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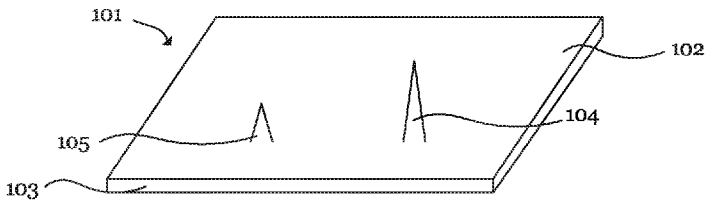

Fig. 1

(57) **Abstract:** A microneedle array (101) comprises a surface (102) and two or more microneedles (104, 105) extending from the surface, wherein at least one of the microneedles has a different shape and/or length compared with a shape and/or length of at least one other of the microneedles. Furthermore method of making.

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MICRONEEDLE ARRAYS AND METHOD OF MAKING

Field

The present disclosure relates to microneedle arrays, methods of manufacturing microneedle arrays and uses of microneedle arrays.

Background

Many users find conventional injection devices, such as intramuscular syringes, uncomfortable or painful to use. Such devices may be associated with increased bleeding at the injection site, as well as other complications. Multiple injections may be required to supply different medicaments to the user.

Microneedle arrays represent a promising means for administering medicament to a user. Some microneedle arrays typically comprise a number of needles coated with a medicament and extending from a surface of the patch. In use, a user presses the surface comprising the microneedles against their skin, which causes the microneedles to penetrate the skin and facilitate the transdermal delivery of the medicament to the user. Relative to conventional injection devices, microneedle arrays may be considered to be minimally invasive. For example, the short length of the microneedles reduces the chance of adverse reactions, such as bleeding and pain, at the site of application. Microneedle arrays may also be attached to a user, which can allow for the delivery of a medicament over an extended period of time.

Summary

According to a first aspect of the disclosure, there is provided a microneedle array comprising a surface and two or more microneedles extending from the surface, wherein at least one of the microneedles has a different shape and/or length compared with a shape and/or length of at least one other of the microneedles.

In some embodiments, the microneedle array comprises at least two microneedle sub-arrays, the microneedles of at least one of the sub-arrays having a different shape and/or length to a shape and/or length of the microneedles of another of the sub-arrays.

In some embodiments, each microneedle has a length of from about 50 μm to about 1500 μm.

In some embodiments, one or more of the microneedles has a length of from about 10 μm to about 500 μm and one or more of the microneedles has a length of from about 501 μm to about 1500 μm.

In some embodiments, the microneedles have a height aspect ratio of up to about 1:20.

In some embodiments, the microneedles have a distance aspect ratio of 2 to 150.

In some embodiments, the microneedle array comprises from 2 to 2000 microneedles.

In some embodiments, each microneedle comprises a tube for transporting fluid to an outlet of each microneedle.

In some embodiments, each microneedle comprises a proximal end and a distal end and a surface extending between the proximal end and the distal end and the outlet is positioned on the surface between the proximal end and the distal end of the respective microneedle.

In some embodiments, the outlet of at least one of the microneedles is positioned at a first position on the surface of the microneedle and wherein the outlet of at least one of the other microneedles is positioned at a second position on the surface of the microneedle, wherein the first position is closer to the proximal end of the microneedle than the second position.

In some embodiments, the microneedle array comprises one or more conduits arranged to provide fluid communication between two or more of the tubes of different microneedles.

In some embodiments, the microneedle array comprises a first sub-array comprising two or more microneedles and a second sub-array comprising two or more microneedles, wherein the microneedle tubes of the first sub-array are arranged to transport a first fluid to their respective outlets and wherein the microneedle tubes of the second sub-array are arrange to transport a second fluid to their respective outlets.

In some embodiments, the microneedle tubes of the first sub-array of microneedles are fluidly isolated from the microneedle tubes of the second sub-array of microneedles.

In some embodiments, each tube is arranged to transport a fluid from at least one fluid reservoir to a fluid outlet of the microneedles.

In some embodiments, the microneedle array is configured such that one or more of the microneedles are arranged to simultaneously transport different fluids to their respective fluid outlets.

In some embodiments, the microneedle array comprises two or more fluid reservoirs, each of the fluid reservoirs being in fluid communication with one or more microneedle sub-arrays.

In some embodiments, the microneedle array is in the form of a patch.

In some embodiments, the patch is for application to the skin of a user.

In some embodiments, the patch is arranged to be attached to a surface and conform to a geometry of the surface.

In some embodiments, the microneedle array comprises an adhesive on the surface.

In some embodiments, the microneedles are arrange such that, when applied to the skin of the user, at least one of the microneedles is arranged to penetrate the skin of the user to a different depth compared with at least one other of the microneedles.

In some embodiments, the microneedles are arranged to deliver a pharmaceutical composition to a user.

According to a second aspect of the disclosure, there is provided a method of manufacturing a microneedle array, wherein the method comprises an additive manufacturing process from a feedstock material.

In some embodiments, the additive manufacturing process is a 3D printing process depositing layer upon layer of a feedstock material.

In some embodiments, the feedstock material is a resin.

According to a third aspect of the disclosure, a microneedle array manufactured according to the method of the second aspect is provided.

According to a fourth aspect of the disclosure, a microneedle array of the first or third aspects is provided for use in administering a medicament to a patient.

According to a fifth aspect of the disclosure, a microneedle array of the first or third aspects is provided for use in a therapeutic and/or cosmetic treatment.

In some embodiments, the microneedle array is for use in the simultaneous delivery of at least two different medicaments to the skin of a user.

Brief Description of the Drawings

Embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 shows a perspective view of a microneedle array;

Figure 1a shows a section view of the microneedle array shown in Figure 1;

Figure 1b shows a perspective view of a microneedle array;

Figure 2 shows a perspective view of a microneedle array;

Figure 3 shows a top-down perspective view of a microneedle array;

Figures to 4 to 6c show section views of parts of various microneedle arrays;

Figure 7 to 11 show section views of various microneedle arrays;

Figure 12a shows a perspective views of a microneedle array; and

Figures 12b and 12c are confocal microscope images of mouse skin pierced by the microneedles of the microneedle array shown in Figure 12a.

Detailed Description

According to a first aspect of the disclosure, there is provided a microneedle array comprising a surface and two or more microneedles extending from the surface, wherein at least one of the microneedles has a different shape and/or length compared to a shape and/or length of at least one other of the microneedles. A microneedle array comprising microneedles having different shapes and/or lengths enables the microneedle array to be used for the delivery of a composition comprising a medicament, to different skin locations and skin depths. The composition can be a fluid or a semi-solid, such as a gel. Preferably, the composition is a fluid, such as a

liquid. In some embodiments, the composition is a hydrogel. The microneedle array may be used for therapeutic treatment and/or for cosmetic treatment.

In some embodiments, at least one of the microneedles extends from the surface by a first distance and at least one of the microneedles extends from the surface by a second distance that is greater than the first distance.

In some embodiments, at least one of the microneedles has a first shape and one or more of the microneedles has a second shape that is different to the first shape.

For example, referring to Figure 1, a microneedle array 101 comprises a first surface 102 and a second surface (not shown) opposite the first surface 102. An edge 103 joins the first surface 102 and the second surface. Extending from the first surface are microneedles 104 and 105.

Referring to Figure 1a, microneedle 104 of the microneedle array extends further from the first surface 102 than microneedle 105. Thus, microneedle 104 is longer than microneedle 105. Each microneedle comprises a distal end 104a and a proximal end 104b. In use, the microneedle array 104 is placed against the skin of a user such that the microneedles penetrate into the skin of the user. As used herein in relation to the microneedles, the term "distal end" refers to the portion of the microneedle furthest from the intended skin penetration site and the term "proximal end" refers to the portion of the microneedle closest to the intended skin penetration site.

In some embodiments, the microneedle array is relatively flexible and has sufficient flexibility to conform to the shape of the intended site of application when in use. The microneedle array can be arranged to be attached to a surface and conform to a geometry of the surface. For example, the microneedle array may be configured to confirm to the curvature of a user's limb. This increases the contact area between the microneedle array and the site of application, which may improve the efficiency of medicament delivery from the microneedles to the user. Alternatively, the microneedle array may be rigid. A relatively rigid microneedle array may be more resistant to damage.

