Title: DEVICE FOR APPLYING A MICRONEEDLE ARRAY

Abstract: A device (100) for applying a microneedle array to a skin surface. The device comprises a base (120) defining a skin contacting plane, an array component having a skin facing side comprising a microneedle array, and at least one connecting member (140) having a first portion affixed through a first hinge (142) to the base and a second portion affixed to the array component. The connecting member has a first equilibrium position with the microneedle array in a recessed position within the device and a second equilibrium position with the microneedle array positioned so as to be able to contact a skin surface.
DEVICE AND METHOD FOR APPLYING A MICRONEEDLE ARRAY

This application claims the benefit of U.S. Provisional Patent Application No. 60/793,564, filed April 20, 2006, the disclosure of which is incorporated by reference herein in its entirety.

Field

The present invention relates to devices for applying a microneedle array to a mammal. The present method also relates to methods of applying a microneedle array to a mammal.

Background

Only a limited number of molecules with demonstrated therapeutic value can be transported through the skin via unassisted or passive transdermal drug delivery. The main barrier to transport of molecules through the skin is the stratum corneum (the outermost layer of the skin).

Devices including arrays of relatively small structures, sometimes referred to as 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 pass through that layer and into the tissues below.

Issues related to applying microneedles include the ability to effectively insert the needles to a desired depth in the skin and the ability to protect the delicate microneedles prior to application to the skin.

Summary of the Invention

In one embodiment, the present invention is a device for applying a microneedle array to a skin surface. The device comprises a base defining a skin contacting plane, an array component having a skin facing side comprising a microneedle array, and at least one connecting member having a first portion affixed through a first hinge to the base and a second portion affixed to the array component. The connecting member has a first
equilibrium position with the microneedle array in a recessed position within the device and a second equilibrium position with the microneedle array positioned so as to be able to contact a skin surface.

The present invention also comprises methods of applying such devices to a skin surface and applying a force to the array component sufficient to move the connecting member to its second equilibrium position.

In another embodiment, the present invention is a method of applying a microneedle array to a skin surface. A device is provided having a first equilibrium position wherein a microneedle array is in a recessed position within the device. The device is placed on a skin surface. A mechanical applicator is then brought into contact with the device and a drive mechanism of the mechanical applicator is aligned with the microneedle array. Force is applied via the drive mechanism to the microneedle array sufficient to move the microneedle array into contact with the skin surface. The mechanical applicator is then removed from contact with the device.

As used herein, certain terms will be understood to have the meaning set forth below:

"Array" refers to the medical devices described herein that include one or more structures capable of piercing the stratum corneum to facilitate the transdermal delivery of therapeutic agents or the sampling of fluids through or to the skin.

"Microstructure," "microneedle" or "microarray" refers to the specific microscopic structures associated with the array that are capable of piercing the stratum corneum to facilitate the transdermal delivery of therapeutic agents or the sampling of fluids through the skin. By way of example, microstructures can include needle or needle-like structures as well as other structures capable of piercing the stratum corneum.

The features and advantages of the present invention will be understood upon consideration of the detailed description of the preferred embodiment as well as the appended claims. These and other features and advantages of the invention may be described below in connection with various illustrative embodiments of the invention. The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The Figures and the detailed description which follow more particularly exemplify illustrative embodiments.
Brief Description of the Drawings

Preferred embodiments of the invention will now be described in greater detail below with reference to the attached drawings, wherein:

FIG. 1 is a perspective view of the skin distal side of a device for applying a microneedle array to a skin surface.

FIG. 2 is a perspective view of the skin facing side of a device for applying a microneedle array to a skin surface.

FIG. 3 is a schematic cross-section of a device in a first equilibrium position.

FIG. 4 is a schematic cross-section of a device in a second equilibrium position.

FIG. 5 is a perspective view of the skin distal side of a device for applying a microneedle array to a skin surface.

FIG. 6 is a schematic cross-sectional view of a connecting member.

FIG. 7 is a schematic top view of another embodiment of a connecting member.

FIG. 8 is a schematic cross-sectional detailed view of one embodiment of a hinged connecting member.

FIG. 9 is a schematic cross-sectional detailed view of another embodiment of a hinged connecting member.

FIG. 10 is a schematic cross-sectional detailed view of still another embodiment of a hinged connecting member.

