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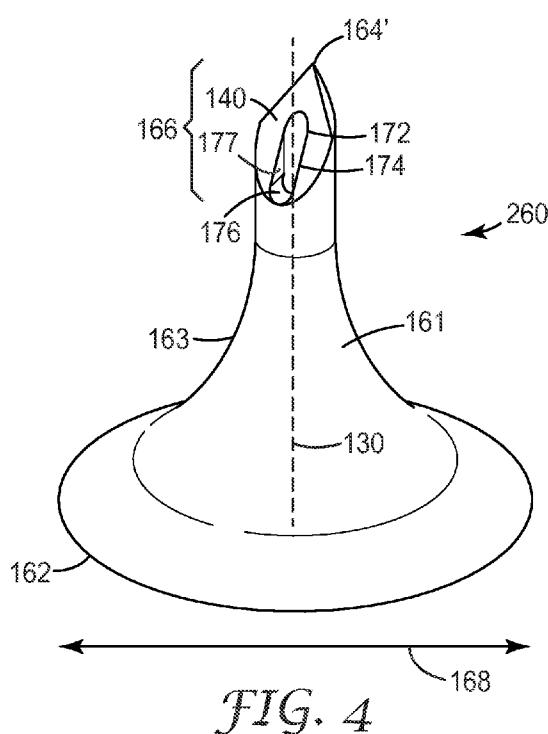
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[Continued on next page]

(54) Title: HOLLOW MICRONEEDLE WITH BEVEL OPENING



(57) Abstract: An article having at least one microneedle (160, 260) is provided. The microneedle includes a base (162), an elongated body (161) having a central axis (130) and a body diameter (168), a tip portion (166), a first channel (170), and a second channel (176). The tip portion includes a tip (164), a beveled surface (140), and a bevel opening (172) in the beveled surface. The first channel extends axially from the bevel opening through at least a portion of the elongated body and has a first wall that is substantially aligned with the central axis. The second channel extends radially from the first channel to the bevel opening and has a second wall that is oriented substantially orthogonal to the central axis. The first channel and second channel merge to form the bevel opening.



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HOLLOW MICRONEEDLE WITH BEVEL OPENING

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority of U.S. Provisional Patent Application No. 5 61/846,945, filed July 16, 2013, the disclosure of which is incorporated by reference in its entirety herein.

BACKGROUND

[0002] Transdermal and topical drug delivery can be used for therapeutic treatment, but the 10 number of molecules that can be effectively delivered using these routes can be limited by the barrier properties of skin. The main barrier to transport of molecules through the skin is the stratum corneum (the outermost layer of the skin).

[0003] A number of different skin treatment methods have been proposed in order to 15 increase the permeability or porosity of the outermost skin layers, such as the stratum corneum, thus enhancing drug delivery through or into those layers. The stratum corneum is a complex structure of compact keratinized cell remnants separated by lipid domains. The stratum corneum is formed of keratinocytes, which comprise the majority of epidermal cells that lose 20 their nuclei and become corneocytes. These dead cells comprise the stratum corneum, which has a thickness of only about 10-30 microns and protects the body from invasion by exogenous substances and the outward migration of endogenous fluids and dissolved molecules. Various skin treatment methods include the use of microneedles, laser ablation, RF ablation, heat ablation, sonophoresis, iontophoresis, or a combination thereof.

[0004] Devices including arrays of relatively small structures, sometimes referred to as 25 microneedles or micro-pins, have been disclosed for use in connection with the delivery of therapeutic agents and other substances through the skin and other surfaces. The devices are typically pressed against the skin in an effort to pierce the stratum corneum such that the therapeutic agents and other substances can sequentially or simultaneously pass through that layer and into the tissues below. Microneedles of these devices pierce the stratum corneum upon contact, making a plurality of microscopic slits which serve as passageways through 30 which molecules of active components can be delivered into the body. In delivering an active component, the microneedle device can be provided with a reservoir for temporarily retaining an active component in liquid form prior to delivering the active component through the stratum corneum. In some constructions, the microneedles can be hollow to provide a liquid flow path directly from the reservoir and through the microneedles to enable delivery of the therapeutic substance through the skin. In alternate constructions, active component(s) may be 35

coated on the microneedle array and delivered directly through the skin after the stratum corneum has been punctured.

[0005] Microneedle arrays can be used in conjunction with an applicator device capable of being used several times or as a single-use device. The microneedle arrays are generally used once and then discarded.

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SUMMARY

[0006] The present inventors recognized that issues related to applying microneedles include the ability to effectively and consistently insert the needles to a desired depth in the skin, the 10 ability to reliably hold the microneedles in proper contact with the skin during the period of administration, and the ability to apply consistent force for delivery.

[0007] The present disclosure generally relates to articles comprising one or more hollow microneedles. In particular, the present disclosure provides a hollow microneedle with an 15 opening that is configured to facilitate the delivery of material from the hollow microneedle into tissue (e.g., skin tissue). In addition, the present disclosure provides a method of making hollow microneedles.

[0008] Some aspects of the present disclosure provide an article. The article can comprise at 20 least one hollow microneedle. The at least one microneedle can comprise a base, an elongated body having a central axis, a tip portion, a first channel, and a second channel. The tip portion can comprise a tip, a beveled surface, and a bevel opening in the beveled surface. The first channel can extend axially from the bevel opening through at least a portion of the elongated body, wherein the first channel has a first wall that is substantially aligned with the central axis. The second channel can extend radially from the first channel to the bevel opening, wherein the second channel has a second wall that is oriented substantially orthogonal to the central axis.

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The first channel and second channel merge to form the bevel opening.

[0009] Other aspects of the present disclosure provide a method of making an article comprising at least one microneedle. The microneedle can comprise an elongated body having 30 body diameter, a base, a tip portion, and a hollow channel extending from the base to the tip portion. The method can comprise providing a first mold half comprising at least one cavity; wherein the at least one cavity includes a cavity opening and a cavity surface having a first projection extending therefrom toward the cavity opening; wherein the first projection defines a first segment of the hollow channel, the first segment extending into the body of the microneedle from the base; wherein the first projection comprises a first longitudinal axis. The method further can comprise providing a second mold half comprising at least one second projection extending therefrom; wherein the at least one second projection defines a tip portion of the microneedle and a second segment of the hollow channel, the second segment extending

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into the body of the microneedle from a bevel opening proximate the tip of the at least one microneedle; wherein the at least one second projection comprises a second longitudinal axis; wherein the second projection is shaped and dimensioned to define the tip portion; wherein the tip portion includes a tip, a beveled surface, a bevel opening in the bevel surface, a first channel 5 that extends axially from the bevel opening through at least a portion of the elongated body, and a second channel that extends radially from the first channel to the bevel opening; wherein the first channel has a first wall that is substantially aligned with the second longitudinal axis; wherein the second channel has a second wall that is oriented substantially orthogonal to the second longitudinal axis; wherein the second projection is shaped and dimensioned such that the first channel and second channel merge to form the bevel opening. The method further can 10 comprise contacting at least the first mold surface or the second mold surface with moldable material and inserting the second projection into the at least one cavity.

[0010] The phrase “injection apparatus” refers to an integrated device capable of delivering or extracting a fluid over a certain period and is not limited to devices intended solely for an infusion. Accordingly, an injection apparatus may be used, for example, for injecting fluid into 15 the dermis or extracting fluid from tissue.

[0011] The term “transdermally” and variations thereof, is generally used to refer to any type of delivery of an active ingredient that crosses any portion of skin. That is, transdermally can generally include systemic delivery (i.e., where the active ingredient is transported across, or 20 substantially through, the dermis such that the active ingredient is delivered into the bloodstream), as well as intradermal delivery (i.e., where the active ingredient is transported partially through the dermis, e.g., across the outer layer (stratum corneum) of the skin, where the active ingredient is delivered into the skin, e.g., for treating psoriasis or for local anesthetic delivery). That is, transdermal delivery as used herein includes delivery of an active ingredient 25 that is transported across at least a portion of skin (but not necessarily all of the layers of skin), rather than merely being topically applied to an outer layer of the skin.

[0012] The phrase “hollow microneedle” refers to a specific microscopic structure that is designed for piercing the stratum corneum to facilitate the delivery of drugs through the skin. By way of example, microneedles can include needle or needle-like structures, as well as other 30 structures capable of piercing the stratum corneum and delivering liquid drug formulations to skin or tissue layers beneath the stratum corneum.

[0013] The words “preferred” and “preferably” refer to embodiments of the invention that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or 35 more preferred embodiments does not imply that other embodiments are not useful, and is not intended to exclude other embodiments from the scope of the invention.

[0014] The terms “comprises” and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

[0015] As used herein, “a,” “an,” “the,” “at least one,” and “one or more” are used interchangeably. Thus, for example, a microneedle can be interpreted to mean “one or more” 5 microneedles.

[0016] The term “and/or” means one or all of the listed elements or a combination of any two or more of the listed elements.

[0017] Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

10 [0018] The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group 15 and should not be interpreted as an exclusive list.

[0019] Additional details of these and other embodiments are set forth in the accompanying drawings and the description below. Other features, objects and advantages will become apparent from the description and drawings, and from the claims.

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BRIEF DESCRIPTION OF DRAWINGS

[0020] The present invention will be further explained with reference to the drawing figures listed below, where like structure is referenced by like numerals throughout the several views.

[0021] FIG. 1 is a perspective view of an embodiment of an article comprising a hollow microneedle.

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[0022] FIG. 2 is a perspective view of an embodiment of a hollow microneedle comprising a bevel face having an opening.

[0023] FIG. 3 is a perspective view of a mold part used to form a tip portion of the hollow microneedle of FIG. 2.

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[0024] FIG. 4 is a perspective view of one embodiment of hollow microneedle having a bevel face with an opening according to the present disclosure.

[0025] FIG. 5 is a side view of the hollow microneedle of FIG. 4, showing the bevel face and the opening.

[0026] FIG. 6 is a side view of the hollow microneedle of FIG. 4, showing an optional secondary bevel.