The dimensions of the microneedle array may be selected depending on the size of the intended application region and the intended dose. The surface from which the

microneedles extend may be any suitable dimension. For example, the microneedle array may be in the form of a patch having a length, a width and a depth. The length and width are greater than the depth of the patch. The distance between the first and second surfaces defines a thickness of the microneedle array. The length of the patch can be the same or different to the width of the patch. For example, the patch can have a length of 5 mm up to about 500 mm and a width of 5 mm up to about 500 mm. Thus, the patch can be from about 25 mm^2 to about 250,000 mm^2. In some embodiments, the patch is from about 25 mm^2 to about 200 mm^2 or 100 mm^2. This may enable the microneedle array to be discretely fixed to a user's skin for an extended period of time. In some embodiments, the microneedle array may have larger dimensions. For example, the microneedle array can be in the form of a flexible sheet that is configured, for example, to wrap at least partially around the limb of a user.

The microneedle array can have any suitable shape including, regular and irregular shapes. The microneedle array can have a square, rectangular, circular or oval shape, for example. In some embodiments, the microneedle array has a shape that is specific and tailored to match a particular shape, such as a shape of the site to which it is intended to apply the microneedle array. The microneedle array may be pre-formed into a desired shape during manufacturing. In some embodiments, the microneedle array may be formed from a material that can be readily cut to allow the shape of the microneedle array to be tailored as required. For example, a microneedle array can be formed using 3D printing and then cut into a plurality of separate microneedle arrays. This may improve manufacturing efficiency.

The microneedle array may comprise a means for facilitating attachment of the microneedle array to the skin of a user when in use. In some embodiments, the microneedle array may comprise adhesive on the surface from which the microneedles extend which adheres to a user's skin when the microneedle array is applied. The adhesive be a layer of adhesive partially or fully covers the surface, but which does not cover the microneedles.

For example, as shown in Figure 1b, a microneedle array 101a comprises a first surface 102a and a second surface (not shown) opposite the first surface 102a. An edge 103a joins the first and second surfaces. Extending from the first surface are microneedles 104c and 105a. Microneedle 104c of the microneedle array extends further from the first surface 102a than microneedle 105a. The microneedle array comprises an

adhesive 102b which partially covers the first surface 102a. Regions 102c around the microneedles 104c, 105a are free from adhesive.

The microneedles can be relatively rigid structures that protrude from a surface of the microneedle array. The microneedles may be arranged to deliver a medicament to a user when the microneedle array is applied to the skin of a user. In some embodiments, the microneedle array comprises a liquid medicament to be delivered to a user. The microneedles can be relatively pointed and sharp such that they pierce, and extend into, the skin of the user when applied. The microneedles may not be of sufficient length to extend all the way through a user's skin. The microneedles may be of sufficient length to extend into one or more layers of a user's skin.

In some embodiments, the microneedles of the microneedle array are solid, hollow, coated or dissolvable. In preferred embodiments, some or all of the microneedles are hollow microneedles. The microneedle array may comprise one or more solid microneedles, one more hollow microneedles, one or more coated microneedles and/or one or more dissolvable microneedles. A hollow microneedle may comprise a tube which terminates at one end in an opening on a surface of the microneedle. The tube may be suitable for conveying liquid to the opening.

The microneedle array may comprise at least two microneedle sub-arrays. A microneedle sub-array comprises one or more microneedles. At least one of the microneedle sub-arrays comprises a microneedle that has a different shape and/or length to a shape and/or length of the microneedles of another of the sub-arrays.

For example, referring to Figure 2, a microneedle array 201 comprises a first surface 202 and a second surface (not shown) opposite the first surface 202. The first surface and the second surface are joined by an edge 203. The microneedle array comprises four microneedle sub-arrays 204a, 204b, 205a and 205b. Each of the sub-arrays 204a, 204b comprises three microneedles 204 of identical length and each of the sub-arrays 205a, 205b comprises three microneedles 205 of identical length. Each microneedle 204 of sub-arrays 204a, 204b is longer than each microneedle 205 of sub-arrays 205a, 205b.

The microneedles may have any suitable shape, such as pyramidal, conical or cylindrical. The edges of the microneedles extending from the surface of the

microneedle array may taper with increasing distance from the surface of the surface to form a point. The point of the microneedles may be sharp enough to pierce the skin of a user when the microneedle array is used. In preferred embodiments, the microneedles are conical and thus have a circular horizontal cross section. Microneedles having other horizontal cross-sections are also envisaged. For example, the needle may have a star-shaped horizontal cross section.

In some embodiments, the microneedles have different relative surface areas. The microneedles may be appropriately shaped in order to increase their relative surface area. Increasing the surface area of one or more of the microneedles may facilitate the delivery of a medicament to the skin of a user when in use. The relative dimensions of the microneedles may be used to control the amount of dose of medicament that is delivered to the skin of a user when in use.

For example, referring to Figure 3, the microneedle array 301 comprises a first microneedle sub-array 302a and second microneedle sub-array 302b. The first microneedle sub-array 302a comprises two microneedles 303 extending from a surface 304 of the microneedle array and having a star-shaped horizontal cross-section. The second microneedle sub-array 302b comprises two microneedles 304 having a different star-shaped horizontal cross-section and extending from the surface 304. As can be seen, microneedles 303 of the first sub-array 302a have a different shape to the microneedles 305 of the second sub-array 302b. Owing to their different shapes, the microneedles 305 may have a higher surface area relative to the microneedles 303.

In some embodiments, the number of microneedles per microneedle array may be varied depending upon the application and also the size of the microneedle array. For example, the number of microneedles per microneedle array may be dependent upon the size of the intended application site and the intended treatment. Larger microneedle arrays may have more microneedles. In some embodiments, the microneedle array comprises from about 2 microneedles up to about 100 microneedles, or from about 2 microneedles up to around 500 microneedles. In some embodiments, the microneedle array comprises from 2 up to around 400, 300, 200 or 100, 75, 50 or 25 microneedles.

The length of the microneedles can be tailored depending on the clinical requirements of the microneedle array, such as the desired skin penetration depth, the type of

medication to be delivered to the user and the number of microneedles. To penetrate deeper into the skin of a user, longer microneedles may be used.

The microneedles can have any suitable length. Each microneedle may have a length of from about 10 μm to about 1500 μm. In some embodiments, the microneedles have a length of from about 50 μm up to about 1500 μm, 1400 μm, 1300 μm, 1200 μm, 1100 μm, 1000 μm, 900 μm, 800 μm, 700 μm, 600 μm, 500 μm, 400 μm, 300 μm, 200 μm or 100 μm. The microneedles may have a length of from about 50 μm to about 1000 μm from about 50 μm to about 600 μm, from about 75 μm to about 550 μm or from about 100 μm to about 500 μm.

At least one of the microneedles may be shorter than another of the microneedles. In some embodiments, one or more of the microneedles has a length of from about 10 μm to about 500 μm and one or more of the microneedles has a length of from about 501 μm to about 1500 μm. In some embodiments, at least one of the microneedles has a length of from about 100 μm to about 500 μm, 150 μm to about 500 μm or from about 200 μm to about 500 μm and at least one of the microneedles has a length of from about 501 μm to about 1400 μm, up to about 1300 μm, up to about 1200 μm, up to about 1100 μm or up to about 1000 μm.

The density of the microneedles extending from the surface of the microneedle array may be from about 50 microneedles per 25 mm^2 of the surface of the microneedle array. For example, the surface of the microneedle array from which the microneedles extend can have an area (width x length) of 100 mm^2 and 200 microneedles may extend from the surface.

The separation between each adjacent microneedles of the microneedle array may be the same or, in some embodiments, it may be different. In some embodiments, the distance between two adjacent microneedles may be different compared with the distance between two other adjacent microneedles.