FIG. 11A-C are schematic cross-sectional detailed views of other hinge embodiments.

FIG. 12A-D is a perspective view of a mechanical applicator being used to apply a microneedle array to a skin surface.

FIG. 13 is a perspective view of the skin facing side of a device showing two cross bars.

FIG. 14 is a perspective view of the skin distal side of a device showing connecting members attached directly to an outer ring.

FIG. 15 is a perspective view of the skin distal side of a device showing internal guides.

FIG. 16 is a perspective view of the skin facing side of a device showing an external guide.
FIG. 17 is a schematic cross-section of a device in a first equilibrium position showing an aperture in the base.

While the above-identified drawing figures set forth several embodiments of the invention, other embodiments are also contemplated, as noted in the discussion. In all cases, this disclosure presents the invention by way of representation and not limitation. It should be understood that numerous other modifications and embodiments can be devised by those skilled in the art, which fall within the scope and spirit of the principles of the invention. The figures may not be drawn to scale. Like reference numbers have been used throughout the figures to denote like parts.

Detailed Description

One embodiment of the microneedle application device 100 is shown in Figures 1 and 2. The skin distal side of the device 100 is shown in Figure 1 and the skin facing, or proximal, side of the device is shown in Figure 2. The application device 100 comprises a base 120 affixed to a first portion of four connecting members 140 (only 3 are visible) through a first hinge 142. A second portion of the connecting members 140 is affixed to an array component 110 through a second hinge 144. The array component 110 comprises a backing plate 116 and a microneedle array 114. The skin facing side of the microneedle array, which comprises one or more microneedles (not shown), is more clearly shown in Figure 2. The connecting members 140 are shown in a first equilibrium position with the array 114 in a recessed position within the device 100. The base 120 comprises a skin-facing, or skin-proximal, side covered with a pressure-sensitive skin adhesive layer 130. The base also comprises an outer ring 122 which can serve a variety of functions, such as lending stiffness and ease of handling to the entire device 100. The outer ring 122 is shown as cylindrical, but can be any shape. As shown, the outer ring 122 extends above the array component 110 on the skin distal side of the device and can provide protection against premature engagement of the array component 110. Figure 14 shows another embodiment of the microneedle application device 100. In this embodiment, device 100 comprises an outer ring 522 affixed to a first portion of four connecting members 540 through a first hinge 542. A second portion of the connecting members 540 is affixed to an array component 510 through a second hinge 544. The base 120 also defines a skin-contacting plane that, as shown, coincides with the skin-facing side of the pressure-
sensitive skin adhesive 130 and extends across the opening in the center of the device. In addition, the skin adhesive layer 130 may be adhered to an optional, removable covering member (not shown), such as a foil and/or plastic film, that can provide protection to the device during storage. The covering member will then be removed and discarded prior to use.

As shown in Figures 3 and 4, the connecting members 140 of the device 100 have two equilibrium positions. A first equilibrium position is shown in Figure 3 where the array component 110 and array 114 are in a recessed position within the device 100. The recessed position allows the device 100 to be placed against a skin surface 160 while preventing the microneedles 118 from prematurely contacting the skin surface 160. The initial position of the microneedle array 114 may be characterized by a setback distance 150, that is, the distance between the skin-contacting plane 162 and the microneedle array 114. Pressure can then be applied to the array component 110 which causes the connecting members 140 to rotate about first and second hinges 142, 144 and thereby moves the connecting members 140 to a second equilibrium position. The hinge can be any of a variety of shapes and structures that allow for the movement or flexure of the connecting member(s) from the first equilibrium position to the second equilibrium position. The array component 110 and microneedle array 114 contact the skin surface 160 in the second equilibrium position, thus allowing the microneedles 118 to penetrate the skin surface. As shown, the microneedle array 114 extends beyond the skin contacting plane 162 by a distance 152. Although not wishing to be bound by theory, it is believed that pressing the microneedle array 114 a small distance beyond the skin-contacting plane 162 and into the skin allows for better retention of the microneedles 118 within the skin.