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[0027] FIG. 7 is a top view of the hollow microneedle of FIG. 5.

[0028] FIG. 8 is a cross-sectional view of the hollow microneedle of FIG. 5, taken along line 8-8.

[0029] FIGS. 9A-B are side views of a mold part used to form a tip portion of the hollow microneedle of FIGS. 4-8.

5 [0030] FIG. 9C is a perspective view of the mold part of FIGS. 9A-B.

[0031] FIG. 10 is a schematic view of one embodiment of portions of mold parts that are used in a molding process to make an article with a hollow microneedle according to the present disclosure.

10 [0032] FIG. 11 is a detail view of the tip portion of the microneedle of FIG. 5, contrasting the area of a bevel opening of a conventional needle tip and the area of the bevel opening in a microneedle according to the present disclosure.

[0033] FIG. 12 is a detail view of the tip portion of the microneedle of FIG. 5, showing an angle β formed by a secondary bevel and a plane that is aligned with the central axis of the microneedle.

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DETAILED DESCRIPTION

[0034] Before any embodiments of the present disclosure are explained in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the following drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, it is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items. Unless specified or limited otherwise, the terms "mounted," "connected," "supported," and "coupled" and variations thereof are used broadly and encompass both direct and indirect mountings, connections, supports, and couplings. It is to be understood that other embodiments may be utilized, and structural or logical changes may be made without departing from the scope of the present disclosure. Furthermore, terms such as "front," "rear," "top," "bottom," and the like are only used to describe elements as they relate to one another, but are in no way meant to recite specific orientations of the apparatus, to indicate or imply necessary or required orientations of the apparatus, or to specify how the invention described herein will be used, mounted, displayed, or positioned in use.

[0035] The present disclosure generally relates to articles comprising hollow microneedles having a tip portion that penetrates skin and provides an opening through which a composition (e.g., a pharmaceutically-active compound) can be delivered into the skin tissue and other

tissue disposed in or underlying the skin tissue. In particular, the present disclosure relates to certain aspects of the tip portion that can provide more-efficient delivery of compositions into the skin tissue. In addition, the aspects generally provide a more-robust method of manufacturing hollow microneedles and particularly provide a more-robust method of manufacturing high-aspect-ratio hollow microneedles.

[0036] Articles comprising hollow microneedles and/or hollow microneedle arrays are used, for example, to deliver compositions (e.g., compositions comprising active ingredients). Such articles are described, for example, in U.S. Patent Nos. 8,088,321 and 8,246,893; and U.S. Patent Application Publication Nos. US2011/0213335, US2012/0123387, US2012/0041337; and International Patent Publication No. WO2012/074576, which are all incorporated herein by reference in their entirety.

[0037] Turning to the drawings, FIG. 1 shows one embodiment of an article 100 comprising at least one microneedle 160. In the illustrated embodiment, the article 100 comprises a circular-shaped array of a plurality of microneedles 160. The article 100 comprises a unitary substrate 110 having a first side 112 from which the microneedles 160 extend. In any embodiment, an article according to the present disclosure can comprise a plurality of hollow microneedles. In any embodiment, the hollow microneedles can be arranged in an array (e.g., a regular array). Non-limiting examples of articles comprising hollow microneedles are described in U.S. Provisional Patent Nos. 61/846,909 and 61/846,905 filed on July 16, 2013, which are both incorporated herein by reference in their entirety.

[0038] FIG. 2 shows one embodiment of a hollow microneedle 160. The microneedle 160 comprises an elongated body 161 having at least one major surface 163, central axis 130, a body diameter 168, a base 162 at one end of the body 161, and a tip portion 166 at the other end of the body 161. The body 161 can take the form of a variety of shapes including, but not limited to, cylindrical, conical, crateriform, pyramidal, and combinations thereof. The tip portion 166 comprises a bevel face 140 that extends diagonally, relative to the central axis, through the body 161 and thereby forming the tip 164. As used herein, the “tip” of a microneedle is a point of the microneedle that is farthest (as measured along the central axis) from the base of the microneedle. Preferably, the angle of the bevel face 140 with respect to the central axis 130 is sufficiently acute such that it forms a sharp edge (e.g., for penetrating skin) at the tip 164. The microneedle 160 further comprises a hollow channel 170 that extends from the tip portion 166 into the body 161 via a bevel opening 172 on the bevel face 140. Although illustrated as a relatively flat plane that is not coplanar with the at least one major surface of the microneedle, it is contemplated that, in any embodiment, the bevel face in which the bevel opening is disposed may be coplanar with the at least one major surface of the microneedle (not shown).

[0039] It will be recognized by a person having ordinary skill in the art that the body diameter 168 of the microneedle 160 may vary along the central axis 130 of the microneedle, depending upon the shape of the microneedle. The body diameter 168 shown in the illustrated embodiment corresponds to the diameter of the microneedle 160 at the base 162.

5 **[0040]** FIG. 3 shows a perspective view of one embodiment of a mold part 150, referenced in the Examples as a “cylindrical projection”, which is used to form the tip portion 166 of the hollow microneedle 160 of FIG. 2. The mold part 150 comprises a base 151. Generally, cross-sectional shape of the base will match the exterior shape of the tip portion to be formed. In the illustrated embodiment of FIG. 3, the base is cylindrical. The mold part further comprises a
10 bevel-forming surface 153 and an extension 154. The bevel-forming surface 153 defines the shape and angle of the bevel face of the microneedle. The extension 154 defines the shape (e.g., circular) and size of the opening in the bevel face and also defines the shape (e.g., cylindrical) and diameter of the hollow channel in the microneedle. In any embodiment, the
15 microneedle may comprise a hollow channel that extends only partially through the body of the microneedle (i.e., the hollow channel is a dead-end channel). In these embodiments, the extension 154 may also define the depth of the hollow channel that is made using the mold part 150.

20 **[0041]** FIGS. 4-8 show various views of one embodiment of a microneedle 260 according to the present disclosure. Similar to the microneedle 160 shown in FIG. 2, the microneedle 260 comprises an elongated body 161 having at least one major surface 163, central axis 130, a body diameter 168, a base 162 at one end of the body 161, and a tip portion 166 at the other end of the body 161. The tip portion 166 includes a bevel face 140 with an opening 172 for a first channel 170 that extends axially into the body 161 of the microneedle 260. The bevel face 140 is oriented diagonally with respect to the central axis 130. The body 161 can take the form
25 of a variety of shapes including, but not limited to, cylindrical, conical, crateriform, pyramidal, and combinations thereof.

30 **[0042]** In contrast to the microneedle 160 of FIG. 2, the tip portion 166 of the microneedle 260 comprises an opening 172 that is formed by a merging of two channels (i.e., first channel 170 and second channel 176. The first channel 170 has at least one wall 178 that is substantially aligned with the central axis 130 of the microneedle 260. The second channel 176 has at least one wall 177 that extends radially outward from the first channel 170. The at least one wall 177 of the second channel 176 is oriented substantially orthogonal to the central axis 130. The first channel 170 and the second channel 176 merge at the bevel face 140 to form the opening 172.

35 **[0043]** Preferably, the angle of the bevel face 140 with respect to the central axis 130 is sufficiently acute such that it forms a sharp edge (e.g., for penetrating skin) at the tip 164. In

the illustrated embodiment of FIGS. 4-8, the tip 164 of the microneedle 260 is located at a point where the bevel face 140 is farthest from the base 162 relative to the central axis.

[0044] In any embodiment, the bevel face 140 has a pitch (i.e., angle in relation to the central axis of about 15° to about 40°. In a preferred embodiment, the bevel face 140 has a pitch of about 20° to about 35°. In a more preferred embodiment, the bevel face 140 has a pitch of about 25° to about 33°.

[0045] The microneedle 260 further comprises a hollow channel 170 that extends axially into the body 161 from the tip portion 166 from a bevel opening 172. The bevel opening 172 is defined by a first edge 174 of the face 140. The bevel face 140 is defined by a second edge 149. In any embodiment, no portion of the opening edge is coincident with any portion of the bevel edge (e.g., the opening may approximately centered within the area defined by the bevel face (not shown). Alternatively, in any embodiment, at least a portion of the first edge 174 is coincident with a portion of the second edge 149, as shown in FIG. 5. In the illustrated embodiment of FIG. 5, the bevel face 140 forms a surface that has the shape of a partial ellipse. The partial ellipse-shaped bevel face 140 substantially surrounds the opening 172.

[0046] In any embodiment, the tip portion 166 of the microneedle 260 optionally comprises at least one secondary bevel 145. As shown in FIG. 5, the secondary bevels 145 are used to form a sharp tip 164 that facilitates penetration of skin by the microneedle 260. An angle (angle β , FIG. 12) can be used to define the angle of the secondary bevels 145. The angle β is defined by an intersection of a plane 132 that extends into the opening of the microneedle (through the central axis) and the edge of the microneedle tip created by the secondary bevel (see Fig. 12). In any embodiment, the at least one secondary bevel has a pitch (i.e., an angle in relation to the plane 132, which is aligned with the central axis) of about 15° to about 40°. In a preferred embodiment, the bevel face 140 has a pitch of about 25° to about 35°. In a more preferred embodiment, the bevel face 140 has a pitch of about 35° to about 35°.

[0047] FIGS. 9A-C show various views of one embodiment of a mold part 150', referenced in the Examples as a "cylindrical projection", which is used to form the tip portion 166 of the hollow microneedle 260 of FIGS. 4-8. The mold part 150' comprises a base 151. Generally, cross-sectional shape of the base will match the exterior shape of the tip portion to be formed.

In the illustrated embodiment of FIG. 9, the base is cylindrical.

[0048] The mold part 150' further comprises a primary bevel-forming surface 153, secondary bevel-forming surfaces 155, and an extension 154'. The primary bevel-forming surface 153 defines the shape and angle, relative to the central axis, of the bevel face of the microneedle. The secondary bevel-forming surfaces 155 define the shape of the secondary bevels and the angle of the secondary bevels relative to the bevel face of the microneedle.