The microneedles can have a distance aspect ratio. As used herein, the term "distance aspect ratio" is defined as the ratio of the centre-to-centre distance D between two microneedles to the radius R of the microneedles. In some embodiments, the microneedle array comprises two adjacent microneedles having different distance aspect ratios compared with two other adjacent microneedles. In some embodiments,

the distance aspect ratio of all adjacent microneedles of the microneedle array is the same. The distance aspect ratio can be precisely controlled using the methods of manufacturing the microneedle array that are described herein. The distance aspect ratio can be between about 1:1 and about 300:1 or from about 1:1 to about 1:300. For example, in some embodiments, the centre-to-centre distance D between two microneedles is 300 μm, the radius of the microneedles is 100 μm and the distance aspect ratio is 3 (300:100). In some embodiments, the distance aspect ratio is about 1:1 to about 300:1, about 2:1 to about 250:1, about 3:1 to about 200:1 or about 4:1 to about 150:1.

For example, referring to Figure 4, two microneedles 401, 402 extend from a surface 403 of a microneedle array. Microneedle 401 has a radius R and the centre-to-centre distance between microneedle 401 and microneedle 402 is D.

Each microneedle may have a height aspect ratio. As used herein, the term "height aspect ratio" is defined as the ratio of the length of a microneedle to the radius of the microneedle. For example, a microneedle having a length of 200 μm and a radius of 20 μm will have a height aspect ratio of 10:1. In some embodiments, all of the microneedles of a microneedle array may have the same height aspect ratio. In some embodiments, some or all of the microneedles have different height aspect ratios to each other.

For example, referring to Figure 5, a microneedle 501 extending from a surface 502 of a microneedle array has a length L and a radius R. The height aspect ratio may be from up to about 1:20. In some embodiments, the height aspect ratio is up to about 1:15, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2 or 1:1.

In some embodiments, at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the microneedles have a first shape and/or length. The remaining microneedles may have one or more different shapes and/or lengths compared to the first shape and/or length. For example, from about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the microneedles have a first shape and/or length and up to about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20% or 10% may have one or more different shapes and/or lengths compared to the first shape and/or length. Adjusting the relative proportions of the microneedles having the first and second shape and or/ length is beneficial where it is required to administer at least two different medicaments of differing quantities.

In some embodiments, some or all of the microneedles comprise a coating comprising the medicament. In some embodiments, at least some of the microneedles are solid microneedles and a coating comprising a medicament is formed on the surface of the coating. The coating may be rapidly transferred to the user upon contact with the user's skin. The use of a coating may be beneficial where the medicament is a solid or semi-solid.

For example, referring to Figure 6a, a microneedle 601 comprises a coating 602 comprising a medicament. In use, the microneedle 601 penetrates the skin of a user and at least some of the coating 602 comprising the medicament is transferred to the user's skin.

In some embodiments, the coating fully or partially coats the surface of the microneedle. The quantity of medicament to be delivered to a user (for example, the dosage) may be controlled by altering the proportion of surface that is covered with the coating of the medicament. Some of the microneedles of the microneedle array may be completed coated with the medicament, whilst other microneedles may be partially coated or not coated at all.

Alternatively or in addition, one or more of the microneedles may comprise a tube for transporting fluid to an outlet of the respective microneedle. The fluid may be stored within the tube prior to use. The fluid may be a composition comprising a medicament for treating a user. When the microneedle array is applied to the skin of a user, the fluid may be delivered to the user's skin by capillary action. Alternatively, the microneedle array may be configured to eject the fluid from the tubes by positive pressure. For example, the microneedle array can be configured such that the application of pressure to the microneedle array (e.g. by a user pressing on or squeezing the microneedle array) causes the ejection of fluid from the tubes. In some embodiments, the tubes of the microneedles are in communication with a syringe containing the fluid. The fluid can be transferrd to the tubes of the microneedles using a micro-syringe pump, an electromechanical pump or a piezo electric pump.

The tubes may have a diameter of 2 μm to about 20 μm. In some embodiments, the tubes have a diameter of from about 3, 4, 5, 6, 7 or 8 μm up to about 19, 18, 17 16, 15, 14, 13 or 12 μm Preferably, the tubes have a diameter of about 9, 10 or 11 μm. The volume

of fluid in the tubes and rate of fluid delivery can be controlled by controlling the diameter of the tubes.

For example, referring to Figure 6b, microneedle 601a comprises a surface 601b a tube 601c extending through the body of the microneedle 601a from a distal end 602a to a proximal end 602b of the microneedle 601a. The proximal end 602b is configured to pierce the skin of a user. The tube 601c terminates to form an outlet 601d near to the proximal end 602b. The tube may be at least partially filled with a liquid medicament.

In some embodiments, including in any of the embodiments described herein, the tube of the microneedle terminates to form an outlet at any point on the surface of the microneedle. When the microneedle array is applied to the skin of a user, the microneedles pierce the skin of the user. The microneedle array is configured to administer medicament to the skin of the user through the tubes of the microneedles. The medicament can be administered to a specific skin depth of the user by controlling the length of the needle (and thus how far into the skin the microneedle penetrates) and/or the position of the tube outlet on the surface of the microneedle. The outlet of the tube can be positioned at any suitable point on the surface of the microneedle between the proximal and distal ends of the microneedle. This enables the depth of skin at which the needle delivers medicament to the user to be precisely controlled.

Referring to Figure 6c, microneedle 611a comprises a distal end 612a a proximal end 612b, a surface 611b extending between the distal end 612a and the proximal end 612b and a tube 611c extending through the body of the microneedle 611a from the distal end 612a and terminating in an outlet 611d on the surface of 611b of the microneedle 611a. The outlet 611d is positioned on the surface of the microneedle 611a approximately midway between the distal end 612a and proximal end 612b of the microneedle.

In some embodiments, the microneedle array comprises two or more microneedles that have different lengths and the outlets of the tubes are positioned at any suitable point on the surface of each microneedle between the proximal and distal ends of each microneedle. The ability to tailor both the relative microneedle lengths and outlet positions of the microneedles provides significant flexibility with regards to the depth of skin at which the medicament is delivered to the user.

In some embodiments, the microneedle array comprises one or more conduits arranged to provide fluid communication between two or more of the tubes of different microneedles. The conduits may interconnected, thereby reducing the requirement to fill each tube of each microneedle individually and facilitating the filling of the tubes with a medicament. A conduit may be formed in the material of the microneedle array between the first surface and the second surface (e.g. it may be within a body of the microneedle array). A single conduit may provide fluid communication between the tubes of all of the microneedles. The conduit and/or the tubes may be supplied with fluid via a fluid supply tube which is configured to receive the fluid from an external source.

For example, referring to Figure 7, a microneedle array 701 comprises a first surface 702a and a second surface 702b. Extending from the first surface 701a are two microneedles 703 and 704. Microneedle 704 is the same length as microneedle 703. In other embodiments, the microneedle 704 is a different length to the microneedle 703. Each of the microneedles 703 and 704 comprises a respective tube 705a and 705b and outlet 703a and 703b. In the illustrated embodiment, although the outlet is positioned at the proximal end of the microneedles, it can be positioned at another point on the surface of the microneedles. A conduit 706 located between the first surface 702a and the second surface 702b is arranged to connect tube 705a and tube 705b such that the tubes are in fluid communication with each other. A fluid supply tube 707 is in fluid communication with the conduit 706 and terminates at a point on the second surface 702b to form a fluid inlet 707a. The fluid supply tube 707 is configured to receive a fluid (such as a medicament) from an external source and supply the fluid to the conduit 706 in a direction indicated by arrow A. The fluid can be transferred from the fluid supply to the microneedle outlets 703a and 703b via conduit 706 and tubes 705a and 705b in the direction indicated by the arrows. The external supply source is configured to supply fluid to the conduit 706 of the microneedle array 701.

The external supply source and the conduit 706 may be configured such that the external supply source can be releasably connected to the conduit 706 to form a fluid-tight pathway between the external supply source and the fluid inlet 707a. The external supply source can be, for example, a syringe or a pump (such as a micro-pump, an electromechanical pump or a piezo electric pump) which is configured to transfer fluid from a fluid reservoir of the external supply source to the conduit 706 of the microneedle array 701.

In some embodiments, the microneedle array comprises a first sub-array comprising two or more microneedles and a second sub-array comprising two or more microneedles and the microneedle tubes of the first sub-array are arranged to transport a first fluid to their respective outlets and the microneedle tubes of the second sub-array are arrange to transport a second fluid to their respective outlets. The microneedle tubes of the first sub-array of microneedles may be fluidly isolated from the microneedle tubes of the second sub-array of microneedles. That is to say, fluid contained within one conduit cannot be transferred to another conduit without the fluid exiting the outlets of the microneedle tubes. This enables a single microneedle array to deliver two different medicaments to a user. The microneedle array may, therefore, by configured such that one or more of the microneedles are arranged to simultaneously transport different fluids to their respective outlets.

