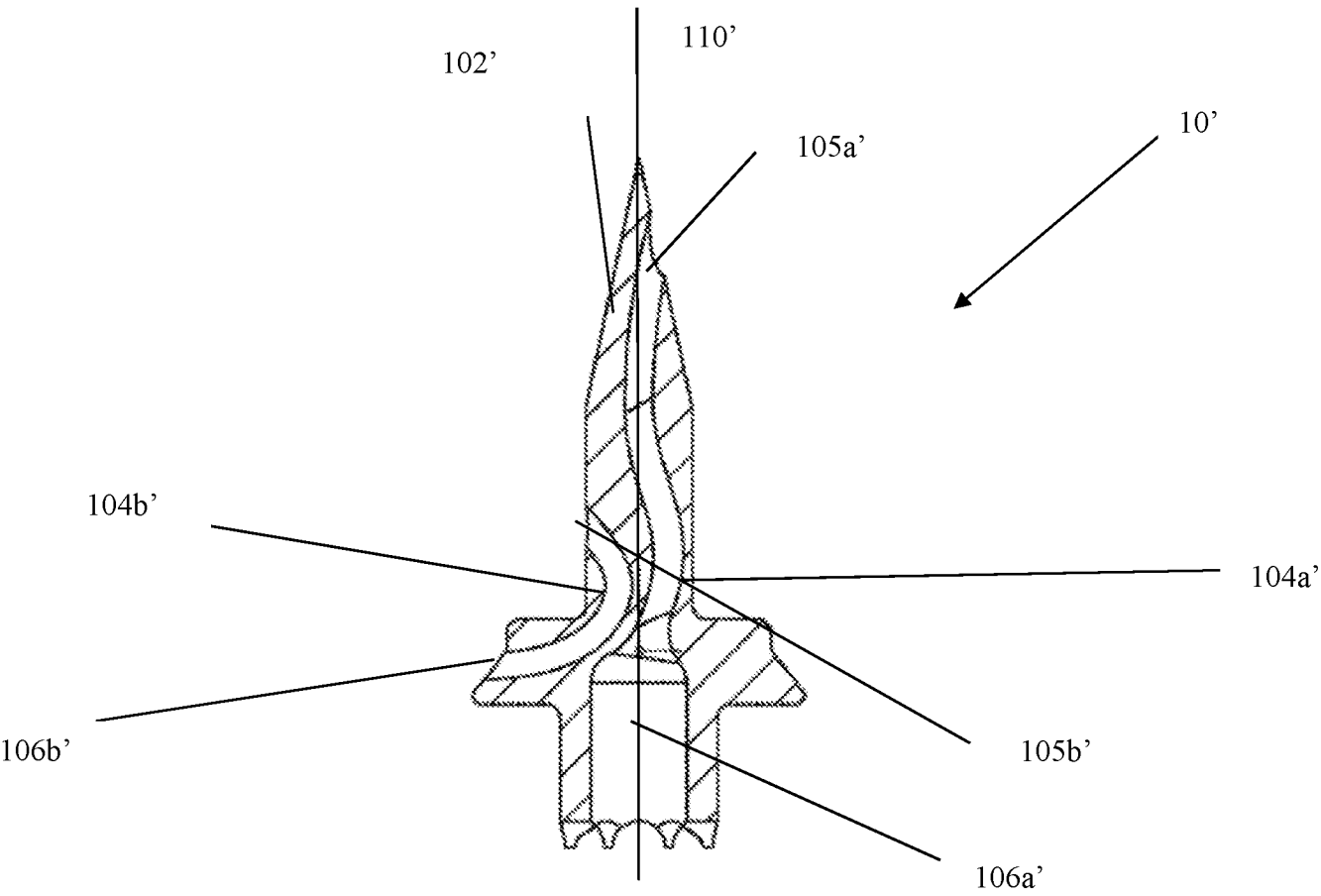


FIGURE 6B

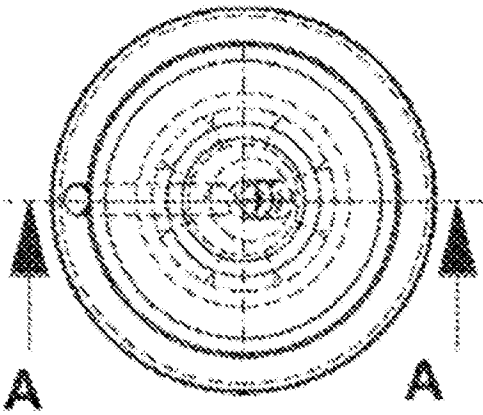


FIGURE 7A