[0049] The extension 154' defines the shape (e.g., circular) and size of the opening in the bevel face and also defines the shape (e.g., cylindrical) and diameter of the hollow channel in the microneedle. In any embodiment, the microneedle may comprise a hollow channel that extends only partially through the body of the microneedle (i.e., the hollow channel is a dead-end channel). In these embodiments, the extension 154' may also define the depth of the hollow channel that is made using the mold part 150'. In any embodiment, an article according to the present disclosure may comprise hollow microneedles having a hollow channel that extends from one side of the article to another (e.g., to a reservoir located on the side opposite the microneedles, not shown).

5 **[0050]** In contrast to the mold part 150 of FIG. 3, the extension 154' of mold part 150' further comprises a protrusion 156 that increases the size of the opening created by the opening that is created by the mold part 150'. The protrusion is truncated at rim 157, which defines a portion of the shape of the second channel (see second channel 176 of FIG. 4) of the microneedle formed using the mold part 150'. In any embodiment, the rim 157 may be 10 oriented substantially perpendicular to the central axis of the microneedle to be formed using the mold part 150'. In any embodiment, the rim 157 may comprise a radius of curvature.

15 **[0051]** In any embodiment, the bevel face of a microneedle according to the present disclosure defines a plane. In any embodiment, the plane is a flat plane. In any embodiment, the plane may be curved or slightly curved. In any embodiment, the bevel face may comprise a plurality of nonparallel planes (e.g. the bevel face may comprise a dihedral bevel face, as 20 described in U.S. Provisional Patent Application No. 61/846,934, filed July 16, 2013 which is incorporated herein by reference in its entirety.

25 **[0052]** Hollow microneedles of the present disclosure can be made using molding processes that are known in the art. U.S. Provisional Patent Application No. 61/740,941, which is incorporated herein by reference in its entirety, for example describes the formation of microneedles using a molding process. FIG. 10 shows a schematic view of an apparatus for use in a molding process to make hollow microneedles of the present disclosure. As described in the Examples herein, a first mold half comprising a mold cavity 190 and the mold part 150' of FIGS. 9A-C is positioned proximate a second mold half 191, thereby creating a cavity 195 having the shape of the one or more hollow microneedle and the article from which the hollow microneedle projects (see FIG. 1, for example). The mold part 150' comprises the extension 154' which, in concert with protrusion 156, defines the opening and first channel proximate the tip of the formed microneedle. Optionally, the second mold half 191 comprises a projection 253 that defines the size and shape of a hollow channel that extends completely 30 through the formed article. As described in U.S. Provisional Patent Application No. 61/740,941, the microneedles are formed in such a manner that results in a hollow channel 35

extending completely through the body of the microneedle. In any embodiment, certain processes (e.g., laser drilling) are used subsequent to the molding in order to complete the hollow channel.

[0053] In another aspect, the present disclosure provides a method of making an article comprising at least one hollow microneedle that comprises a body having a central axis, a body diameter, a base, a tip portion, and a hollow channel. The method comprises providing a first mold half comprising at least one cavity. The at least one cavity includes a cavity opening and a cavity surface having a first projection extending therefrom toward the cavity opening. The first projection defines a first segment of the hollow channel, the first segment extending into the body of the microneedle from the base. The first projection comprises a first longitudinal axis. The method further comprises providing a second mold half comprising at least one second projection extending therefrom. The at least one second projection defines a tip portion of the at least one microneedle and a second segment of the hollow channel, the second segment extending into the body of the microneedle from a bevel opening proximate the tip of the at least one microneedle. The at least one second projection comprises a second longitudinal axis. The second projection is shaped and dimensioned to define the tip portion, as described herein. The method further comprises contacting at least the first mold half or the second mold half with moldable material (e.g., polymeric material, thermoplastic polymeric material), inserting the at least one second projection into the cavity opening so that the first projection is substantially aligned with the second projection, and forming the article. In any embodiment, after forming the article, the second projection causes the tip portion of the at least one microneedle to comprise a tip, a bevel face oriented diagonally with respect to the central axis and an opening that is formed by the merging of two channels that extend into the tip portion of the hollow microneedle. The first channel extends axially into the microneedle and the second channel extends radially, in an orientation that is substantially orthogonal to the central axis, from the first channel to the opening. In any embodiment, the second projection is inserted into the at least one cavity before contacting at least the first mold half or the second mold half with the moldable material. Alternatively, in any embodiment, at least the first mold half or the second mold half is contacted with the moldable material before inserting the second projection into the at least one cavity.

[0054] In any of the above embodiments of the method, the at least one cavity has a cavity aspect ratio (cavity length to cavity base width) of at least 1.5 to 1. In any of the above embodiments of the method, the first mold half comprises a plurality of the at least one cavities, wherein the second mold half comprises a plurality of the at least one second projections, wherein the plurality of second projections is aligned to be inserted simultaneously into the plurality of cavities.

[0055] Microneedle articles that are made according to the present disclosure can have a variety of configurations and features, such as those described in the following patents and patent applications, the disclosures of which are incorporated herein by reference in their entirety. One embodiment for the microneedle articles includes the structures disclosed in U.S. Patent No. 6,312,612 (Sherman et al.), which describes tapered structures having a hollow central channel. Yet still another embodiment for the microneedle array articles includes the structures disclosed in U.S. Patent No. 6,379,324 (Gartstein et al.), which describes hollow microneedles having at least one longitudinal blade at the top surface of the tip of the microneedle. A further embodiment for the microneedle array articles includes the structures disclosed in U.S. Patent Application Publication Nos. US2012/0123387(Gonzalez et al.) and US2011/0213335 (Burton et al.), which both describe hollow microneedles. A still further embodiment for the microneedle array articles includes the structures disclosed in U.S. Patent Nos. 6,558,361 (Yeshurun) and 7,648,484 (Yeshurun et al.), which both describe hollow microneedle arrays and methods of manufacturing thereof.

[0056] Various embodiments of features of microneedles that can be employed in the microneedle articles of the present disclosure are described in PCT Publication No. WO 2012/074576 (Duan et al.), which describes liquid crystalline polymer (LCP) microneedles; and PCT Publication No. WO 2012/122162 (Zhang et al.), which describes a variety of different types and compositions of microneedles that can be employed in the microneedles of the present disclosure.

[0057] Articles comprising hollow microneedles having features according to the present disclosure can be made, for example, by injection molding processes that are known in the art. In some embodiments, the microneedle material can be (or include) a metal, a ceramic, or a polymeric material, preferably a medical grade polymeric material. The microneedle material can be (or include) silicon or a metal such as stainless steel, titanium, or nickel titanium alloy. Exemplary types of medical grade polymeric materials include polycarbonate, liquid crystalline polymer (LCP), polyether ether ketone (PEEK), cyclic olefin copolymer (COC), polybutylene terephthalate (PBT). Preferred types of medical grade polymeric materials include polycarbonate and LCP.

[0058] The microneedle articles of the present disclosure can be manufactured in any suitable way such as by injection molding, compression molding, metal injection molding, stamping, photolithography, or extrusion. In any embodiment, hollow microneedle arrays can be made by injection molding of a polymer such as medical grade polycarbonate or LCP, followed by laser drilling to form the channels of the hollow microneedles. Nonlimiting examples of molding processes for molding polymeric materials into solid microneedle articles can be found in U.S. Patent No. 8,088,321 (Ferguson et al.) and U.S. Patent Application

Publication Nos. 2012/0258284 (Rendon) and 2012/0041337 (Ferguson et al.), each of which is incorporated herein by reference in its entirety. A non-limiting example of a publication that discloses the formation of hollow channels in articles comprising microneedles is U.S.

Provisional Patent Application No. 61/746,198, which is incorporated herein by reference in its

5 entirety.

[0059] In some embodiments, the microneedle material can be (or include) a biodegradable polymeric material, preferably a medical grade biodegradable polymeric material. Exemplary types of medical grade biodegradable materials include polylactic acid (PLA), polyglycolic acid (PGA), PGA and PLA copolymer, polyester-amide polymer (PEA).

10 **[0060]** In some embodiments, the hollow microneedles can be prepared from a dissolvable, degradable, or disintegrable material referred to herein as “dissolvable microneedles”. A dissolvable, degradable, or disintegrable material is any solid material that dissolves, degrades, or disintegrates during use. In particular, a “dissolvable microneedle” dissolves, degrades, or disintegrates sufficiently in the tissue underlying the stratum corneum to allow a therapeutic agent to be released into the tissue. The therapeutic agent may be coated on or 15 incorporated into a dissolvable microneedle. In some embodiments, the dissolvable material is selected from a carbohydrate or a sugar. In some embodiments, the dissolvable material is polyvinyl pyrrolidone (PVP). In some embodiments, the dissolvable material is selected from the group consisting of hyaluronic acid, carboxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinyl alcohol, sucrose, glucose, dextran, trehalose, maltodextrin, and a combination thereof.

20 **[0061]** In any embodiment, the hollow microneedles can be made from (or include) a combination of two or more of any of the above mentioned materials. For example, the tip of a microneedle may be a dissolvable material, while the remainder of the microneedle is a medical 25 grade polymeric material.

25 **[0062]** A microneedle or the plurality of hollow microneedles in a microneedle-containing article of the present disclosure can have a variety of shapes that are capable of piercing the stratum corneum. In some of the embodiments, one or more of the plurality of microneedles can have a square pyramidal shape, triangular pyramidal shape, stepped pyramidal shape, 30 conical shape, microblade shape, or the shape of a hypodermic needle. In any embodiment, one or more of the plurality of microneedles can have a square pyramidal shape. In any embodiment, one or more of the plurality of microneedles can have a triangular pyramidal shape. In any embodiment, one or more of the plurality of microneedles can have a stepped pyramidal shape. In any embodiment, one or more of the plurality of microneedles can have a conical shape. In any embodiment, one or more of the plurality of microneedles can have the 35 shape of a hypodermic needle. In any embodiment, a microneedle array article may comprise

an array of microneedles having a combination of any two or more of the foregoing microneedle shapes. The shape of any microneedle in the microneedle array article can be symmetric or asymmetric. The shape of any microneedle in the microneedle array article can be truncated (for example, the plurality of microneedles can have a truncated pyramid shape or truncated cone shape). In a preferred embodiment, each microneedle of the plurality of microneedles in a microneedle array article has a square pyramidal shape.