For example, referring to Figure 8, a microneedle array 801 comprises a first surface 802a and a second surface 802b. Extending from the first surface 802a are four microneedles 803a, 803b, 804a and 804b. Each of the microneedles comprises a tube 805a, 805b, 805c and 805d. A first conduit 806 located between the first surface 802a and the second surface 802b is arranged to connect tubes 805a and tube 805b such that the tubes 805a, 805b are in fluid communication with each other. A second conduit 807 located between the first surface 802a and the second surface 802b is arranged to connect tubes 805c and tube 805d such that the tubes are in fluid communication with each other. Each of the conduits 806 and 807 is in fluid communication with a respective fluid supply tube (not shown) for supplying fluid to the conduits. Each fluid supply tube is configured to receive a fluid (such as a liquid medicament) from an external source and supply the fluid to the conduits 806 and 807. A different fluid can be supplied to each of the conduits 806 and 807 via their respective fluid supply tubes.

In some embodiments, the microneedle array comprises one or more reservoirs. The reservoirs may be configured to contain a medicament. The reservoirs increase the medicament storage capacity of the microneedle arrays and may also allow for the medicament to be released from the microneedles over a longer period of time. The reservoirs may be in fluid communication with one or more of the tubes of the microneedles. The tubes of one or more of the microneedles may be arranged to transport a fluid from at least one fluid reservoir to the outlets of the microneedles.

In some embodiments, all of tubes of the microneedles in fluid communication with a single central fluid reservoir. This may be beneficial where the microneedle array is for delivering a single medicament and/or a large quantity of a single medicament.

The microneedle array may comprise more than one fluid reservoir. Where the reservoir comprises two or more fluid reservoirs, each reservoir may comprise a different medicament. A fluid reservoir may be configured to contain a larger volume of medicament than a fluid conduit.

For example, referring to Figure 9, a microneedle array 901 comprises a first surface 902a and a second surface 902b. Extending from the first surface 902a are four microneedles 903a, 903b, 904a and 904b. Each of the microneedles comprises a tube 905a, 905b, 905c and 905d. Each microneedle tube 905a, 905b, 905c and 905d is in fluid communication with a respective reservoir 906a, 906b, 906c and 906d located between the first surface 902a and the second surface 902b. The reservoirs 906a, 906b, 906c and 906d are arranged to supply tubes 905a, 905b, 905c and 905d, respectively, with a fluid. In use, each reservoir 906a, 906b, 906c and 906d may contain the same fluid such that each of the microneedle tubes 905a, 905n, 905c and 905d are configured to supply the same medicament. Alternatively, one or more of the reservoirs 906a, 906b, 906c and 906d can contain a different medicament. For example, reservoirs 906a and 906d may contain a fluid that is different to the fluid contained in reservoirs 906b and 906c. This enables the microneedle array 901 to deliver multiple different medicaments.

Optionally, each reservoir 906a, 906b, 906c and 906d is in fluid communication with a respective fluid supply tube (not shown) for supplying fluid to the reservoirs 906a, 906b, 906c and 906d. Each of the fluid supply tubes is configured to receive a fluid (such as a medicament) from an external source.

As noted previously, in some embodiments, the microneedle array comprises one or more microneedle sub-arrays. The microneedle array may comprise more than one reservoir and each reservoir may be associated with a respective one or more sub-arrays. For example, the microneedle array may comprise first and second sub-arrays and first and second reservoirs. The first reservoir may supply the microneedles of the first sub-array with fluid (e.g. a medicament) via conduits and the second reservoir may

supply the microneedles of the second sub-array with a fluid (e.g. a medicament) via conduits.

In some embodiments, the reservoirs associated with each microneedle array may be in fluid communication with each other. In such embodiments, the microneedle array may comprise fluid conduits arranged to transfer fluid between the reservoirs. In some embodiments, the conduits supplying fluid to the microneedles of the first microneedle array may be in fluid communication with the conduits supplying fluid to the microneedles of the second microneedle array. In some embodiments, the microneedle array is arranged such that one or more of the microneedles are arranged to simultaneously transport different fluids to their respective outlets. This may facilitate the delivery of relatively large doses of fluid from the reservoirs to the microneedle outlets.

For example, referring to Figure 10, a microneedle array 1001 comprises a first surface 1002a and a second surface 1002b. Extending from the first surface 1002a are four microneedles 1003a, 1003b, 1004a and 1004b. In the illustrated embodiment, microneedles 1003a and 1003b are the same length and microneedles 1004a and 1004b are the same length and longer than microneedles 1003a and 1003b. However, in other embodiments, the microneedles are all the same length. Microneedles 1003a and 1003b constitute a first microneedle array and microneedles 1004a and 1004b constitute a second microneedle array. Each of the microneedles comprises a tube 1005a, 1005b, 1005c and 1005d. Each microneedle tube 1005a, 1005b, 1005c and 1005d is in fluid communication with a respective reservoir 1006a, 1006b, 1006c and 1006d located between the first surface 1002a and the second surface 1002b. The reservoirs 1006a, 1006b, 1006c and 1006d are arranged to supply tubes 1005a, 1005b, 1005c and 1005d, respectively, with a fluid. Fluid conduits 1007a, 1007b and 1007c provide fluid communication between each of the reservoirs 1006a, 1006b, 1006c and 1006d. In use, each reservoir 1006a, 1006b, 1006c and 1006d may contain the same fluid such that each of the microneedle tubes 1005a, 1005b, 1005c and 105d is configured to supply the same medicament. Optionally one or more of the reservoirs 1006a, 1006b, 1006c and 1006d is in fluid communication with a respective fluid supply tube (not shown) for supplying fluid to the reservoirs 1006a, 1006b, 1006c and 1006d. Each of the fluid supply tubes is configured to receive a fluid (such as a medicament) from an external source.

It may be desirable for a single microneedle array to deliver two or more different medicaments. This may enable the single microneedle array to be used to provide medicament for two or more therapeutic or cosmetic treatments or to provide medicament for the therapeutic treatment of a disease and cosmetic treatment.

The different medicaments may be delivered by different microneedle sub-arrays. Each microneedle sub-array can be associated with a respective reservoir and each reservoir can contain a different reservoir. Each reservoir may be in fluid communication via fluid conduits with the microneedle tubes and outlets of the microneedles of its associated microneedle sub-array. The reservoir and conduits supplying a first microneedle sub-array may be fluidly isolated from the reservoir and conduits supplying a second microneedle sub-array. This prevents the different medicaments from mixing with each other prior to delivery of the medicaments from the outlets of the microneedles.

For example, referring to Figure 11, a microneedle array 1101 comprises a first surface 1102a and a second surface 1102b. Extending from the first surface 1102a are four microneedles 1103a, 1103b, 1104a and 1104b. Microneedles 1103a and 1103b constitute a first microneedle array and microneedles 1103c and 1103d constitute a second microneedle array. Each of the microneedles comprises a tube 1105a, 1105b, 1105c and 1105d. Each microneedle tube 1105a, 1105b is in fluid communication with a first reservoir 1106a located between the first surface 1102a and the second surface 1102b. Each microneedle tube 1105c and 1105d is in fluid communication with a second reservoir 1106b located between the first surface 1102a and the second surface 1102b. The reservoirs 1106a, 1106b are arranged to supply tubes 1105a, 1105b, 1105c and 1105d, respectively, with a fluid. In use, each reservoir 1106a, 1106b may contain the same fluid such that each of the microneedle tubes 1105a, 1105b, 1105c and 1105d is configured to supply the same medicament. Alternatively, one or more of the reservoirs 1106a, 1106b can contain a different medicament. This enables the microneedle array 1106a, 1106b to deliver multiple different medicaments. Optionally each reservoir 1106a, 1106b is in fluid communication with a respective fluid supply tube (not shown) for supplying fluid to the reservoirs 1106a, 1106b. Each of the fluid supply tubes is configured to receive a fluid (such as a medicament) from an external source.