In one embodiment, the microneedle array 114 may be releasably attached to the backing plate 116. In addition, a portion of the skin-facing side of the array may be covered with a pressure-sensitive adhesive. After application to the skin (as shown in Figure 4), the base 120, connecting member 140, and backing plate 116 can then be removed from the skin leaving the microneedle array 114 in place. In another aspect, the microneedle array 114 could comprise an adhesive patch releasably attached to the backing plate 116. Such an adhesive patch with a microneedle array could then be applied and left in place after removal of the remainder of the device as described above.
At least one connecting member connects the base and array component. In one embodiment, a single, flexible connecting member is employed, as shown in Figure 5. A first portion of the connecting member 240 (i.e., the outer edge of the connecting member 240) is affixed to the base 220 through a first hinge 242 that encircles the connecting member 240. A second portion of the connecting member 240 is affixed to an array component 210 through a second hinge 244 that encircles the array component 210. Other features of the device, such as base 220, outer ring 222, and pressure-sensitive skin adhesive layer 230 are as described in the embodiment shown in Figures 1 and 2. In other embodiments, a plurality of connecting members may be used. Four equally spaced connecting members are shown in Figures 1 and 2, however two, three, or more than four connecting members may also be used. In one embodiment, multiple connecting members are symmetrically spaced around the array component. Figure 14 shows another embodiment, wherein the connecting member(s) 540 may be affixed to the outer ring 522.

Although the array may be held in any orientation, it will typically be aligned substantially parallel to the skin contacting plane in both the first and second equilibrium positions. Such an orientation is generally desirable, as the microneedles will often be aligned so as to be perpendicular to the skin surface. Parallel alignment of the array thus allows for the microneedles to be pressed straight downward into the skin, thus minimizing the chance of bending the microneedles and allowing for reproducible penetration to a desired depth in the skin. In one embodiment, the array will also remain substantially parallel to the skin contacting plane when moving from the first equilibrium position to the second equilibrium position. Such an orientation between the equilibrium positions may be desirable, since the microneedles may contact the skin surface prior to the device reaching its second equilibrium position. By substantially parallel, it should be understood that the skin is a biological surface and as such has some natural roughness and irregularity. Thus variations in alignment of the array with respect to parallel having a magnitude similar to that of the natural roughness of a skin surface are considered to be substantially parallel.

In another embodiment, internal or external guides may be used to maintain the array's substantially parallel position to the skin contacting plane. Figure 15 shows a device 100 comprising an outer ring 522 and four connecting members 540. Also affixed to the outer ring 522 are four internal guides 572. The internal guides 572 are affixed to
the outer ring 522 and extend radially inward towards the array cylinder 570 with the inward end abutting the array cylinder 570. The array cylinder 570 is shown as a cylindrical ring, but may be of any shape. The array cylinder 570 is affixed to the skin distal surface of the array component 510 and is preferably of a height at least the same as the inner surface of the outer ring. Upon actuation the exterior surface of the array cylinder 570 moves along the internal guides 572 to maintain the substantially parallel orientation of the array 510. External guides are shown in Figure 16, which shows a device 100 comprising a base 520, connecting members 540 and an array component 510. In this embodiment the base is slightly extended radially outward from the outer ring 522.

Outer ring 522 has one or more protrusions 584 on the exterior surface. An array cap 580 is placed over the array 510 and connecting members 540. Upon actuation the array cap 580 comes down over the protrusions 584 on outer ring 522 to the base 520. The array cap 580 has an internal diameter that is at least as wide as the outer diameter of the outer ring 522. The array cap 580 may optionally comprise one or more channels 582 that correspond to the one or more protrusions 584 along the exterior surface of the outer ring 522 thus decreasing any potential rotational movement.

In some cases the force of the application method may cause the skin to dome or protrude through the opening underneath the applicator, potentially causing a variety of effects, including the skin coming into contact with the array prior to the application, the skin being an unequal distance from the array or the actuation occurring in an uneven manner or direction or with an uneven velocity. In order to avoid premature contact of the needles with the skin, the needles could be recessed further away from the skin contacting surface. Another approach is a cross-bar or other grid arrangement at the base of the applicator to help reduce skin doming. Two cross-bars are shown in a criss-cross pattern in Figure 13, however, one or three or more cross-bars may also be used. Figure 13 comprises an outer ring 522 to which connecting members 540 are affixed. Also attached to the outer ring 522 are two cross bars 560 on the skin facing side of the device 100. The cross-bars 560 can either be integrally formed or separate components. In other embodiments, the opening in the base can be modified. Figure 17 shows a cross-sectional view of a device similar to Figure 14 wherein the connecting members 540 are affixed directly to an outer ring 522. This embodiment shows an aperture 550 in the base 520 that can be a variety of sizes. It may be of a size small enough to just allow the diameter of the
array 514 and any necessary portion of the connecting member 540 to fit through on
application, or be of a size that is equal to the diameter of the inner surface of the outer
ring 522.