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[0063] In any embodiment, each microneedle of the plurality of microneedles in a microneedle array article is a hollow microneedle (that is, the microneedle contains a hollow bore through the microneedle). The hollow bore can be from the base of the microneedle to the tip of the microneedle or the bore can be from the base of the microneedle to a position offset from the tip of the microneedle. In any embodiment, one or more of the plurality of hollow microneedles in a hollow microneedle array can have a conical shape, a cylindrical shape, a square pyramidal shape, a triangular pyramidal shape, or the shape of a hypodermic needle.

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[0064] In any embodiment, one or more microneedle of the plurality of hollow microneedles in a hollow microneedle array article can have a conical shape; optionally, with a radius of curvature. In any embodiment, one or more microneedle of the plurality of hollow microneedles in a hollow microneedle array article can have a cylindrical shape. In any embodiment, one or more microneedle of the plurality of hollow microneedles in a hollow microneedle array article can have a segment having a square pyramidal shape. In any

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embodiment, one or more microneedle of the plurality of hollow microneedles in a hollow microneedle array article can have a segment having a triangular pyramidal shape. In any embodiment, one or more microneedle of the plurality of hollow microneedles in a hollow microneedle array article can have a segment having the shape of a hypodermic needle. In a preferred embodiment, each microneedle of the plurality of hollow microneedles in a hollow microneedle array article has a segment with the shape of a conventional hypodermic needle.

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[0065] In any embodiment, an article comprising a hollow microneedle according to the present disclosure may comprise a plurality of the microneedles. The plurality of the microneedles optionally may form an array. In any embodiment, the article can comprise an array of about 3 to about 30, inclusive, of the hollow microneedles of the present disclosure. In a preferred embodiment, the article can comprise an array of about 8 to about 20, inclusive, of the hollow microneedles of the present disclosure. In a more-preferred embodiment, the article can comprise an array of 12, 16, or 18 of the hollow microneedles of the present disclosure.

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[0066] In any embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, the overall height of each microneedle is about 400 μm to about 3000 μm . In any embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, the overall height of each microneedle is about 400 μm to

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about 2000 μm . In any embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, the overall height of each microneedle is about 750 μm to about 1600 μm .

[0067] In any embodiment of an article comprising a plurality of hollow microneedles 5 according to the present disclosure, a hollow channel extending through each of the microneedles has a diameter, proximate the tip of the microneedle, of about 10 μm to about 200 μm . In any embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, a hollow channel extending through each of the microneedles has a diameter, proximate the tip of the microneedle, of about 10 μm to about 120 μm . In any 10 embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, a hollow channel extending through each of the microneedles has a diameter, proximate the tip of the microneedle, of about 25 μm to about 75 μm .

[0068] In any embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, a hollow channel extending through each of the 15 microneedles has a cross-sectional area of about 75 μm^2 to about 32,000 μm^2 . In any embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, a hollow channel extending through each of the microneedles has a cross-sectional area of about 75 μm^2 to about 18,000 μm^2 . In any embodiment of an article comprising a plurality of hollow microneedles according to the present disclosure, a hollow 20 channel extending through each of the microneedles has a cross-sectional area of about 700 μm^2 to about 3,000 μm^2 .

[0069] The hollow microneedle array articles of the present disclosure can be manufactured by injection molding of a polymer such as medical grade polycarbonate or LCP. Typically, these processes use molds to form the substrate with the microneedles extending therefrom.

[0070] Microneedles of the present disclosure advantageously provide a larger opening, with 25 respect to a predetermined microneedle wall thickness, than can be attained using conventional process known in the art. The larger opening facilitates the delivery of material (e.g., pharmaceutically-active compositions) from the hollow channel of the microneedle into the skin tissue and underlying layers of tissue. FIG. 11 shows the area 185 defined by a

30 conventional opening in a hollow microneedle. Typically, a conventional opening is created by bisecting the body of the microneedle with a bevel face and the area 185 represents the cross-sectional area of the opening that is created along the bevel face. FIG. 11 also shows the additional area 186 that is gained by making a microneedle according to the present disclosure.

[0071] In addition, using a process according to the present disclosure, the microscopic mold 35 parts that are used to form the tip portion of the needle are significantly less susceptible to

damage during extended use because the extensions that form the tip-proximal hollow channel in the microneedle are made stronger by the presence of the protrusion that forms the second bevel face.

[0072] Any of the above embodiments of a microneedle according to the present disclosure can be used for injecting fluid into a body. Any of the above embodiments of a microneedle according to the present disclosure can be used for extracting fluid from a body.

EXEMPLARY EMBODIMENTS

[0073] Embodiment A is an article, comprising:

10 at least one microneedle, the at least one microneedle comprising:

a base;

an elongated body having a central axis;

a tip portion comprising a tip, a beveled surface, and a bevel opening in the beveled surface;

15 a first channel that extends axially from the bevel opening through at least a portion of the elongated body, wherein the first channel has a first wall that is substantially aligned with the central axis; and

20 a second channel that extends radially from the first channel to the bevel opening, wherein the second channel has a second wall that is oriented substantially orthogonal to the central axis;

wherein the first channel and second channel merge to form the bevel opening.

[0074] Embodiment B is the article of Embodiment A, wherein the article further comprises a substrate having a first side and a second side, wherein the at least one microneedle extends from the first side of the substrate, wherein the first channel extends from the bevel opening through the elongated body to a second opening on the second side of the substrate.

[0075] Embodiment C is the article of Embodiment A or Embodiment B, wherein the at least one microneedle comprises a plurality of microneedles.

[0076] Embodiment D is the article of any one of the preceding Embodiments, wherein the bevel opening is an elongated opening comprising a first end proximate the tip and a second end proximate the base.

[0077] Embodiment E is the article of any one of Embodiments A through D, wherein the beveled surface is defined by a bevel edge surrounding the beveled surface, wherein the opening is defined by an opening edge surrounding the opening, wherein no portion of the opening edge is coincident with any portion of the bevel edge.

[0078] Embodiment F is the article of any one of Embodiments A through D, wherein the beveled surface is defined by a bevel edge surrounding the beveled surface, wherein the

opening is defined by an opening edge surrounding the opening, wherein at least a portion of the opening edge is coincident with a portion of the bevel edge.

[0079] Embodiment G is the article of any one of the preceding Embodiments, wherein the tip portion comprises plurality of intersecting planes.

5 **[0080]** Embodiment H is the article of any one of the preceding Embodiments, wherein the bevel face defines a first plane, wherein a first two-dimensional area defined by the bevel opening is larger than a second two-dimensional area defined by a cross-sectional area of the first channel taken along the first plane.

[0081] Embodiment I is a use of the article of any one of Embodiments A through H for 10 injecting fluid into a body.

[0082] Embodiment J is a use of the article of any one of Embodiments A through H for removing fluid from a body.

[0083] Embodiment K is a method of making an article comprising at least one microneedle that comprises an elongated body having body diameter, a base, a tip portion, and a hollow 15 channel extending from the base to the tip portion; the method comprising:

providing a first mold half comprising at least one cavity;

wherein the at least one cavity includes a cavity opening and a cavity surface having a first projection extending therefrom toward the cavity opening ;

wherein the first projection defines a first segment of the hollow channel, the first segment extending into the body of the microneedle from the base;

wherein the first projection comprises a first longitudinal axis;

20 providing a second mold half comprising at least one second projection extending therefrom;

wherein the at least one second projection defines a tip portion of the 25 microneedle and a second segment of the hollow channel, the second segment extending into the body of the microneedle from a bevel opening proximate the tip of the at least one microneedle;

wherein the at least one second projection comprises a second longitudinal axis;

30 wherein the second projection is shaped and dimensioned to define the tip portion;

wherein the tip portion includes a tip, a beveled surface, a bevel opening in the bevel surface, a first channel that extends axially from the bevel opening through at least a portion of the elongated body, and a second channel that extends radially from the first channel to the bevel opening;

wherein the first channel has a first wall that is substantially aligned with the second longitudinal axis; and

wherein the second channel has a second wall that is oriented substantially orthogonal to the second longitudinal axis;

5 wherein the second projection is shaped and dimensioned such that the first channel and second channel merge to form the bevel opening;

contacting at least the first mold surface or the second mold surface with polymeric material; and

inserting the second projection into the at least one cavity.

10 [0084] Embodiment L is the method of Embodiment K, wherein the second projection is inserted into the at least one cavity before contacting at least the first mold surface or the second mold surface with the moldable material.

[0085] Embodiment M is the method of Embodiment K, wherein at least the first mold surface or the second mold surface is contacted with the moldable material before inserting the 15 second projection into the at least one cavity.

[0086] Embodiment N is the method of any one of Embodiments K through M, wherein the moldable material comprises a metal, a ceramic material, or a polymeric material.

[0087] Embodiment O is the method of any one of Embodiments K through N, wherein the at least one cavity has a cavity aspect ratio (cavity length to cavity base width) of at least 1.5 to 20 1.

[0088] Embodiment P is the method of any one of Embodiments K through), wherein the first mold half comprises a plurality of the at least one cavities, wherein the second mold half comprises a plurality of the at least one second projections, wherein the plurality of second projections is aligned to be inserted simultaneously into the plurality of cavities.