The microneedle arrays described herein may be manufactured using an additive manufacturing process. 3D printing is an additive manufacturing process that may be used to form the microneedle array.

The microneedles may comprise intricate channels (e.g. the tubes and conduits referred to herein) and the dimensional tolerances of the microneedles can be narrow. Manufacturing the microneedle array using additive manufacturing is beneficial because this manufacturing technique enables the precise positioning of the microneedles. Furthermore, the microneedle array may be easily tailored to meet the requirements of the intended site of application. For example, the microneedles can be printed such that their length can be precisely matched with the depth of skin into which they will penetrate into when use.

The microneedle array may be designed on computer-aided design (CAD) software and then directly printed using an additive manufacturing technique. This system allows for greater flexibility in the design and production of the microneedle array. The relative positioning of the microneedles, as well as their size (e.g. length) and shape, can be readily tailored depending on the desired application of the microneedle array. Additive manufacturing also allows for the incorporation of intricate fluid delivery channels and the precise positioning and dimensioning of the microneedles and the microneedle fluid tubes and outlets. The use of additive manufacturing may also enable the rapid production of microneedle arrays.

The microneedle arrays described herein may be printed using SL, DLP or 2PP technologies and it may be formed from Class II resins. The microneedle arrays can be printed using customised resins using, for example, the following:

i. methacrylate end-functionalized poly(D,L-lactide) star-shaped oligomers of varying molecular architectures, which can be synthesised and photo-crosslinked in the presence of ethyl lactate;

ii. poly(D,L-lactide-co-εcaprolactone) copolymer with varying lactic acid and εcaprolactone ratios (photoactive methacryl-groups can be developed through the addition of methacryloyl chloride and sodium bicarbonate solution);

iii. PEGDA photopolymers combined with PCL-Triol and photoinitiators; and

iv. PEGDA photopolymers combined with Polyethylene Glycol (PEG), such as PEG200, PEG300 or PEG400.

The microneedle arrays described herein may be used for therapeutic and/or cosmetic treatments, in particular skin treatments. Particular applications include wound healing and skin regeneration. For example, the microneedle arrays can be used for the treatment of skin injuries in order to facilitate wound healing. Traumatic and diabetic skin injuries are example applications. When used in this way, the microneedle arrays can assist with infection prevention and scarring prevention.

The microneedle arrays may be used to provide specific treatments to different layers of skin simultaneously by allowing independent administration of different therapeutic components at different targeted skin regions at once. For example, two different medicaments can be simultaneously administrated. One of the medicaments (e.g. a topical skin medicament) can be delivered from the microneedle array to the epidermis layer of the skin via shorter microneedles whilst the other medicament (e.g. a functional medicament, such as a growth factor (such as VEGF, TGF-alpha, TGF-beta, PDGF, FGF, EGF and IGF)) can be delivered from the same microneedle array to the dermis layer via longer microneedles. Topical skin medicaments include, but are not limited to, inflammation prevention, infection prevention and aesthetic enhancement (e.g. anti-scarring, hyperpigmentation) medicaments. Functional medicaments include, but are not limited to, dermal tissue regeneration, vascularization, nerve regeneration and hair regrowth medicaments. By a topical skin medication and a medicament that encourages functional skin healing, the microneedle arrays disclosed herein provide a holistic and convenient approach for full skin recovery.

Experimental

3D Printing of Microneedle Array

A variety of microneedle arrays were designed using SolidWorks and then printed from resin using a 3D printer.

Referring to Figure 12a, a microneedle array was designed with four hollow microneedles. Two of the microneedles were longer than the other two microneedles. Two of the microneedles were 1 mm long.

Various synthesized or commercially available resins were poured into a build tray and covered by a UV blocking shield. MiiCraft BV007A was one such resin. The following materials were also explored as suitable resins:

i. methacrylate end-functionalized poly(D,L-lactide) star-shaped oligomers, synthesised and photo-crosslinked in the presence of ethyl lactate;

ii. poly(D,L-lactide-co-εcaprolactone) copolymer;

iii. PEGDA photopolymers combined with PCL-Triol and photoinitiators; and

iv. PEGDA photopolymers combined with Polyethylene Glycol (PEG), including PEG200, PEG300 or PEG400.

A build plate then was gently lowered down into the build tray and the printing of the microneedle array was initiated layer-by-layer until the whole microneedle array was 3D printed. The microneedle array was printed at various orientations from 0 to 90 degrees. The light intensity and exposure time were controlled for the 3D printing to avoid overcuring. Once printed, the UV blocking shield was removed and the resulting microneedle array was gently removed from the build plate with an aid of a tweezer. Once removed, the microneedle array was taken to a washing station to be washed for 15 minutes. The inner channels of the microneedle array were then flushed by using a washing fluid (isopropanol) to ensure the channels were free of uncured resin. The microneedles were then dried at room temperature for 2 hours, then placed into a curing station and cured with UV exposure at 40 °C for at least 1 hour. Suitable 3d printing techniques include stereolithography (SLA), masked stereolithography (MSLA), micro stereolithography (μSLA), Two photon polymerization (2pp), Continuous Liquid Interface Production (CLIP) and digital light printing (DLP). In the present examples, μSLA, SLA and DLP were used.

Referring to Figure 12a, the microneedle array comprised two microneedles of 500 μm length and two microneedles of 1000 μm length.

The ability of the microneedle array to pierce the skin of a mouse of was tested by applying the microneedle array to the skin of the mouse. The microneedles pierced the skin of the mouse and the skin penetration depth was determined using confocal microscopy.

Referring to Figure 12b, the 500 μm microneedles were capable of piercing the skin to a depth of at least around 309 μm. Referring to Figure 12c, the 1000 μm microneedles were capable of piercing the skin to a depth of at least around 518 μm.

Claims

1. A microneedle array comprising a surface and two or more microneedles extending from the surface, wherein at least one of the microneedles has a different shape and/or length compared with a shape and/or length of at least one other of the microneedles.

2. The microneedle array according to claim 1, wherein the microneedle array comprises at least two microneedle sub-arrays, the microneedles of at least one of the sub-arrays having a different shape and/or length to a shape and/or length of the microneedles of another of the sub-arrays.

3. The microneedle array according to either claim 1 or claim 2, wherein each microneedle has a length of from about 50 μm to about 1500 μm.

4. The microneedle array according to any one of the preceding claims, wherein one or more of the microneedles has a length of from about 10 μm to about 500 μm and one or more of the microneedles has a length of from about 501 μm to about 1500 μm.

5. The microneedle array according to any one of the preceding claims, wherein the microneedles have a height aspect ratio of up to about 1:20.

6. The microneedle array according to any one of the preceding claims, wherein the microneedles have a distance aspect ratio of about 2 to about 150.

7. The microneedle array according to any one of the preceding claims, wherein the microneedle array comprises from 2 to 2000 microneedles.

8. The microneedle array according to any one of the preceding claims, wherein each microneedle comprises a tube for transporting fluid to an outlet of each microneedle.

9. The microneedle array according to claim 8, wherein each microneedle comprises a proximal end and a distal end and a surface extending between the proximal end and the distal end and the outlet is positioned on the surface between the proximal end and the distal end of the microneedle.

10. The microneedle array according to claim 9, wherein the outlet of at least one of the microneedles is positioned at a first position on the surface of the microneedle and wherein the outlet of at least one of the other microneedles is positioned at a second position on the surface of the microneedle, wherein the first position is closer to the proximal end of the microneedle than the second position.

11. The microneedle array according to any one of claims 8 to 10, wherein the microneedle array comprises one or more conduits arranged to provide fluid communication between two or more of the tubes of different microneedles.

12. The microneedle array according to any one of claims 8 to 11, wherein the microneedle array comprises a first sub-array comprising two or more microneedles and a second sub-array comprising two or more microneedles, wherein the microneedle tubes of the first sub-array are arranged to transport a first fluid to their respective outlets and wherein the microneedle tubes of the second sub-array are arrange to transport a second fluid to their respective outlets.

13. The microneedle array according to claim 12, wherein the microneedle tubes of the first sub-array of microneedles are fluidly isolated from the microneedle tubes of the second sub-array of microneedles.