The connecting member(s) will typically have some flexibility, so as to allow the
device to move from the first to the second equilibrium position. It should be appreciated
that the connecting member(s) is in an extended position in both equilibrium positions, as
the distance between the base and array component is at a maximum. As the array passes
between first and second equilibrium positions, however, the distance between base and
array component is generally reduced. The force required to move the array from a first
equilibrium position to a second equilibrium position may be modified through a variety
of means including the shape of the connecting members or the rigidity of the connecting
members, the selection of the hinge type or by adjusting the relative rigidity of the base
and/or outer ring through a variety of means including material selection or thickness of
the material. In particular, if the array remains substantially parallel to the skin-contacting
surface, then the distance between base and array will reach a minimum at a so-called
'neutral' plane where the array component, connecting member(s), and base are
substantially co-planar. If the base is fixed in space, is relatively rigid and inflexible and
the array component is relatively rigid and inflexible, then the connecting member(s) must
be either compressed or flexed to accommodate the reduction in distance between base
and array component. In one embodiment, the connecting member is made of a thin,
flexible material that may form a bow or arch as the device moves from first to second
equilibrium position. Figure 6 shows a connecting member 640 affixed to a base 620
through a first hinge 642 and affixed to an array component 610 through a second hinge
644. Connecting member 640 has an S-shaped curved section 646 which can aid in
flexure and/or compression of the connecting member 640. It may be desirable to have
one or more non-linear sections in the connecting member having any of a variety of
shapes, such as an S-shape (shown in Figure 6), a V-shape, a double S-shape, a W-shape,
or any other suitable shape that allows for increased flexibility of the connecting member.
Another embodiment of a device (shown in Figure 7) has two connecting members 690
affixed to a base 670 through first hinges 692 and affixed to an array component 660
through second hinges 694. Connecting members 690 each have an S-shaped curved
section 696 which can aid in flexure and/or compression of the connecting member 690.
In one embodiment, the connecting member(s) 740 connects to the base 720 through a first hinge 742 and to the array component 710 through a second hinge 744. As shown in Figure 8, the hinges 742, 744 are separate components that operate on the same principles as a common door hinge. The orientation 746 of the connecting member 740 in its second equilibrium position is shown by dashed lines.

In another embodiment, shown in Figure 9, the hinges 842, 844 may be inherently formed by the joint between a relatively thin connecting member 840 and relatively thick base 820 and array component 810. The orientation 846 of the connecting member 840 in its second equilibrium position is shown by dashed lines.

In still another embodiment, shown in Figure 10, a hinge 942 may be constructed as an integral piece of the connection between a connecting member and the base 920 or array component (not shown). Such hinges are often called living hinges. The hinge 942 is a narrow portion connecting base 920 and connecting member 940 and is shown in a position intermediate between the first and second equilibrium positions. The orientation of the connecting member 940 in the first and second equilibrium positions 945, 946 is shown by dashed lines. Detailed view of other embodiments of living hinges are shown in Figures 11A-C.

The device may be placed and/or pressed against the skin manually or with the aid of a separate application device. In one embodiment, a device having a pressure-sensitive skin adhesive on the skin facing side of the device may be manually placed and adhered onto a skin surface. The microneedle array will be in the first, recessed position when placed on the skin. The array may then be moved from the first to the second equilibrium position manually, such as by thumb or finger pressure. Alternatively, a separate applicator 400 as shown in Figures 12A-D may be positioned over the device 300 and activated so as to press the microneedle array into the skin 360. As shown, the device 300 is initially placed against the skin 360 in Figure 12A. The applicator 400 is then brought into contact with the device 300 and positioned with the aid of cylindrical outer housing 410 of the applicator 400 as shown in Figure 12B. The cylindrical outer housing 410 serves as an alignment structure to ensure that the spring-loaded piston 430 will press against the center of the device. Any other suitable alignment structures, such as one or more pins or shafts that can mate with corresponding holes or slots on the device 300, may be employed to ensure proper alignment of the piston 430 with respect to the device 300.
-10-