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EXAMPLES

[0089] **Example 1. Fabrication of microneedle articles**

[0090] The microneedle articles were prepared from polymeric material using standard injection molding procedures. The molded microneedle articles were prepared using a mold 30 assembly prepared from three mold sections with each section machined from steel. The first mold section contained projections that defined the beveled shape of the needle tip in the molded array. Each projection in the first mold section had a further cylindrical extension that defined features of the tip segment of the microneedles tip, including the opening on a bevel proximate the tip of the microneedle and a portion of the hollow channel extending through the 35 body of each microneedle. The second mold section served as a template to define the pattern of the microneedles in the molded article, the external shape and size of the microneedles in the

5 molded article, and the first side of the article (including the central cavity portion, platform portion, and peripheral portion, as described above). The third mold section contained cylindrical projections emerging from a planar surface with each projection defining a second (base-proximal) part of the microneedle hollow channel and the opening located at the base of each microneedle in the molded article. The planar surface from which the projections emerged served to define the second major surface of the base segment of the molded article. The first and second mold sections were assembled to form a tight fit by inserting the projections of the first mold section into the corresponding openings in the second mold section. The assembled first and second mold sections formed the first mold half. The third mold section was used as 10 the second mold half.

[0091] The first and second mold halves were installed in a mold base in a 60-ton injection molding press (Sodick Plustech LA 60, Sodick Plustech Co., Yokohama, Japan). As is common in the art, the parting line of the mold assembly had both primary and secondary vents for general air evacuation during injection of the polymeric material. Vectra MT1300 liquid crystal polymer (LCP) pellets (Ticona Engineering Polymers, Florence, KY) were loaded into a reciprocating screw and heated until molten. The first mold half and second mold half were heated to a temperature (hereafter referred to as the "mold temperature at injection") of 200 °F (93.3 °C). The molding cycle was initiated by closing the first mold half with the second mold half. The molds were clamped together with approximately 20 to 60 tons of force. In the clamped position, the surfaces at the tips of the projections in the second mold half were aligned with and in contact with the surfaces at the tips of the projections in the first mold half. A first portion (approx. 50-95% of the part size volume) of the total amount of material from the reciprocating screw was injected into the mold chamber at a fixed velocity (hereafter referred to as the "injection velocity") of about 7 inches/second (17.8 cm/second). After injecting the first portion of material, the process was switched from an injection-driven to a pressure-driven mode by applying a fixed pressure (hereafter referred to as the "pack pressure") of about 13,500 psi (93,079 kilopascal) to force the remainder of the molten material into the negative mold insert. The pack pressure was applied for a fixed time (hereafter referred to as the "hold time") of 5 seconds. The pack pressure was subsequently released and the mold chamber was cooled to an ejection temperature set below the softening temperature of LCP. The mold chamber was opened and the microneedle article was ejected.

[0092] Example 2. Injection apparatus used to test the microneedle articles.

[0093] Fully assembled microneedle article injection apparatuses similar to apparatuses described in U.S. Patent Application Publication No. US2012/0123387 (FIGS. 1-13) and U.S. Provisional Patent Application No. 61/740,941 (FIGS. 2, 14 and 15) were used. The drug cartridge in each apparatus contained a 1 mL solution of 0.005% methylene blue in five percent

aqueous dextrose. The injection apparatus from Example 1 of U.S. Provisional Patent Application No. 61/740,941 was used with the following exceptions. First, the section of the apparatus joined to the adhesive assembly was not milled to remove material. Second, the construction of the adhesive assembly was different. Instead of using the four layer adhesive of U.S. Provisional Patent Application No. 61/740,941, the adhesive assembly used was a laminate composed of only two layers. The first layer was a 0.10 mm thick sheet of 3M 1510 double sided tape (available from the 3M Company). The second layer was a 0.07 mm sheet of 3M 1524 transfer adhesive. The two layer adhesive assembly was positioned to cover the first major surface of base member of the lower housing at the rounded end section of the device.

10 The adhesive assembly laminate was laser cut so that the size and shape of the adhesive assembly was matched to that of the device. The two layers of the adhesive assembly each contained cut-out regions that were aligned to each other and exactly matched the opening in the device housing. The device and adhesive assembly were oriented so that the first layer of the adhesive assembly was adhered to the lower housing of the device. The adhesive assembly was aligned with the device so that the opening in the first layer of the adhesive assembly was coincident with the opening in the device. A release liner was used during storage of the device to protect the exposed adhesive of the second layer of the adhesive assembly.

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[0094] The hollow microneedle article used in the microneedle article injection apparatus (as shown in FIG. 1) was molded (as described in Example 1) from Vectra MT1300 liquid crystal polymer (LCP) in the shape of a circle approximately 1.25 cm in diameter. The circular platform portion projected about 1.0 mm from the outside edge of the article and the peripheral portion canted away from the platform portion with a 36.9 degree cant, relative to the plane of the platform portion. The closed circular cavity of the article was centered on the article with a diameter of about 6.8 mm defined by the circular region formed by the inner perimeter of the platform), a depth of about 500 microns at the center of the cavity, and a radius of curvature of about 11 mm. The diameter of the circular region formed by the outer perimeter of the platform was about 10.3 mm. The width of the platform was about 1.75 mm. The article featured a linear array of 12 hollow microneedles extending from the circular platform portion of the article. The microneedles were evenly spaced with the distance between neighboring microneedles being about 2.2 mm (as measured from tip to tip). Each microneedle was oriented so that the opening at the tip was facing toward the outer perimeter of the article along a radial vector. The external diameter of each microneedle at the base was about 1.5 mm. The flared base segment of each microneedle had a radius of curvature of about 1 mm. The tip segment of each microneedle was in the shape of a conventional hypodermic needle with a 33.6 degree bevel and a chamfered tip that had an included angle of 70 degrees. The opening near the tip was obround in shape (as shown in FIG. 5) with dimensions of 303 microns by 80

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microns. Each microneedle had a total height of about 1500 microns as measured from the base of the microneedle at the platform surface to the tip of the microneedle. The distance from the tip of each microneedle to the center of the opening near the tip was about 382 microns. The average diameter of the hollow channel proximate the tip of each microneedle was about 5 80 microns.

[0095] Example 3. Injection apparatus.

[0096] The same microneedle injection apparatus as described in Example 2 was used with the exception that the wire diameter of the U-shaped leaf-like insertion spring (i.e. first stored energy device as described in U.S. Patent Application Publication No. US2012/0123387 (FIGS. 10 1-13) and U.S. Provisional Patent Application No. 61/740,941 (FIGS. 2, 14 and 15)) was 1.50 mm instead of 1.59 mm.

[0097] Example 4. Alternative injection apparatus.

[0098] The same microneedle injection apparatus as described in Example 2 was used with the exception that the wire diameter of the U-shaped leaf-like insertion spring (i.e. first stored 15 energy device as described in U.S. Patent Application Publication No. US2012/0123387 (FIGS. 1-13) and U.S. Provisional Patent Application No. 61/740,941 (FIGS. 2, 14 and 15)) was 1.40 mm instead of 1.59 mm.

[0099] Example 5. Use of microneedle article to inject a substance.

[0100] The study was conducted using Yorkshire cross domestic pigs (Midwest Research 20 Swine, Gibbon, MN) *in vivo*. A soft region of the belly having minimal muscle content was selected as the application site for microneedle insertion. The application site was first trimmed with an electric clipper and then shaved using a razor and shaving cream. The shaved area was scrubbed using soapy water and a BUF-PUF exfoliation sponge (3M Company, St. Paul, MN) and then rinsed with deionized water. The animal was placed in a lateral recumbent position on 25 a heated table (38 °C). The animal was anesthetized with isofluorene gas and maintained under anesthesia throughout the experiment. The application site was then wiped with a 70% isopropanol in water solution.

[0101] The injection apparatus of Example 4 was used. The release liner was removed from the adhesive assembly and the apparatus was adhered to the skin of the pig. During attachment 30 of the device to the pig, the skin at the application site was gently stretched to provide a slight tension to the skin. The skin was then allowed to relax and the push-button was depressed to cause release of the applicator element and insertion of the microneedle article into the skin of the pig. Removal of the tapered pin from the housing released the coiled spring which initiated the injection of the methylene blue solution into the pig. After completion of the injection, the apparatus was maintained on the skin for one additional minute. The apparatus was removed 35 from the skin and the skin surface was examined to determine if there was any methylene blue

solution on the surface of the skin. The presence of methylene blue solution on the skin was an indication that not all of the methylene blue was injected into the animal. The injection site was wiped with a pre-tared absorbent wipe and the wipe was then weighed to determine the amount of methylene blue that was not successfully delivered.

5 [00102] A total of three replicates were conducted. The injection times ranged from 29 to 111 seconds with the average injection time being 63 seconds. Two of the apparatuses successfully delivered the methylene blue solution without any “leakage” (i.e. no methylene blue solution was observed on the skin surface). The third apparatus successfully delivered 97% of the methylene blue solution.

10 [00103] **Example 6. Use of microneedle article.**

[00104] A study was conducted to determine the depth of penetration (DOP) of the microneedles of the article when applied to the skin surface of a Yorkshire cross domestic pigs (Midwest Research Swine), *in vivo*. The hollow microneedle article described in Example 2 was used.

15 [00105] The microneedles on the article were coated using a three step process. The first two steps involved applying primer coatings to the microneedles and the third step involved applying a thin coating of Rhodamine B to the microneedles. In Step 1, the articles were flood coated with a 35 microliter solution containing 0.5 mg/mL polyvinyl alcohol (80% hydrolyzed) (Sigma-Aldrich, Inc., St. Louis, MO) and 35 µg/ml of TWEEN® 80 (Sigma-Aldrich) in 90% (w/v) ethanol. The coated articles were then dried at 35 °C for 20 minutes. In Step 2, the articles from Step 1 were flood coated with 35 microliters of an aqueous solution of 33.3 mg/ml aluminum potassium sulfate (Penta Manufacturing, Livingston, NJ). The coated articles were then dried at 35 °C for 30 minutes. In Step 3, the primed articles from Step 2 were flood coated with 40 microliters of an aqueous solution of 0.08% (w/v) Rhodamine B (Sigma-Aldrich). The coated articles were dried at 35 °C for 30 minutes. The three step process provided articles in which the microneedles were completely covered with a thin, opaque coating of Rhodamine B.