14. The microneedle array according to any one of claims 8 to 13, wherein each tube is arranged to transport a fluid from at least one fluid reservoir to a fluid outlet of the microneedles.

15. The microneedle array according to any one of the preceding claims, wherein the microneedle array is configured such that one or more of the microneedles are arranged to simultaneously transport different fluids to their respective fluid outlets.

16. The microneedle array according to any one of the preceding claims, wherein the microneedle array comprises two or more fluid reservoirs, each of the fluid reservoirs being in fluid communication with one or more microneedle sub-arrays.

17. The microneedle array according to any one of the preceding claims, wherein the microneedle array is in the form of a patch.

18. The microneedle array according to claim 17, wherein the patch is for application to the skin of a user.

19. The microneedle array according to either claim 17 or claim 18, wherein the patch is arranged to be attached to a surface and conform to a geometry of the surface.

20. The microneedle array according to any of the preceding claims, wherein the microneedle array comprises an adhesive on the surface.

21. The microneedle array according to any one of the preceding claims, wherein the microneedles are arrange such that, when applied to the skin of the user, at least one of the microneedles is arranged to penetrate the skin of the user to a different depth compared with at least one other of the microneedles.

22. The microneedle array according to any one of the preceding claims, wherein the microneedles are arranged to deliver a pharmaceutical composition to a user.

23. A method of manufacturing a microneedle array, wherein the method comprises an additive manufacturing process from a feedstock material.

24. The method according to claim 23, wherein the additive manufacturing process is a 3D printing process depositing layer upon layer of a feedstock material.

25. The method according to either claim 23 or claim 24, wherein the feedstock material is a resin.

26. The method according to any one of claims 23 to 25, wherein the microneedle array is a microneedle array as claimed in any one of claims 1 to 22.

27. A microneedle array manufactured according to the method as claimed in any one of claims 23 to 26.

28. A microneedle array according to any one of claims 1 to 22 or claim 27, for use in administering a medicament to a patient.

29. A microneedle array according to any one of claims 1 to 22, 27 or 28 for use in a therapeutic and/or cosmetic treatment.

30. The microneedle array according to claim 29, wherein the microneedle array is for use in the simultaneous delivery of at least two different medicaments to the skin of a user.