A button 420 is pressed to release a spring-loaded piston 430 that presses the device 300 from the first to second equilibrium position so as to press the microneedle array into the skin surface 360 as shown in Figure 12C. The applicator 400 may then be removed from the device 300, as shown in Figure 12D, thus leaving the deployed device 300 in place on the skin surface 360. In another embodiment (not shown), the device may be releasably affixed to the applicator and both placed and pressed against the skin with the use of the applicator. The applicator may then be removed from the device leaving the deployed device in place on the skin surface as in Figure 12D, or alternatively, the applicator may be used to remove the device immediately after the device is pressed into the skin. Where the device is removed immediately after application, it is desirable that the base be a non-adhesive surface.

In another embodiment, the present invention is a method of applying a microneedle array to a skin surface. A device is provided having a first equilibrium position wherein a microneedle array is in a recessed position within the device. The device is placed on a skin surface. A mechanical applicator is then brought into contact with the device and a drive mechanism of the mechanical applicator is aligned with the microneedle array. Force is applied via the drive mechanism to the microneedle array sufficient to move the microneedle array into contact with the skin surface. The mechanical applicator is then removed from contact with the device.

In one embodiment, an applicator may be used to allow the device to contact the skin with a desired velocity that is effective to pierce the microneedles into the skin. The desired velocity is preferably controlled to limit or prevent stimulation of the underlying nerve tissue. The maximum velocity achieved by the microneedle device upon impact with the skin is often 20 meters per second (m/s) or less, potentially 15 m/s or less, and possibly 10 m/s or less. In some instances, the maximum velocity is 8 m/s or less. In other instances, the minimum velocity achieved by the microneedle device upon impact with the skin is often 2 m/s or more, potentially 4 m/s or more, and possibly 6 m/s or more. Suitable applicators may include various types of driving mechanisms, including a spring-loaded piston, such as those disclosed in United States Patent Application Publication Nos. 2002/009 1357 (Trautman et al), 2002/0087 182 (Trautman et al), and International Publication No. WO 2005/123 173 (Frederickson et al) or a swinging member, such as disclosed in co-pending United States Patent Application Serial No.
60/694447, filed June 27, 2005, the disclosures of which are herein incorporated by reference.

The base, connecting member(s), hinge(s), and backing plate of the array component may be constructed of any suitable material, including metal, polymer, or ceramic, but is preferably polymer. Exemplary polymers include acrylonitrile-butadiene-styrene (ABS) polymers, polyphenyl sulfides, polycarbonates, polypropylenes, polyethylene, acetals, acrylics, polyetherimides, polybutylene terephthalates, polyethylene terephthalates, and blends and co-polymers thereof. Polyethylene, polypropylenes, and polycarbonate are preferred polymers.

The microneedle array may be constructed of any suitable material, including metal, polymer, or ceramic. Examples of metallic microneedle arrays include those disclosed in United States Patent Application Publication Nos. 2002/0128599 (Trautman et al), 2002/0193729 (Cormier et al), and 2002/0177839, the disclosures of which are herein incorporated by reference. Examples of ceramic microneedle arrays include those disclosed in United States Patent Application Publication Nos. 2002/0138049 (Allen et al) and 2002/0082543 (Park et al), the disclosures of which are herein incorporated by reference. The microneedle array may be constructed of a wide variety of polymeric materials. In one embodiment, the material is selected so that it is capable of forming relatively rigid and tough microneedles that resist bending or breaking when applied to a skin surface. In one aspect, the polymeric material has a melt-flow index greater than about 5 g/10 minutes when measured by ASTM D1238 at conditions of 300 °C and 1.2 kg weight. The melt-flow index is often greater than or equal to about 10 g/10 minutes and sometimes greater than or equal to about 20 g/10 minutes. In another embodiment, the tensile elongation at break as measured by ASTM D638 (2.0 in/minute) is greater than about 100 percent. In still another embodiment, the impact strength as measured by ASTM D256, "Notched Izod", (73°F) is greater than about 5 ft-lb/inches. Examples of suitable materials include polycarbonate, polyetherimide, polyethylene terephthalate, and mixtures thereof. In one embodiment the material is polycarbonate.