20 [00106] The ham region was selected as the application site for microneedle insertion. The application site was first trimmed with an electric clipper and then shaved using a razor and shaving cream. The shaved area was scrubbed using soapy water and a BUF-PUF exfoliation sponge (3M Company) and then rinsed with deionized water. The animal was placed in a lateral recumbent position on a heated table (38 °C). The animal was anesthetized with isofluorene gas and maintained under anesthesia throughout the experiment. The application site was then wiped with a 70% isopropanol in water solution.

25 [00107] The injection apparatus described in Example 2 with a Rhodamine B coated article was used. The release liner was removed from the adhesive assembly and the apparatus was adhered to the skin of the pig. The push-button was depressed to cause release of the applicator

element and insertion of the microneedles of the microneedle article into the skin of the pig. The injection apparatus was maintained on the skin for an additional 5 minutes.

5 [00108] The injection apparatus was removed from the animal. The depth of penetration (DOP) of the microneedles into the pig skin was determined indirectly by measuring the distance from the tip of the microneedle to where the Rhodamine B coating was wiped or dissolved from the microneedle after application into the skin. The measurement was conducted using a Nikon LV-100 microscope at 100X magnification (Nikon Instruments, Melville, NY) with Image Pro® Plus digital image analysis software (Media Cybernetics, Bethesda, MD). A total of two replicates were conducted. The mean microneedle DOP was determined by 10 sampling all of the microneedles from each article (n=24). The results are presented in Table 1.

[00109] Table 1: Depth of Penetration (DOP) when Microneedle Article was Applied to the Ham Area (Example 6).

Minimum DOP	729 microns
Maximum DOP	901 microns
Mean DOP (n=32)	827 microns
Standard Deviation	48 microns
% RSD	6%

[00110] **Example 7. Use of microneedle article**

15 [00111] The procedure as described in Example 6 was used with the exception that the injection apparatus of Example 3 was used instead of the injection apparatus of Example 2. The results are presented in Table 2.

[00112] Table 2: Depth of Penetration (DOP) when Microneedle Article was Applied to the Ham Area (Example 7).

Minimum DOP	558 microns
Maximum DOP	849 microns
Mean DOP (n=24)	751 microns
Standard Deviation	74 microns
% RSD	10%

[00113] **Example 8.**

20 [00114] **Use of microneedle article.**

[00115] The procedure as described in Example 6 was used with the exception that the injection apparatus of Example 4 was used instead of the injection apparatus of Example 2. The results are presented in Table 3.

[00116] Table 3: Depth of Penetration (DOP) when Microneedle Article was Applied to the Ham Area (Example 8)

Minimum DOP	709 microns
Maximum DOP	863 microns
Mean DOP	787 microns
Standard Deviation	45 microns
% RSD	6%

[00117] The complete disclosure of all patents, patent applications, and publications, and electronically available material cited herein are incorporated by reference. In the event that any inconsistency exists between the disclosure of the present application and the disclosure(s) of any document incorporated herein by reference, the disclosure of the present application shall govern. The foregoing detailed description and examples have been given for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described, for variations obvious to one skilled in the art will be included within the invention defined by the claims.

[00118] All headings are for the convenience of the reader and should not be used to limit the meaning of the text that follows the heading, unless so specified.

[00119] Various modifications may be made without departing from the spirit and scope of the invention. These and other embodiments are within the scope of the following claims.

CLAIMS:

1. An article, comprising:
 - 5 at least one microneedle, the at least one microneedle comprising:
 - a base;
 - an elongated body having a central axis;
 - a tip portion comprising a tip, a beveled surface, and a bevel opening in the beveled surface;
 - 10 a first channel that extends axially from the bevel opening through at least a portion of the elongated body, wherein the first channel has a first wall that is substantially aligned with the central axis; and
 - a second channel that extends radially from the first channel to the bevel opening, wherein the second channel has a second wall that is oriented substantially orthogonal to the central axis;
 - 15 wherein the first channel and second channel merge to form the bevel opening.
2. The article of claim 1, wherein the article further comprises a substrate having a first side and a second side, wherein the at least one microneedle extends from the first side of the substrate, wherein the first channel extends from the bevel opening through the elongated body to a second opening on the second side of the substrate.
 - 20
3. The article of claim 1 or claim 2, wherein the at least one microneedle comprises a plurality of microneedles.
 - 25
4. The article of any one of the preceding claims, wherein the bevel opening is an elongated opening comprising a first end proximate the tip and a second end proximate the base.
 - 30
5. The article of any one of claims 1 through 4, wherein the beveled surface is defined by a bevel edge surrounding the beveled surface, wherein the opening is defined by an opening edge surrounding the opening, wherein no portion of the opening edge is coincident with any portion of the bevel edge.
 - 35
6. The article of any one of claims 1 through 4, wherein the beveled surface is defined by a bevel edge surrounding the beveled surface, wherein the opening is defined by an

opening edge surrounding the opening, wherein at least a portion of the opening edge is coincident with a portion of the bevel edge.

5 7. The article of any one of the preceding claims, wherein the tip portion comprises plurality of intersecting planes.

10 8. The article of any one of the preceding claims, wherein the bevel face defines a first plane, wherein a first two-dimensional area defined by the bevel opening is larger than a second two-dimensional area defined by a cross-sectional area of the first channel taken along the first plane.

9. A use of the article, as claimed in any one of claims 1 through 8, for injecting fluid into a body.

15 10. A use of the article, as claimed in any one of claims 1 through 8, for extracting fluid from a body.

20 11. A method of making an article comprising at least one microneedle that comprises an elongated body having body diameter, a base, a tip portion, and a hollow channel extending from the base to the tip portion; the method comprising:

providing a first mold half comprising at least one cavity;

wherein the at least one cavity includes a cavity opening and a cavity surface having a first projection extending therefrom toward the cavity opening ;

25 wherein the first projection defines a first segment of the hollow channel, the first segment extending into the body of the microneedle from the base;

wherein the first projection comprises a first longitudinal axis;

providing a second mold half comprising at least one second projection extending therefrom;

30 wherein the at least one second projection defines a tip portion of the microneedle and a second segment of the hollow channel, the second segment extending into the body of the microneedle from a bevel opening proximate the tip of the at least one microneedle;

wherein the at least one second projection comprises a second longitudinal axis;

35 wherein the second projection is shaped and dimensioned to define the tip portion;

wherein the tip portion includes a tip, a beveled surface, a bevel opening in the bevel surface, a first channel that extends axially from the bevel opening through at least a portion of the elongated body, and a second channel that extends radially from the first channel to the bevel opening;

5 wherein the first channel has a first wall that is substantially aligned with the second longitudinal axis; and

wherein the second channel has a second wall that is oriented substantially orthogonal to the second longitudinal axis;

10 wherein the second projection is shaped and dimensioned such that the first channel and second channel merge to form the bevel opening;

contacting at least the first mold surface or the second mold surface with moldable material; and

inserting the second projection into the at least one cavity.

15 12. The method of claim 11, wherein the second projection is inserted into the at least one cavity before contacting at least the first mold surface or the second mold surface with the moldable material.

20 13. The method of claim 11, wherein at least the first mold surface or the second mold surface is contacted with the moldable material before inserting the second projection into the at least one cavity.

14. The method of any one of claims 11 through 13, wherein the moldable material comprises a metal, a ceramic, or a polymeric material.

25 15. The method of any one of claims 11 through 13, wherein the at least one cavity has a cavity aspect ratio (cavity length to cavity base width) of at least 1.5 to 1.

30 16. The method of any one of claims 11 through 15, wherein the first mold half comprises a plurality of the at least one cavities, wherein the second mold half comprises a plurality of the at least one second projections, wherein the plurality of second projections is aligned to be inserted simultaneously into the plurality of cavities.

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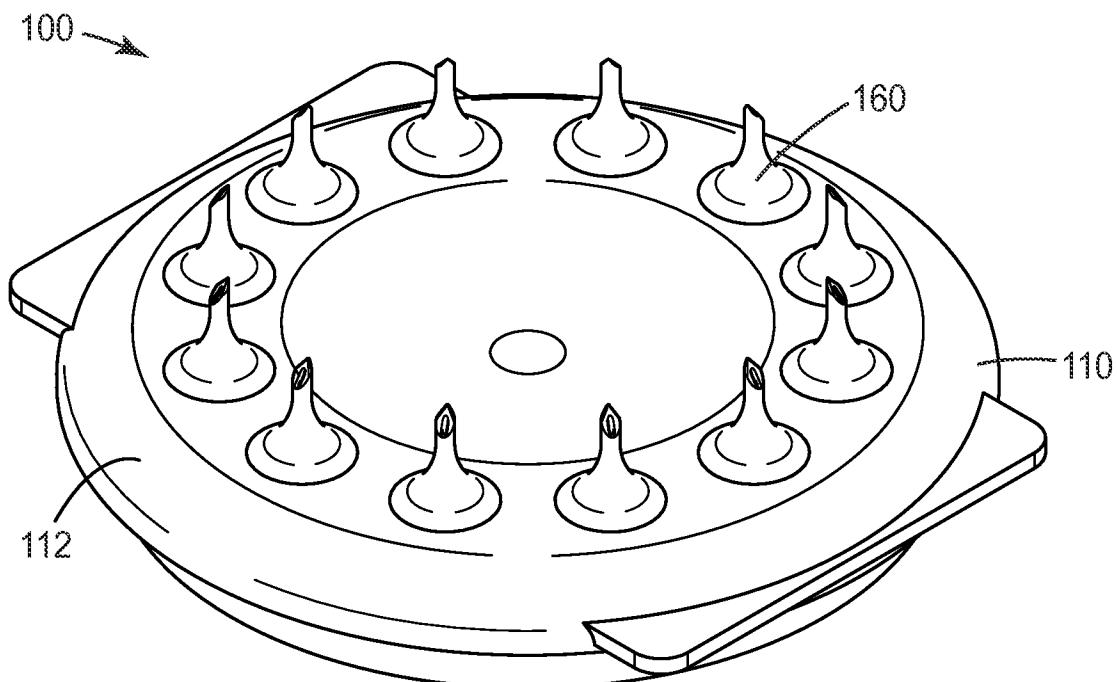


