

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 June 2001 (14.06.2001)

PCT

(10) International Publication Number
WO 01/41863 A1

(51) International Patent Classification⁷: **A61M 37/00**,
5/42

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(21) International Application Number: PCT/US00/33318

(22) International Filing Date: 7 December 2000 (07.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/172,703 10 December 1999 (10.12.1999) US
60/216,877 7 July 2000 (07.07.2000) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

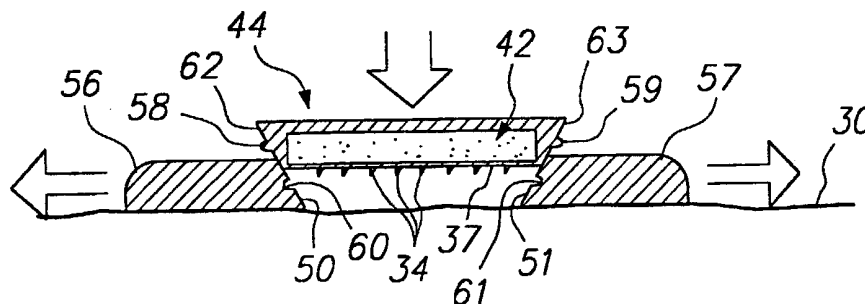
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Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DEVICE AND METHOD FOR ENHANCING MICROPROTRUSION SKIN PIERCING



(57) Abstract: A device (100, 101, 102, 103, 104, 105, 106, 107) and method for enhancing skin piercing by microprotrusions involves pre-stretching the skin (30) to enhance pathway formation when the microprotrusions (34) are pressed into the skin. An expandable device (100) includes skin engaging opposite ends (56, 57) that contact the skin surface (30) so that when the device (100) is expanded the skin (30) is stretched. The skin is placed under a tension of about 0.01 to about 10 megapascals, preferably about 0.05 to about 2 megapascals. The device (100) has a plurality of microprotrusions (34) which penetrate the skin (30), while the skin is being stretched by the expanded device (100) and optionally during agent delivery therethrough. Another stretching device (106) employs suction for skin stretching.



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5 DEVICE AND METHOD FOR ENHANCING MICROPROTRUSION SKIN PIERCING

TECHNICAL FIELD

10 The present invention relates to transdermal agent delivery and more particularly, to the transdermal delivery of macromolecular agents such as polypeptides, proteins, oligonucleotides and polysaccharides. The present invention relates to devices which have microprotrusions to pierce the outermost layer of a body surface (e.g., the skin) to enhance the transdermal
15 flux of the agents during transdermal delivery.

BACKGROUND ART

Interest in the percutaneous or transdermal delivery of peptides, proteins, and other macromolecules, such as oligonucleotides, to the human body continues to grow with the increasing number of medically useful peptides and proteins becoming available in large quantities and pure form. The transdermal delivery of peptides and proteins still faces significant problems. In many instances, the rate of delivery or flux of polypeptides through the skin is insufficient to produce a desired therapeutic effect due to the low transdermal permeability coefficient of macromolecules and the binding of the polypeptides to the skin. In addition, polypeptides and proteins are easily degraded during and after penetration into the skin, prior to reaching target cells. Likewise, the passive transdermal flux of many low molecular weight compounds is too limited to be therapeutically effective.

One method of increasing the transdermal delivery of agents relies on the application of an electric current across the body surface referred to as “electrotransport.” “Electrotransport” refers generally to the passage of a beneficial agent, e.g., a drug or drug precursor, through a body surface, such as skin, mucous membranes, nails, and the like. The transport of the agent is induced or enhanced by the application of an electrical potential, which

5 results in the application of electric current, which delivers or enhances delivery of the agent. The electrotransport of agents through a body surface may be attained in various manners. One widely used electrotransport process, iontophoresis involves the electrically induced transport of charged ions. Electroosmosis, another type of electrotransport process, involves the
10 movement of a solvent with the agent through a membrane under the influence of an electric field. Electroporation, still another type of electrotransport, involves the passage of an agent through pores formed by applying a high voltage electrical pulse to a membrane. In many instances, more than one of these processes may be occurring simultaneously to a
15 different extent. Accordingly, the term "electrotransport" is given herein its broadest possible interpretation, to include the electrically induced or enhanced transport of at least one charged or uncharged agent, or mixtures thereof, regardless of the specific mechanism or mechanisms by which the agent is actually being transported. Electrotransport delivery generally
20 increases agent delivery and reduces polypeptide degradation during transdermal delivery.