In one embodiment, the base, connecting member(s), and hinge(s) may be made as a single, integrally molded piece. In another embodiment, the base, connecting member(s), hinge(s), and backing plate may be made as a single, integrally molded piece. The microneedle array may be affixed to the backing plate, for example, with the aid of an
optional adhesive layer or by directly welding the array to the backing plate. In still another embodiment, the base, connecting member(s), hinge(s), backing plate, and microneedle array may be made as a single, integrally molded piece. In all of the foregoing embodiments, a single, integrally molded piece may be made using a single polymeric material for the entire piece. Alternatively, dissimilar materials may be used to form different portions of the single, integrally molded piece, for example, with the use of two-shot molding processes. In one embodiment, the base, connecting member(s), hinge(s), and backing plate will be made from a single material type, such as polyethylene or polypropylene and the microneedle array will be made of a different material type, such as polycarbonate. Such a construction may allow for the desired toughness of the microneedles while employing relatively inexpensive polymeric material for the remainder of the device. Examples of suitable molding methods are disclosed in International Publication No. WO 05/82596 (Boone et al.) and co-pending United States Patent Application Serial No. 60/ 634319, filed December 7, 2004.

Any suitable pressure-sensitive skin adhesive may be used to allow the device to be affixed to a skin surface. As shown in Figure 2, the pressure-sensitive skin adhesive 130 is a continuous layer on the base 120 of the device, but the pressure sensitive adhesive may be present in any of a variety of patterns and only partially cover the surface of the base 120. For example, the adhesive layer may be patterned or non-patterned, and may be continuous or discontinuous. The adhesive layer may additionally be interrupted by spaces, gaps or other structures. Typical pressure-sensitive skin adhesives include acrylates, polyisobutylene, synthetic rubber, silicones, and blends thereof.

The microneedle arrays prepared by methods of the present invention may comprise any of a variety of configurations, such as those described in the following patents and patent applications, the disclosures of which are herein incorporated by reference. One embodiment for the microneedle devices comprises the structures disclosed in U. S. Patent Application Publication No. 2003/0045837. The disclosed microstructures in the aforementioned patent application are in the form of microneedles having tapered structures that include at least one channel formed in the outside surface of each microneedle. The microneedles may have bases that are elongated in one direction. The channels in microneedles with elongated bases may extend from one of the ends of the elongated bases towards the tips of the microneedles. The channels formed along the sides of the
microneedles may optionally be terminated short of the tips of the microneedles. The microneedle arrays may also include conduit structures formed on the surface of the substrate on which the microneedle array is located. The channels in the microneedles may be in fluid communication with the conduit structures. Another embodiment for the microneedle devices comprises the structures disclosed in U. S. Patent Application Publication No. 2005/0261631 which describes microneedles having a truncated tapered shape and a controlled aspect ratio. Still another embodiment for the microneedle arrays comprises the structures disclosed in U. S. Patent No. 6,312,612 (Sherman, et al.) which describes tapered structures having a hollow central channel. Still another embodiment for the microneedle arrays comprises 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 tip of the microneedle and solid, "star-shaped" microneedles having multiple bladed edges.

The microneedles are typically less than 500 microns in height, and sometimes less than 300 microns in height. The microneedles are typically more than 20 microns in height, often more than 50 microns in height, and sometimes more than 125 microns in height. The height of the microneedles may be measured as the distance that they protrude from a flat base or substrate. In one embodiment, the microneedles may protrude from an irregular substrate, for example, each microneedle may rest upon a flat base or pedestal that itself protrudes from a planar substrate.

Microneedle devices suitable for use in the present invention may be used to deliver drugs (including any pharmacological agent or agents) through the skin in a variation on transdermal delivery, or to the skin for intradermal or topical treatment, such as vaccination.

Microneedle devices of the present invention may be useful when applied to the skin as a "pretreatment" step, that is, when applied to the skin to disrupt the stratum corneum layer of skin and then removed. The disrupted area of skin may then be useful for allowing enhanced delivery of a solution or patch containing a pharmacological agent that is applied to the disrupted area. Microneedle devices of the present invention may also be useful when provided with a dried coating comprising a pharmacological agent that dissolves from the microneedles after they are inserted into the skin. Microneedle devices of the present invention may also be useful when provided with a fluid reservoir of
pharmacological agent that can pass through one or more conduits in the device to be delivered into the skin after the microneedles are inserted into the skin.