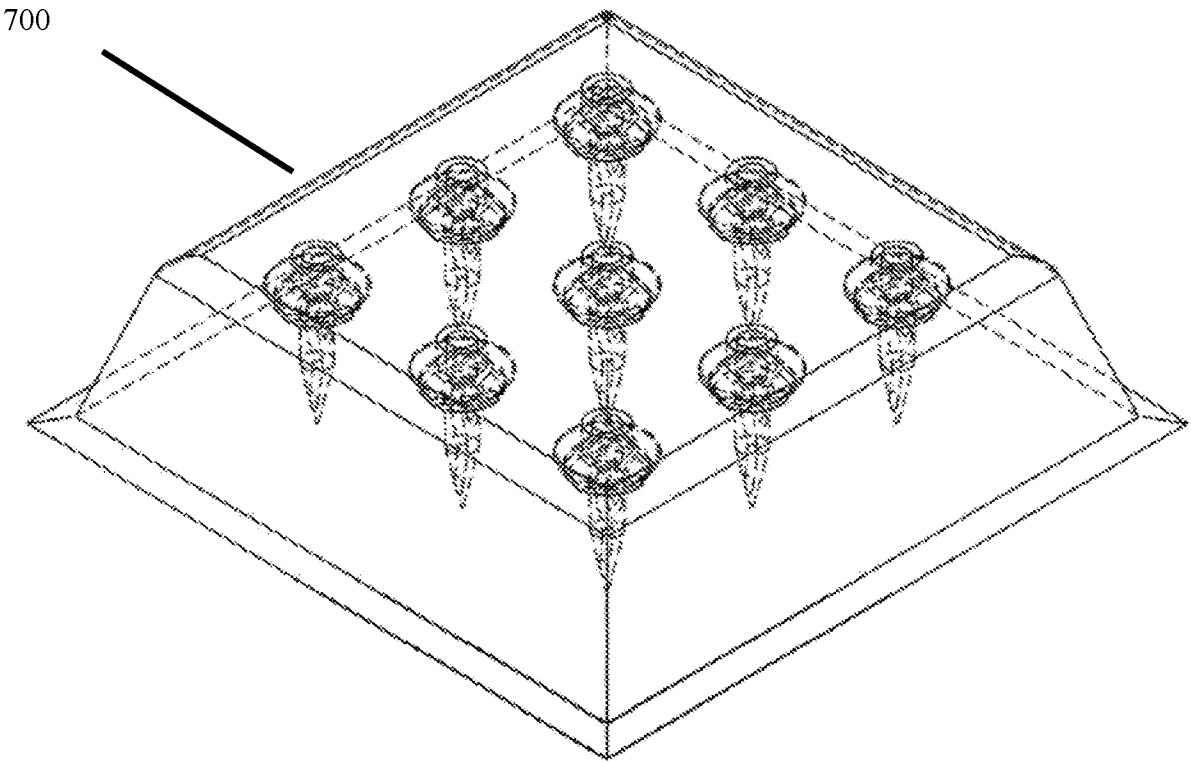
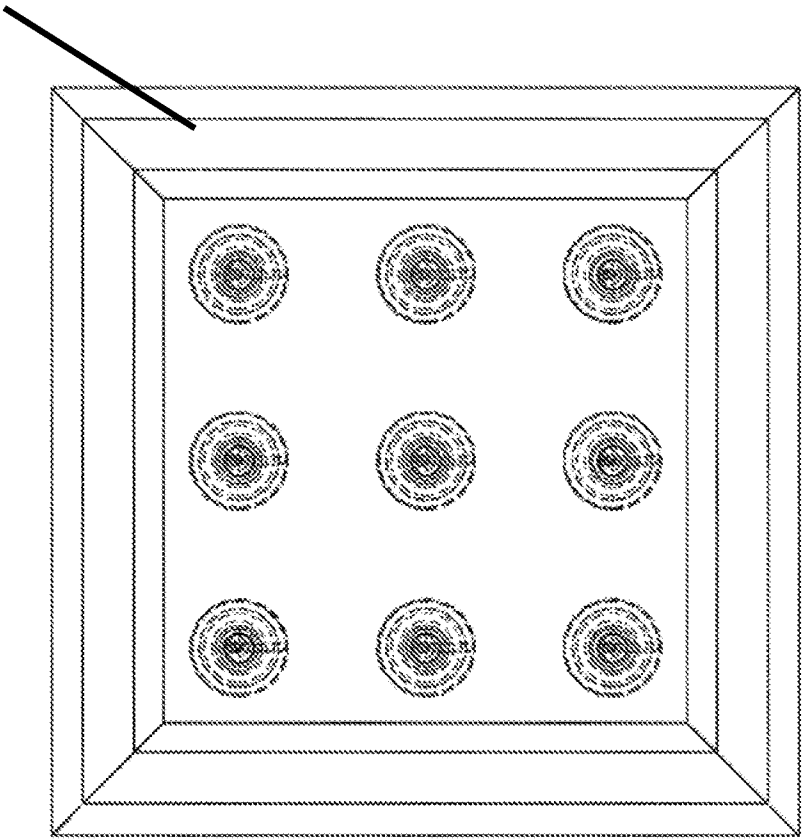
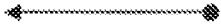