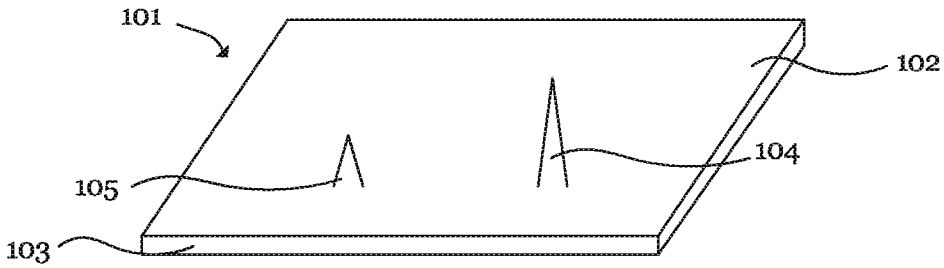


Fig. 1

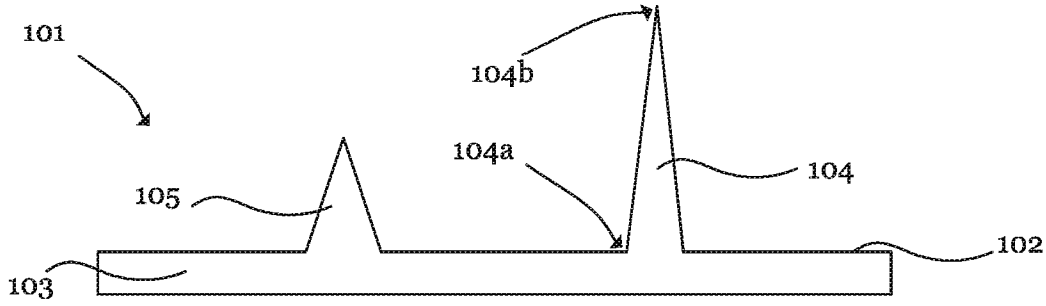


Fig. 1a

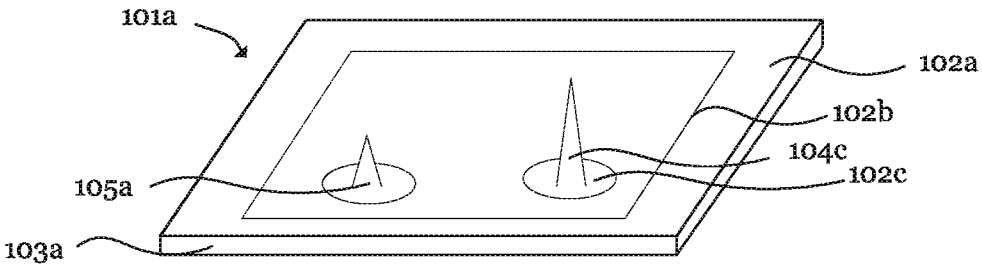


Fig. 1b

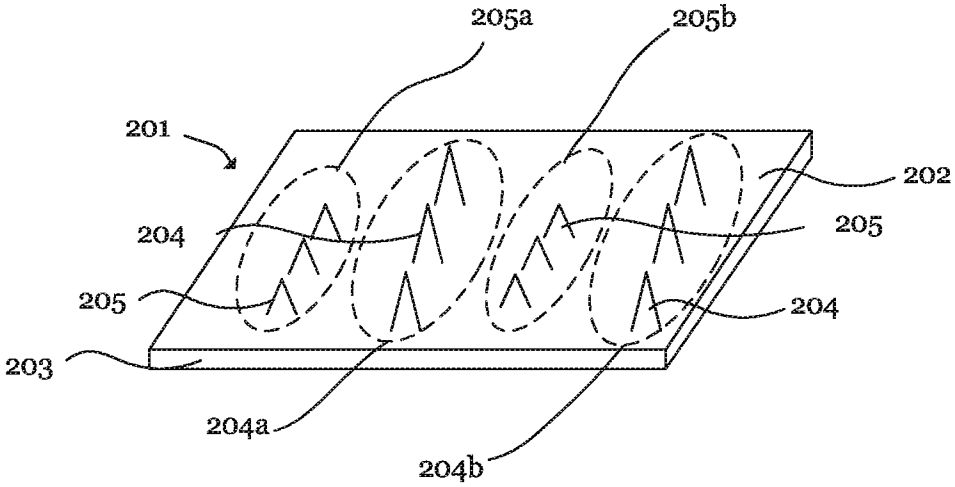


Fig. 2

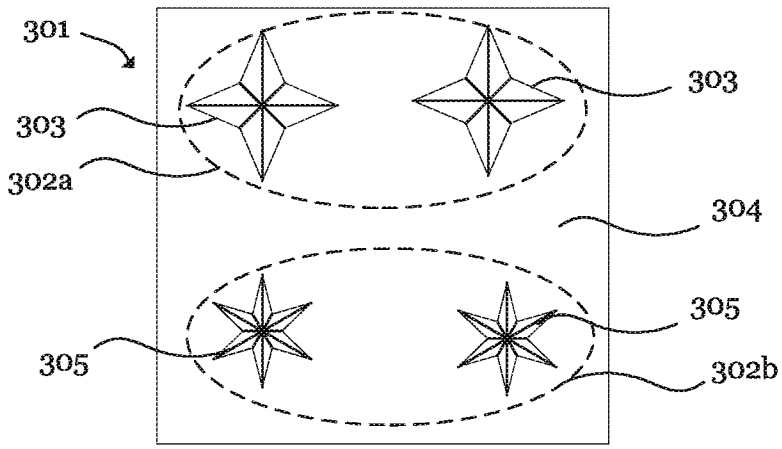


Fig. 3

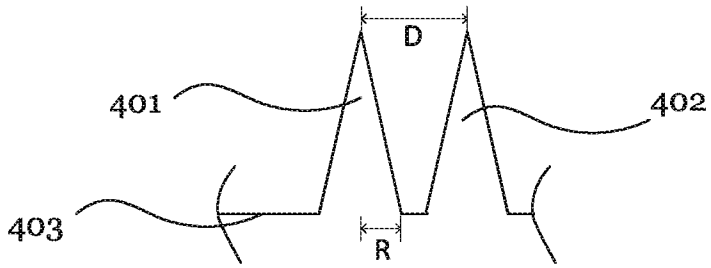


Fig. 4

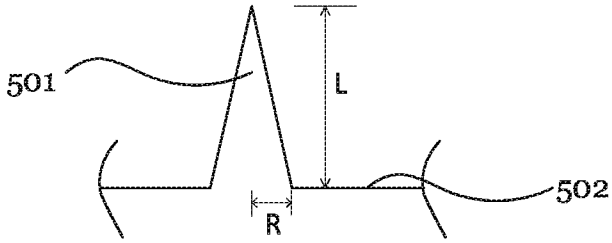


Fig. 5

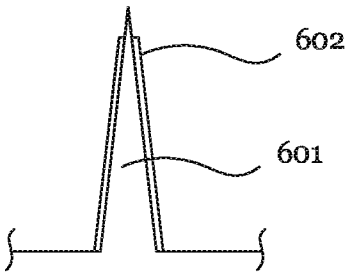


Fig. 6a

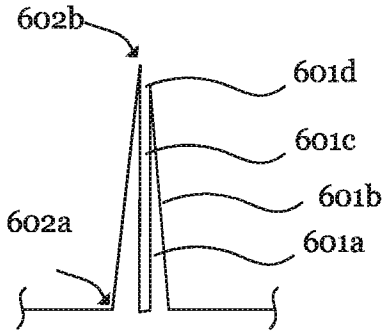


Fig. 6b

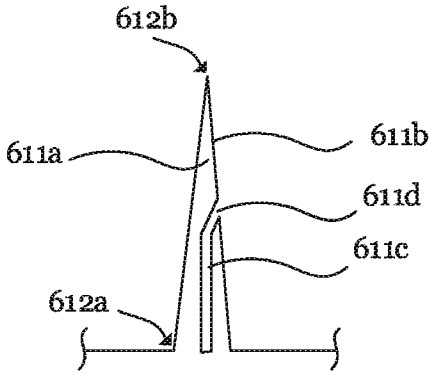


Fig. 6c

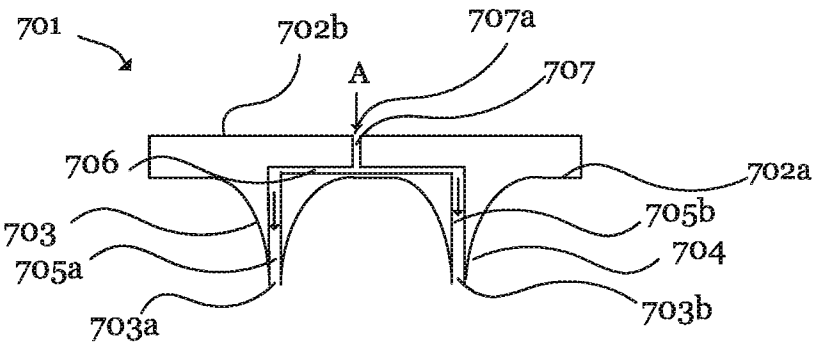


Fig. 7

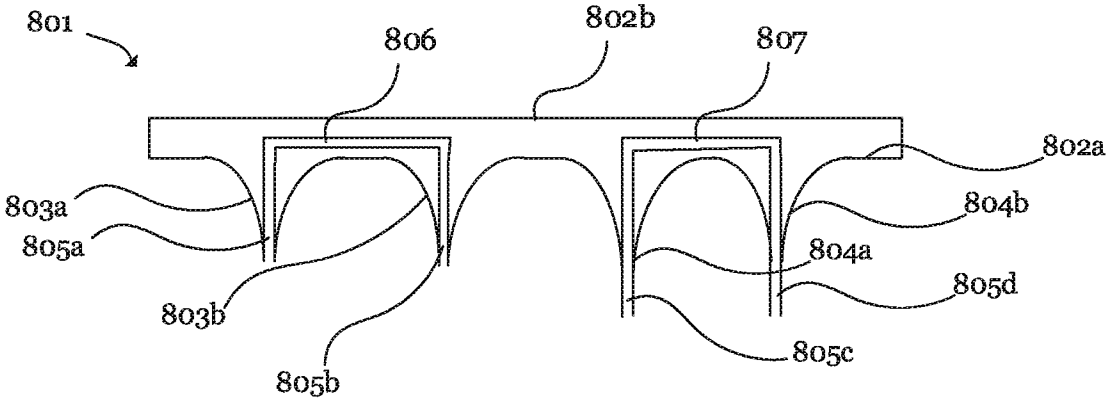


Fig. 8

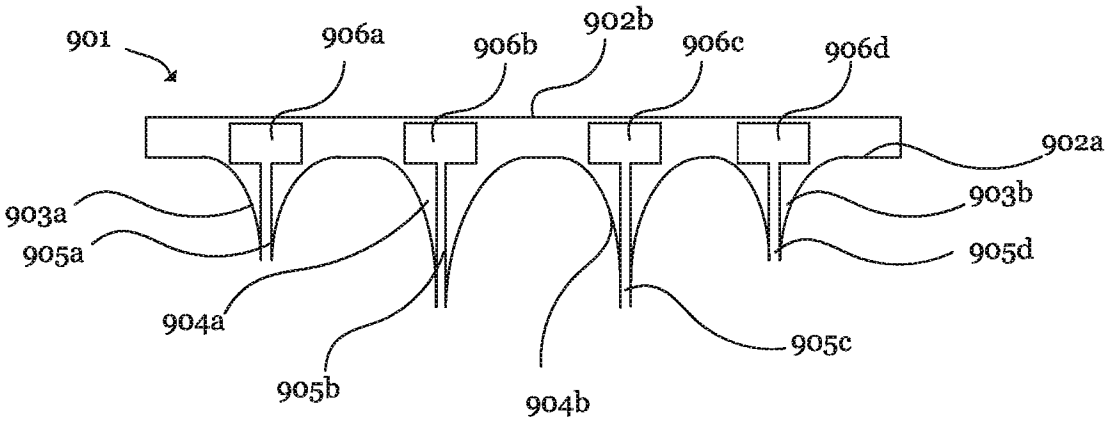
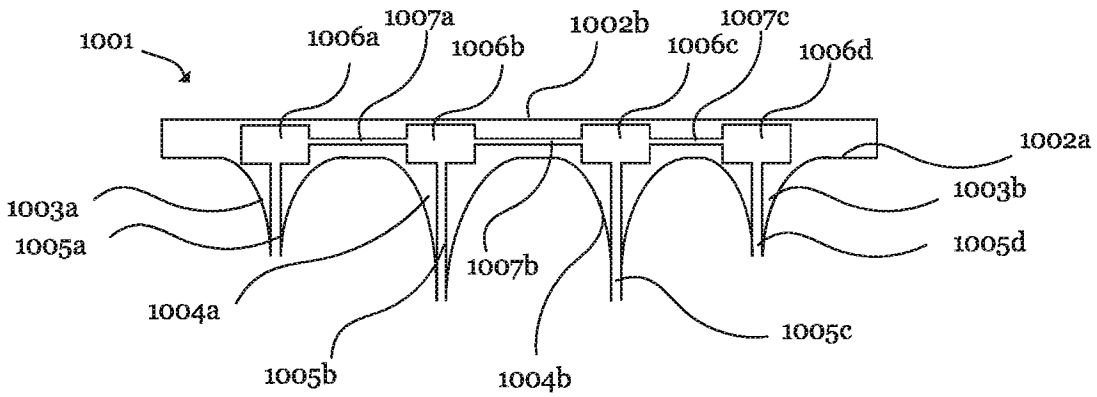


Fig. 9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1005d
1007b
1004a
1005c
1005b
1004b