In one aspect, drugs that are of a large molecular weight may be delivered transdermally. Increasing molecular weight of a drug typically causes a decrease in unassisted transdermal delivery. Microneedle devices suitable for use in the present invention have utility for the delivery of large molecules that are ordinarily difficult to deliver by passive transdermal delivery. Examples of such large molecules include proteins, peptides, nucleotide sequences, monoclonal antibodies, DNA vaccines, polysaccharides, such as heparin, and antibiotics, such as ceftriaxone.

In another aspect, microneedle devices suitable for use in the present invention may have utility for enhancing or allowing transdermal delivery of small molecules that are otherwise difficult or impossible to deliver by passive transdermal delivery. Examples of such molecules include salt forms; ionic molecules, such as bisphosphonates, preferably sodium alendronate or pamedronate; and molecules with physicochemical properties that are not conducive to passive transdermal delivery.

In another aspect, microneedle devices suitable for use in the present invention may have utility for enhancing delivery of molecules to the skin, such as in dermatological treatments, vaccine delivery, or in enhancing immune response of vaccine adjuvants. In one aspect, the drug may be applied to the skin (e.g., in the form of a solution that is swabbed on the skin surface or as a cream that is rubbed into the skin surface) prior to applying the microneedle device.

Microneedle devices may be used for immediate delivery, that is where they are applied and immediately removed from the application site, or they may be left in place for an extended time, which may range from a few minutes to as long as 1 week. In one aspect, an extended time of delivery may from 1 to 30 minutes to allow for more complete delivery of a drug than can be obtained upon application and immediate removal. In another aspect, an extended time of delivery may be from 4 hours to 1 week to provide for a sustained release of drug.

The present invention has been described with reference to several embodiments thereof. The foregoing detailed description and examples have been provided for clarity of understanding only, and no unnecessary limitations are to be understood therefrom. It will be apparent to those skilled in the art that many changes can be made to the described
embodiments without departing from the spirit and scope of the invention. Thus, the
scope of the invention should not be limited to the exact details of the compositions and
structures described herein, but rather by the language of the claims that follow.
We claim:

1. A device for applying a microneedle array to a skin surface comprising:
   a base defining a skin contacting plane;
   an array component having a skin facing side comprising a microneedle array;
   a connecting member having a first portion affixed through a first hinge to the base
   and a second portion affixed to the array component;
   wherein the connecting member has a first equilibrium position with the
   microneedle array in a recessed position within the device; and
   wherein the connecting member has a second equilibrium position with the
   microneedle array positioned so as to be able to contact a skin surface.

2. A device as claimed in claim 1, wherein the second portion of the connecting
   member is affixed to the array component through a second hinge.

3. A device as claimed in any preceding claim, wherein the connecting member is a
   single, flexible member generally encircling the array component.

4. A device as claimed in claim 1 or 2, further comprising a plurality of connecting
   members.

5. A device as claimed in claim 4, wherein the device has four connecting members.

6. A device as claimed in any preceding claim, wherein the base comprises a
   pressure-sensitive skin adhesive disposed along the skin-contacting plane.

7. A device as claimed in any preceding claim, wherein the microneedle array is
   substantially parallel to the skin contacting plane in both the first equilibrium position and
   the second equilibrium position.

8. A device as claimed in claim 7, wherein the microneedle array remains
   substantially parallel to the skin contacting plane when moving from the first equilibrium
   position to the second equilibrium position.
9. A device as claimed in any preceding claim, wherein at least one connecting member, at least one hinge, and the base are integrally formed.

10. A device as claimed in any preceding claim, wherein at least one connecting member, at least one hinge, the base, and the array component are integrally formed.

11. A device as claimed in any preceding claim, wherein the array component and at least one connecting member are formed of dissimilar materials.

12. A device as claimed in any preceding claim, wherein the device is in the first equilibrium position and further comprises a covering member releasably affixed to the base.

13. A device as claimed in any preceding claim, wherein the microneedle array comprises a plurality of microneedles with a height of less than about 500 microns.

14. A device as claimed in any preceding claim, wherein the array component comprises a backing plate and a microneedle array.

15. A device as claimed in claim 14 wherein the microneedle array is releasably attached to the backing plate.

16. A device as claimed in any preceding claim, wherein the microneedle array further comprises a dried coating on at least a portion of the microneedle surfaces.