FIGURE 7B

700



7C



7D



700

FIGURE 7C

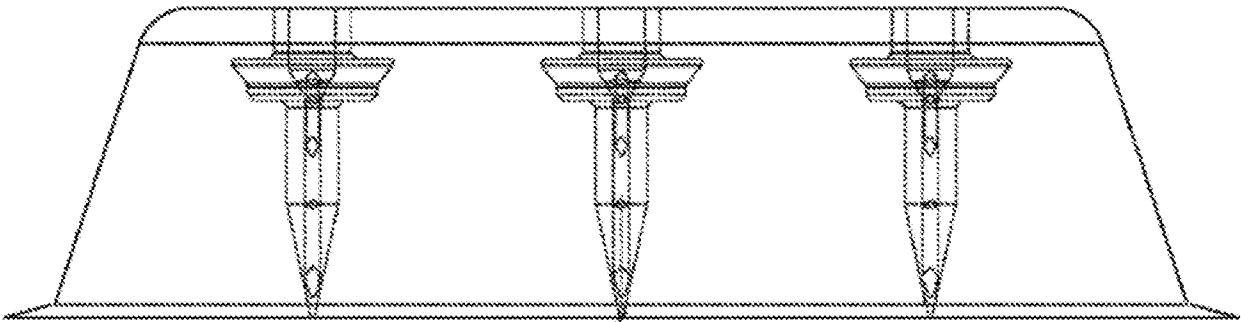


FIGURE 7D

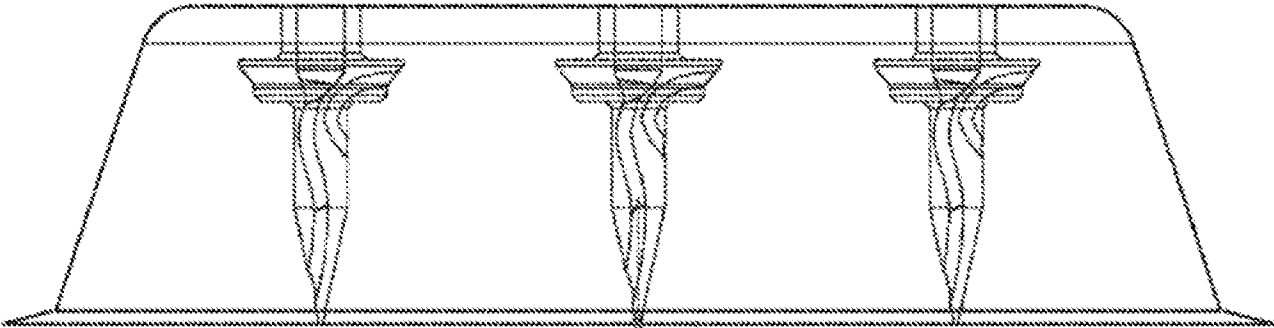


FIGURE 8

700

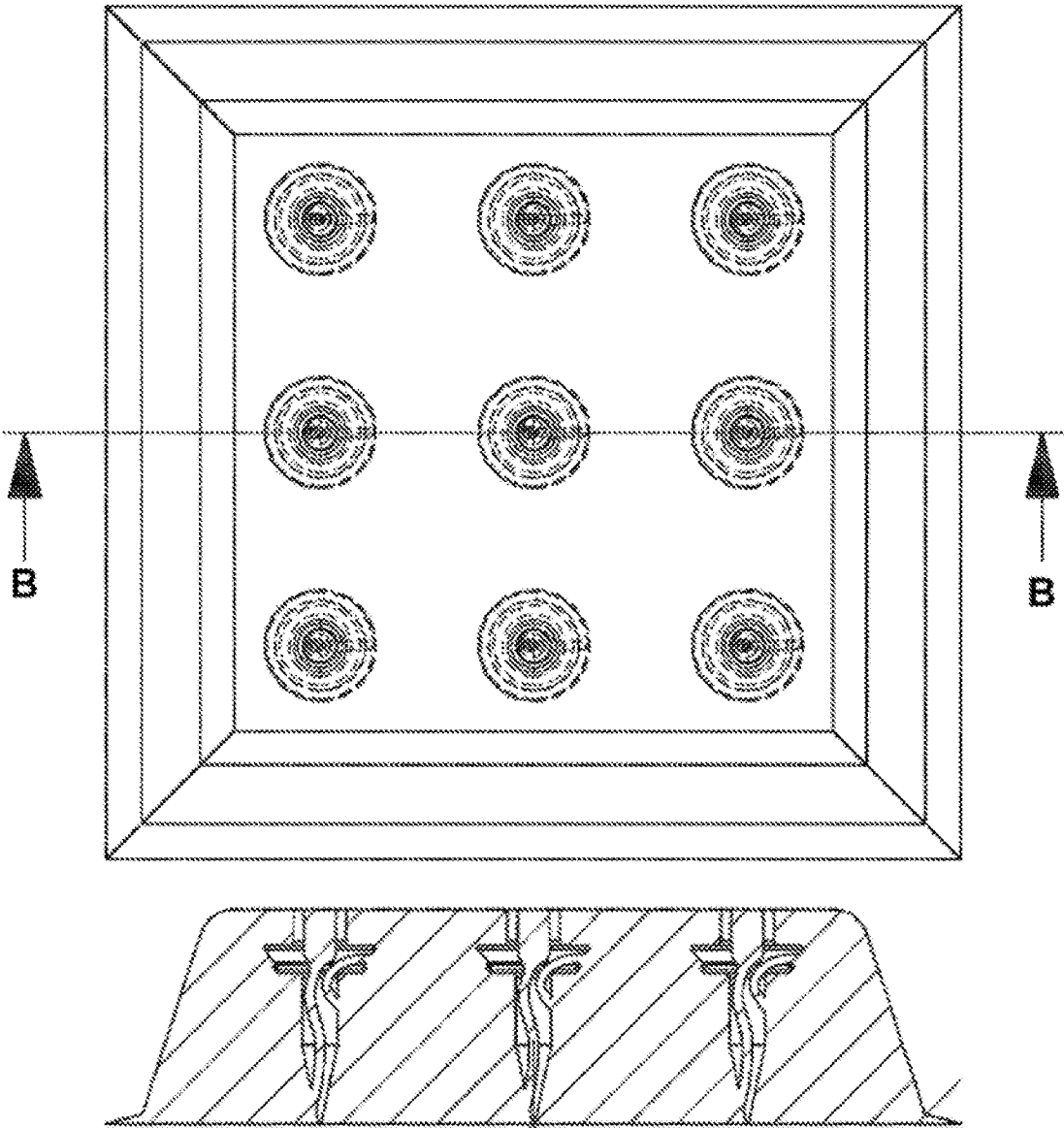
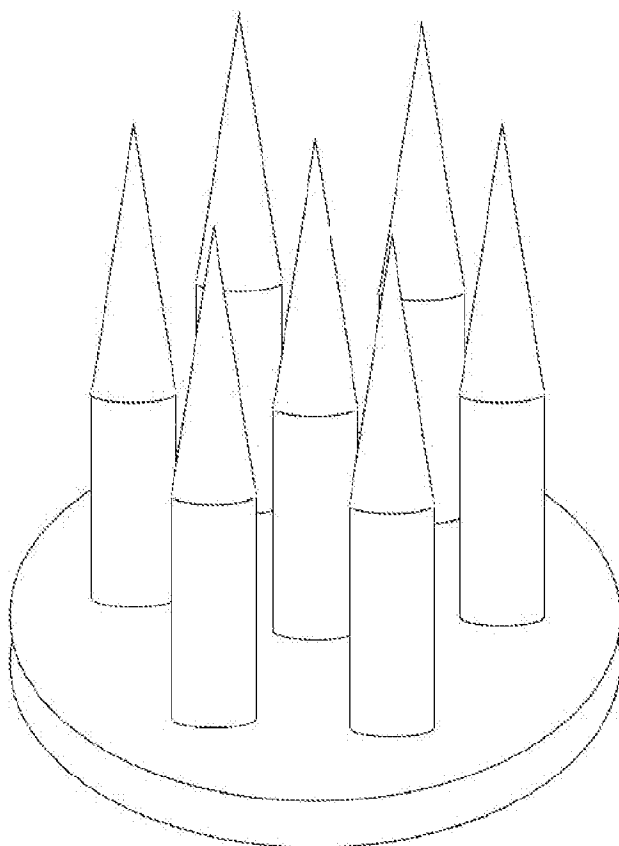


FIGURE 9

900



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/28497

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61M 5/32; A61M 37/00; A61M 5/00 (2020.01)

CPC - A61M 37/0015; A61M 5/32; A61M 37/00; A61M 5/00

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0172820 A1 (CANNEHAN, F et al.) 05 July 2012; Figure 3	1-3, 16-18
A	US 2009/0093776 A1 (YUE, R et al.) 09 April 2009; Entire Document	1-3, 16-18
A	WO 2017/143149 A1 (POLYMER TECHNOLOGY SYSTEMS) 24 August 2017; Entire Document	1-3, 16-18

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

02 June 2020 (02.06.2020)

Date of mailing of the international search report

16 JUL 2020

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/28497

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-15, 19-32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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