FIG. 1

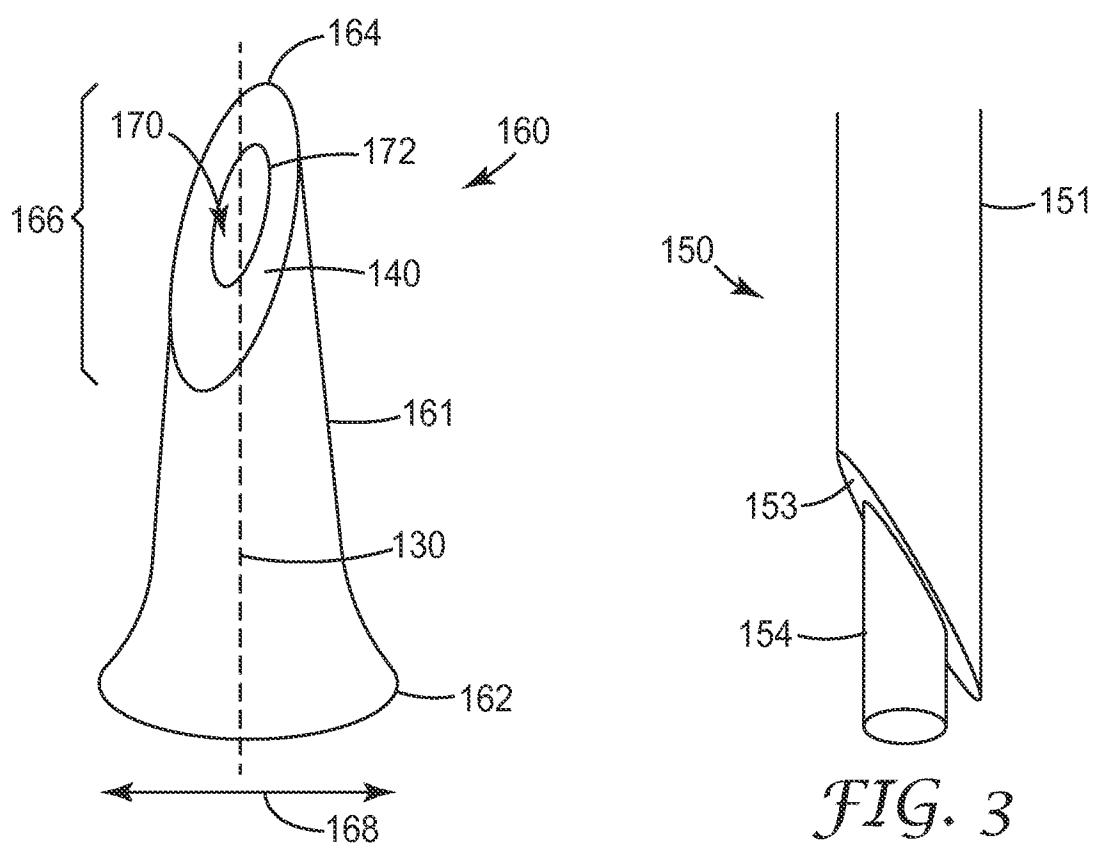
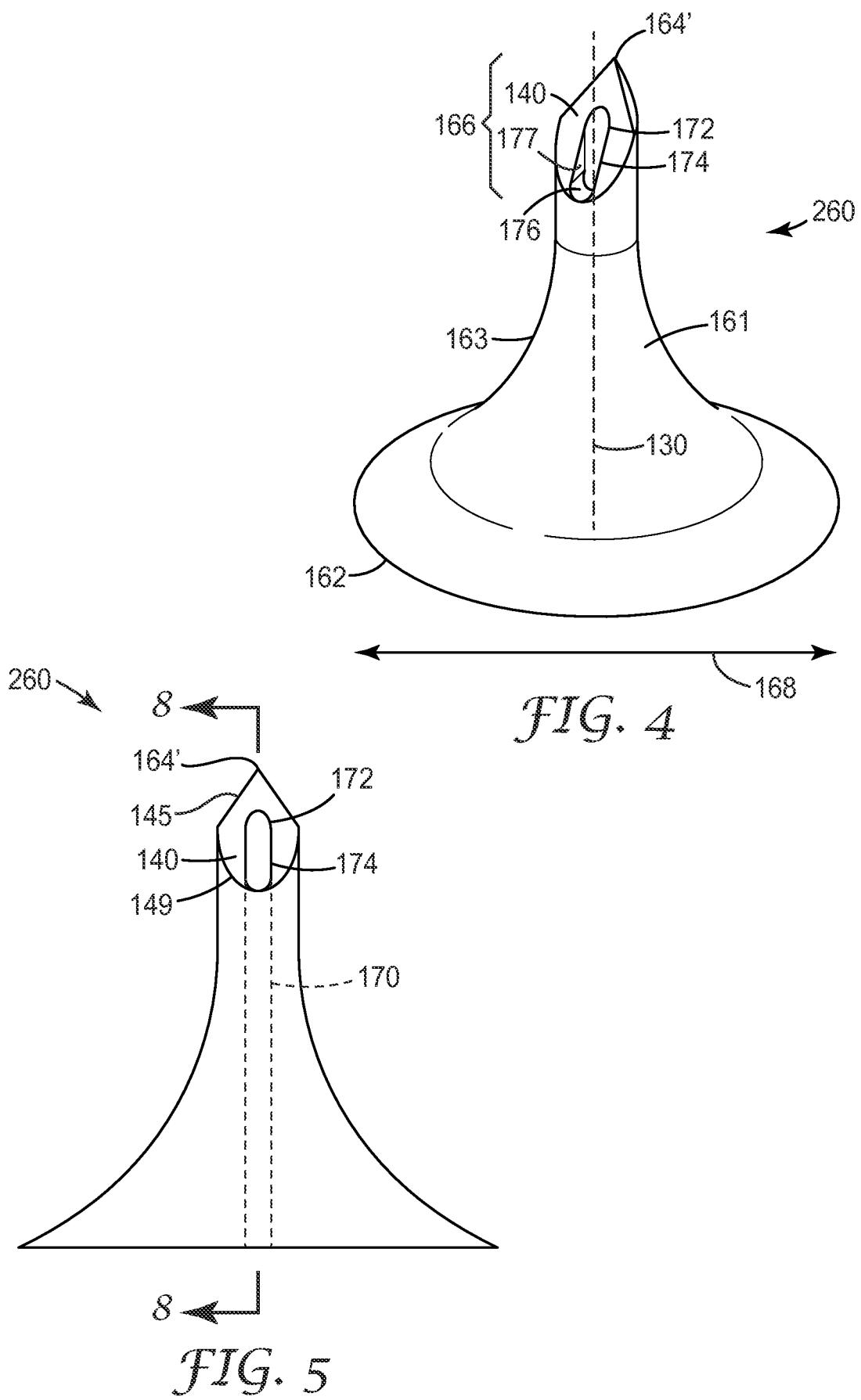


FIG. 2

FIG. 3



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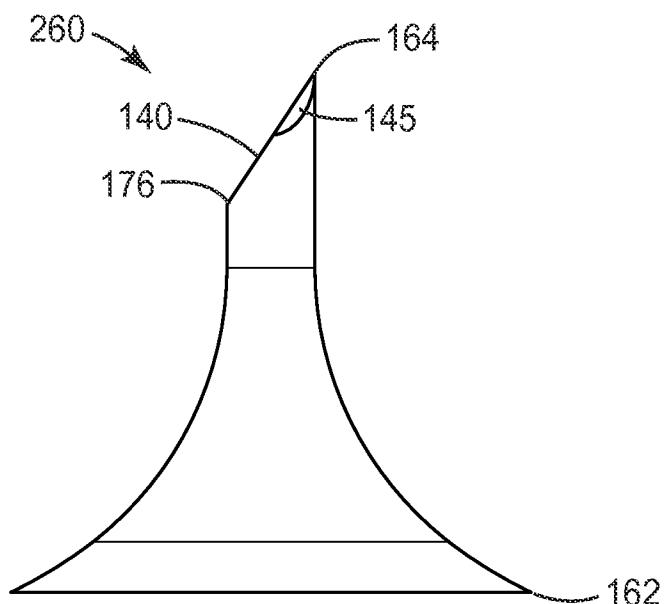