17. A device as claimed in claim 16, wherein the dried coating comprises a drug.

18. A device as claimed in claim 16, wherein the dried coating comprises a vaccine.

19. A method of applying a microneedle array to a skin surface comprising the steps of:
i) providing a device as claimed in any preceding claim, wherein at least one connecting member is in its first equilibrium position with the microneedle array in a recessed position within the device;

ii) placing the device on a skin surface;

iii) applying a force to the array component sufficient to move the connecting member to its second equilibrium position.

20. A method as claimed in claim 19, wherein the force is applied using a mechanical applicator.

21. A method as claimed in claim 20, wherein the mechanical applicator has a driving mechanism aligned with the center of the device using an alignment structure.

22. A method as claimed in claim 20 or 21, wherein the applicator contacts the device prior to applying the force to the array component and is subsequently removed from contact with the array component, leaving the device in place on the skin surface.

23. A method of applying a microneedle array to a skin surface comprising the steps of:

i) providing a device having a first equilibrium position wherein a microneedle array is in a recessed position within the device;

ii) placing the device on a skin surface;

iii) bringing a mechanical applicator into contact with the device and aligning a drive mechanism of the mechanical applicator with the microneedle array;

iv) applying a force via the drive mechanism to the microneedle array sufficient to move the microneedle array into contact with the skin surface;

v) removing the mechanical applicator from contact with the device.

24. A method of applying a microneedle array as claimed in claim 23 and further comprising the step of removing at least a portion of the device from the microneedle array while leaving the microneedle array in contact with the skin surface.
25. A device as claimed in claim 1, 2, or 3 wherein the connecting member comprises one or more non-linear portions.

26. A device for applying a microneedle array to a skin surface comprising:
   an outer ring;
   an array component having a skin facing side comprising a microneedle array;
   a connecting member having a first portion affixed through a first hinge to the outer ring and a second portion affixed to the array component;
   wherein the connecting member has a first equilibrium position with the microneedle array in a recessed position; and
   wherein the connecting member has a second equilibrium position with the microneedle array positioned so as to be able to contact a skin surface.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61N1/30 A61M37/00

According to International Patent Classification (IPC) onto both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M A61B A61N

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 practical search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 01/93931 A (BECTON DICKINSON CO [US]; PALMER PHYLLIS J [US]) 13 December 2001 (2001-12-13) page 9, line 8 - page 15, line 2; figures 3-10</td>
<td>1-18,26</td>
</tr>
</tbody>
</table>

Further categories of cited documents

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

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

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

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

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

"X" 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

"Y" 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

"X" 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

"S" document member of the same patent family

Special categories of cited documents

Date of the actual completion of the international search

13 September 2007

Date of mailing of the international search report

01/10/2007

Name and mailing address of the ISA/
European Patent Office, P B 5818 Patentaal 2
NL-2280 HV Rijswijk
Tel (+31-70) 340-2040 Fax 31 651 epi nl,
Authorised officer

Krassow, Heiko

Form POT/ISA/210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
</table>

Form PCT/ISA/21 (0) (continuation of second sheet) (Apr 2005)
INTERNATIONAL SEARCH REPORT

Box ii Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claims Nos 19-25**
   - because they relate to subject matter not required to be searched by this Authority, namely
     - Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
     - When carrying out the methods defined the microneedle device is moved to the skin contacting position, i.e. the microneedle device pierces the skin of a

2. **Claims Nos**
   - because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out specifically

3. **Claims Nos**
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a)

Box iii Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos

Remark on Protest
- The additional search fees were accompanied by the applicant’s protest
- No protest accompanied the payment of additional search fees

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
Continuation of Box II.1

Claims Nos.: 19-25

Rule 39.1(Iv) PCT - Method for treatment of the human or animal body by surgery

When carrying out the methods defined the microneedle device is moved to the skin contacting position, i.e. the microneedle device pierces the skin of a human body.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 0193931 A</td>
<td>13-12-2001</td>
<td>AT 315944 T</td>
<td>15-02-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 7526001 A</td>
<td>17-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60116764 T2</td>
<td>02-11-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2254435 T3</td>
<td>16-06-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003534881 T</td>
<td>25-11-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6537242 B1</td>
<td>25-03-2003</td>
</tr>
<tr>
<td>WO 2007002523 A</td>
<td>04-01-2007</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2587386 A1</td>
<td>26-05-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2587505 A1</td>
<td>26-05-2006</td>
</tr>
</tbody>
</table>