Fig. 10

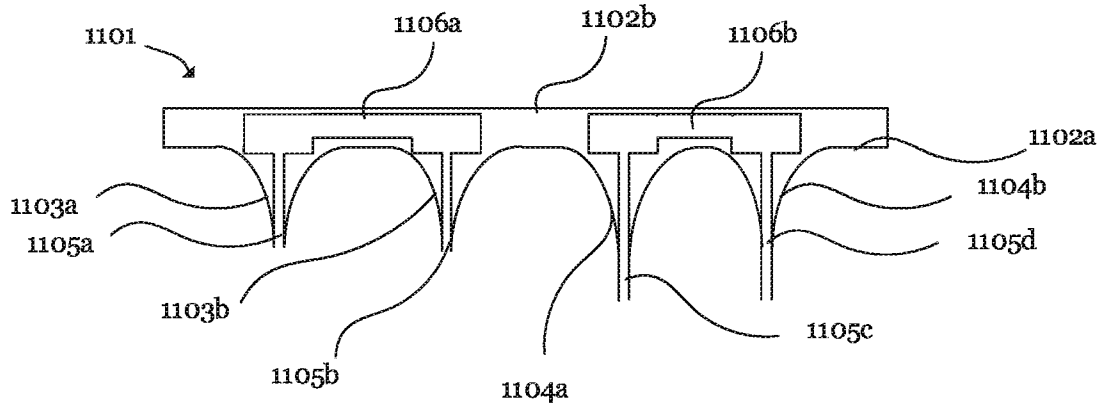
1101
1106a
1102b
1106b
1102a
1103a
1105a
1104b
1105d
1103b
1105c
1105b
1104a

Fig. 11

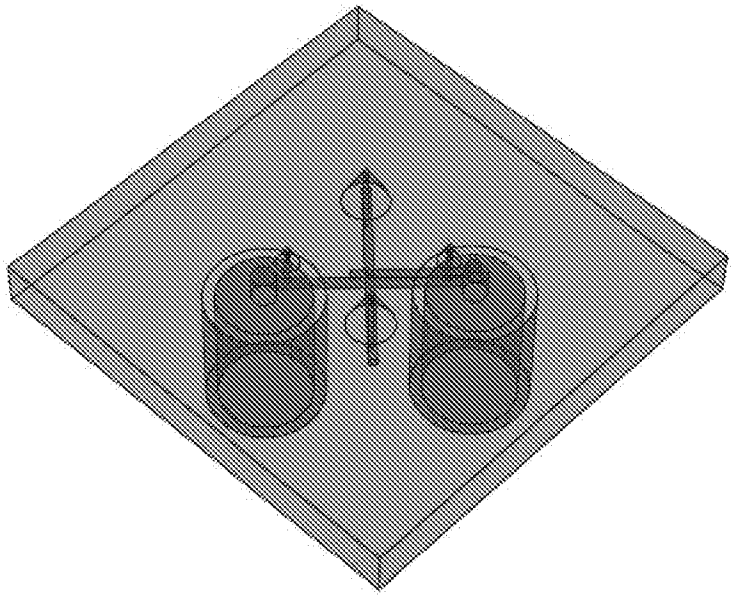

Fig. 12a

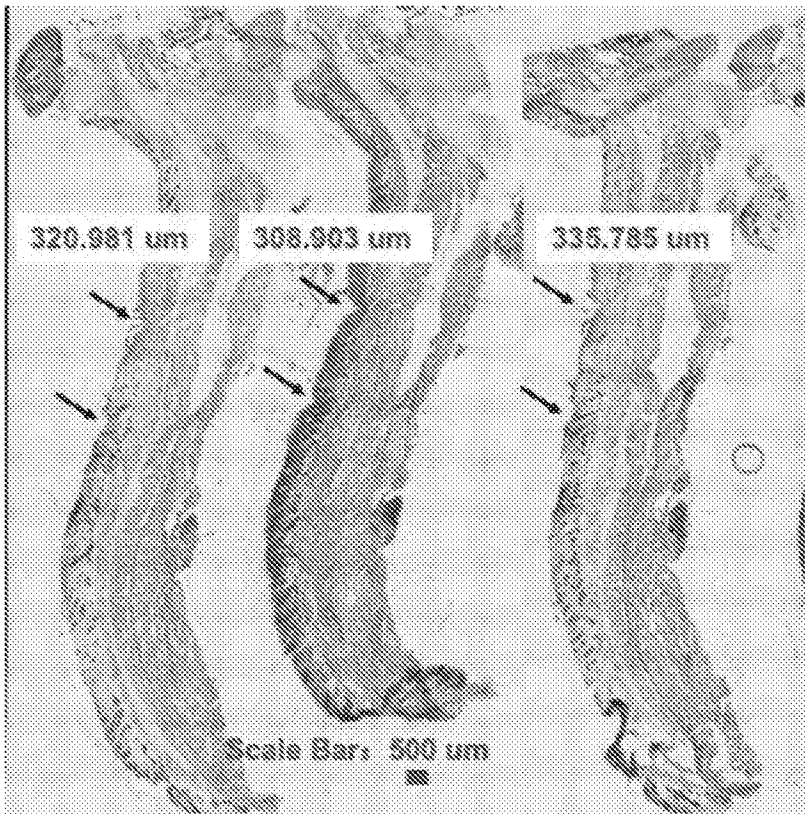

Fig. 12b

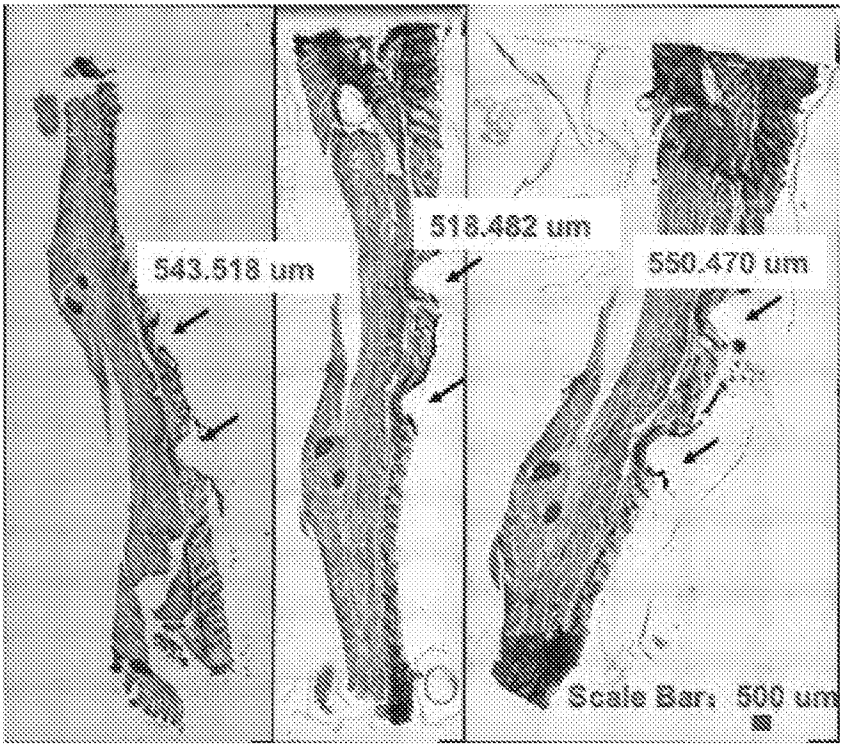

Fig. 12c

INTERNATIONAL SEARCH REPORT

International application No
PCT/CN2022/113934

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M37/00 B33Y80/00
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 B33Y

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 2020/001064 A1 (ALARY MARC [US] ET AL) 2 January 2020 (2020-01-02) paragraphs [0061], [0067], [0078], [0091], [0132] - [0134]; figures 6, 7, 9, 10, 11	1-30
X	US 2018/177990 A1 (ALARY MARC [US] ET AL) 28 June 2018 (2018-06-28) paragraphs [0027] - [0030], [0058] - [0060]; figures 4-7	1-30
X	JP 2015 226649 A (WORKS CO LTD) 17 December 2015 (2015-12-17)	1
A	figures 6a, 6b	2-30

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 February 2023	24/02/2023

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

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INTERNATIONAL SEARCH REPORT

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PCT/CN2022/113934

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 1 287 847 A1 (LIFESCAN INC [US]) 5 March 2003 (2003-03-05) paragraphs [0044], [0045]; figures 2A-3D	1-30
A	CN 101 332 327 A (UNIV TSINGHUA [CN]) 31 December 2008 (2008-12-31) figures 1a, 1b, 3a, 3b	1-30

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