FIG. 6

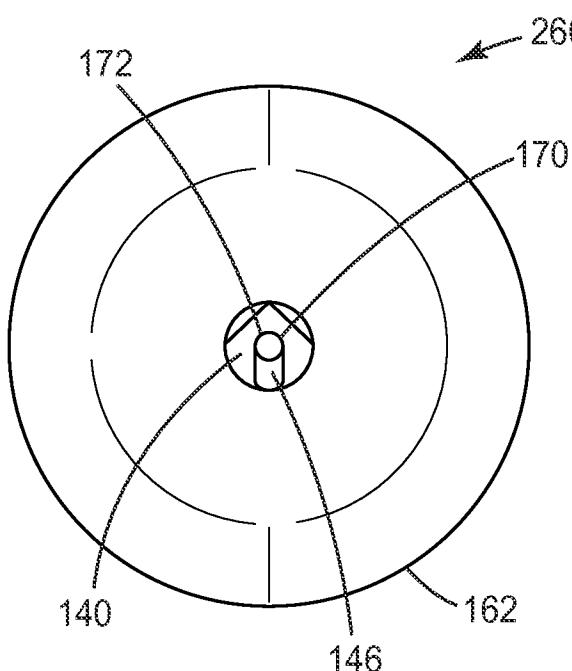


FIG. 7

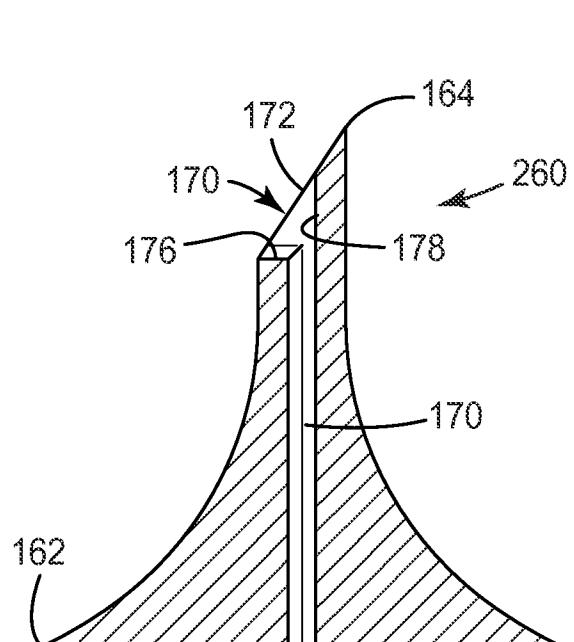
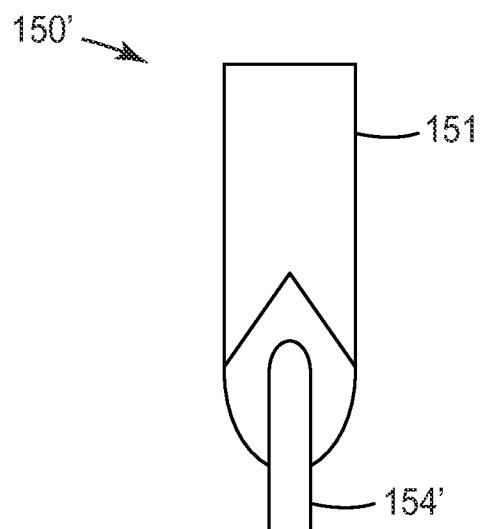
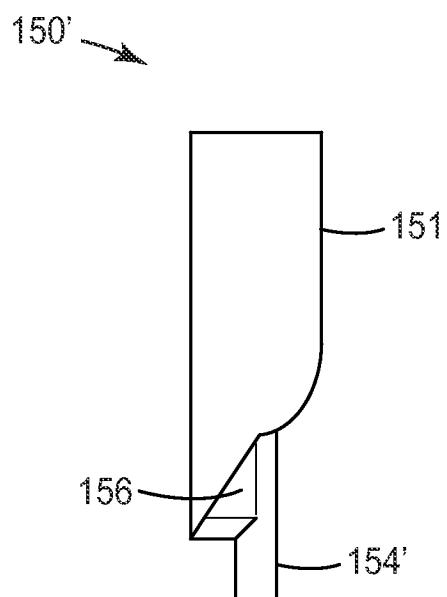
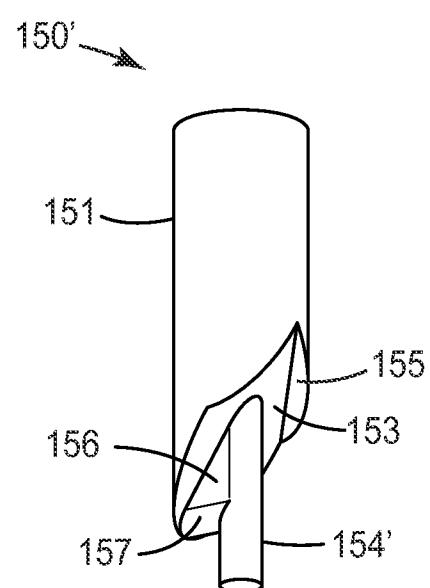


FIG. 8

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*FIG. 9A**FIG. 9B**FIG. 9C*

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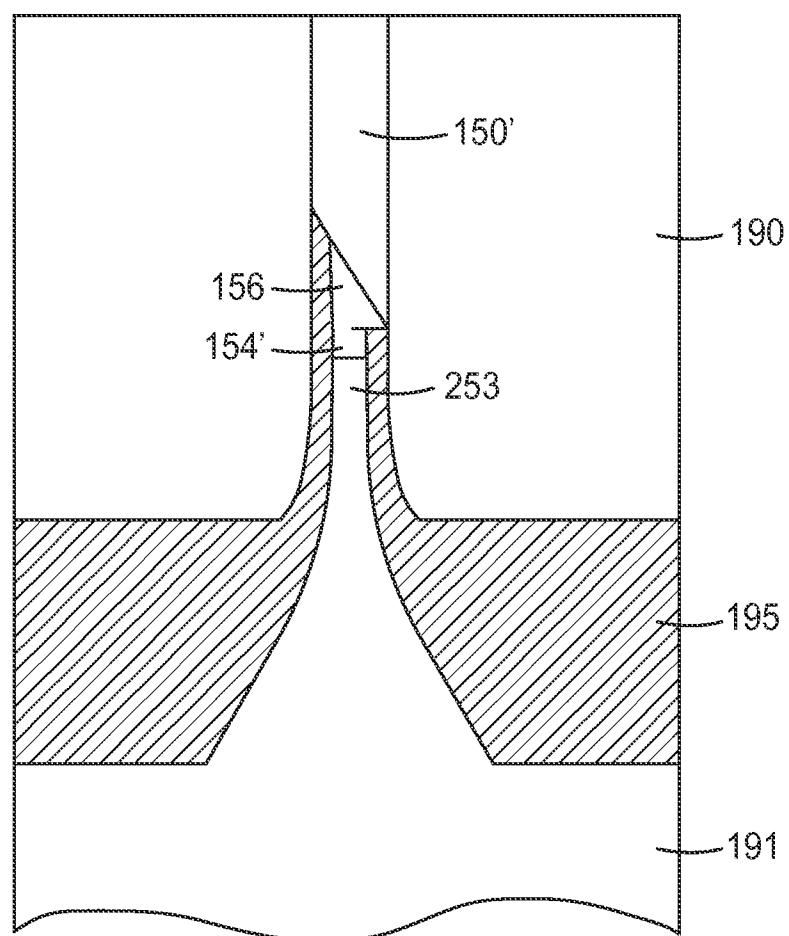


FIG. 10

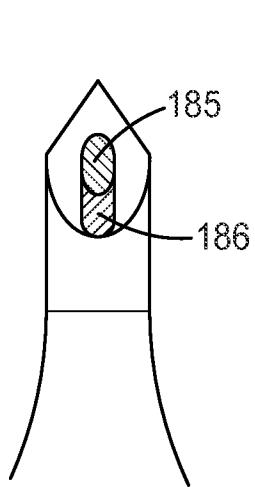


FIG. 11

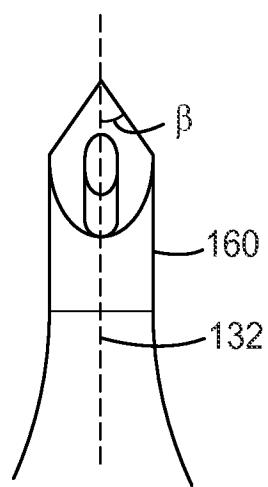


FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/046097

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61M37/00 A61B5/15 A61B5/00 B29C45/00
 ADD.

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)
 A61M A61B B29C

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/305516 A1 (XU YUAN [SG] ET AL) 2 December 2010 (2010-12-02) figures 13B, 13C, 24B paragraph [0001] paragraph [0078] - paragraph [0079] paragraph [0068] - paragraph [0075] ----- DE 10 2008 052749 A1 (HAHN SCHICKARD GES [DE]) 27 May 2010 (2010-05-27) figures 1G, 1H, 1I, 1P, 5, 6A, 6B, 7, 10A paragraph [0001] paragraph [0053] paragraph [0060] - paragraph [0061] paragraph [0078] - paragraph [0089] ----- -/-	1-16
X		1-16

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
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2014	29/09/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Przykutta, Andreas

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/046097

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/025786 A1 (BONSENS AB [SE]; STEMME GOERAN [SE]; GRISS PATRICK [CH]) 9 March 2006 (2006-03-09) figure 7 -----	1-16
A	US 2009/054842 A1 (YESHURUN YEHOOSHUA [IL] ET AL) 26 February 2009 (2009-02-26) figures 1a-2c -----	1-16
A	WO 2013/061825 A1 (TOPPAN PRINTING CO LTD [JP]) 2 May 2013 (2013-05-02) figures 2, 5, 6 -----	1-16
A	US 2011/172605 A1 (BERENSCHOT JOHAN WILLEM [NL] ET AL) 14 July 2011 (2011-07-14) figures 1A-2B -----	1-16
A	WO 2008/027011 A1 (AGENCY SCIENCE TECH & RES [SG]; LIM CHEE YEN [SG]) 6 March 2008 (2008-03-06) figure 2 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/046097

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
US 2010305516	A1 02-12-2010	CN 1993156 A EP 1732640 A1 JP 4500851 B2 JP 2007535343 A US 2010305516 A1 WO 2005087305 A1			04-07-2007 20-12-2006 14-07-2010 06-12-2007 02-12-2010 22-09-2005
DE 102008052749	A1 27-05-2010	NONE			
WO 2006025786	A1 09-03-2006	AT 444096 T EP 1796778 A1 JP 2008511382 A US 2007255205 A1 WO 2006025786 A1			15-10-2009 20-06-2007 17-04-2008 01-11-2007 09-03-2006
US 2009054842	A1 26-02-2009	CA 2546443 A1 EP 1699524 A2 JP 2007511318 A US 2009054842 A1 WO 2005049107 A2			02-06-2005 13-09-2006 10-05-2007 26-02-2009 02-06-2005
WO 2013061825	A1 02-05-2013	CN 103889499 A EP 2772279 A1 KR 20140079862 A US 2014236075 A1 WO 2013061825 A1			25-06-2014 03-09-2014 27-06-2014 21-08-2014 02-05-2013
US 2011172605	A1 14-07-2011	CN 102123759 A EP 2303766 A2 JP 5542811 B2 JP 2011525402 A NL 2001718 C2 US 2011172605 A1 WO 2009157765 A2			13-07-2011 06-04-2011 09-07-2014 22-09-2011 28-12-2009 14-07-2011 30-12-2009
WO 2008027011	A1 06-03-2008	EP 2073888 A1 JP 2010502267 A US 2009326415 A1 WO 2008027011 A1			01-07-2009 28-01-2010 31-12-2009 06-03-2008