Another method of increasing the agent flux involves pre-treating the skin with, or co-delivering with the beneficial agent, a skin permeation enhancer. A permeation enhancer substance, when applied to a body
25 surface through which the agent is delivered, enhances its flux therethrough such as by increasing the permselectivity and/or permeability of the body surface, reducing the electrical resistance of the body surface to the passage of the agent and/or creating hydrophilic pathways through the body surface in the case of transdermal electrotransport delivery, and/or reducing the
30 degradation of the agent.

There also have been many attempts to mechanically penetrate or disrupt the skin in order to enhance the transdermal flux. See for example U.S. Patent Nos. 3,814,097 issued to Ganderton, et al., 5,279,544 issued to Gross, et al., 5,250,023 issued to Lee, et al., 3,964,482 issued to Gerstel, et
35 al., Reissue 25,637 issued to Kravitz, et al., and PCT Publication Nos. WO 96/37155, WO 96/37256, WO 96/17648, WO 97/03718, WO 98/11937,

5 WO 98/00193, WO 97/48440, WO 97/48441, and WO 97/48442. These devices use piercing elements of various shapes and sizes to pierce the outermost layer (i.e., the stratum corneum) of the skin. The piercing elements disclosed in these references generally extend perpendicularly from a thin, flat member, such as a pad or sheet. The piercing elements in some of these
10 devices are extremely small, some having dimensions (i.e., a microblade length and width) of only about 25 - 400 μm and a microblade thickness of only about 5 - 50 μm . These tiny piercing/cutting elements are meant to make correspondingly small microslits/microcuts in the stratum corneum for enhanced transdermal agent delivery therethrough.

15 A limitation on devices having such tiny skin penetrating elements is that the elastic properties of the patient's skin 30 allow the skin to conform around the individual skin penetrating elements 32 significantly before those elements actually breach the skin as shown in Figure 1. In order to overcome this conforming effect and offsetting the condition in which the patient's skin is
20 slack between the penetrating elements 32 as shown in Figure 2, the skin penetrating elements are sometimes designed to be four to five times longer than what is necessary for the desired penetration depth. The conformance of the skin around the individual skin penetrating elements can also diminish the advantage of a sharp tip on each element because the entire bottom
25 edge of the skin penetrating element is pushed against the skin, as can be seen in Figure 1. In addition, the tissue layers under the stratum corneum can cause uneven distribution of the total force applied by allowing more conformance around some microprotrusions than others, resulting in several different local pressures across the site. As can be seen in Figure 2, this
30 results in nonuniform penetration depth across the site by the individual skin penetrating elements which each penetrate the skin to a different depth 35. It is desirable to produce devices for more reliable penetration for producing more uniform flux of an agent being delivered.

5

DESCRIPTION OF THE INVENTION

The device of the present invention more consistently and reliably penetrates a body surface, e.g., the outermost layer of skin, to enhance agent delivery through 1) greater uniformity of the penetration pattern, 2) deeper
10 penetration with the same size or smaller microprotrusions, and 3) increased size of the resulting pathways. The present invention provides enhanced penetration by controlling the effective mechanical properties of the body surface by reducing the compliance, i.e., extensibility, of the body surface 30. The compliance or extensibility is reduced by applying tension at the
15 application site, i.e., stretching the skin taut, during penetration of the body surface with skin penetrating elements 34 as shown in Figure 3. Applying tension to the body surface 30 with the device of the present invention reduces the extensibility of the patient's skin, and makes the extensibility more uniform from patient to patient, resulting in reproducibility of penetration
20 from site to site and application to application.

The device of the present invention stretches the patient's skin during penetration by a plurality of microprotrusions. As used herein, the term "microprotrusions" refers to very tiny skin piercing elements, typically having a length of less than 500 μm , a width of less than 400 μm and a thickness of 5
25 to 100 μm which make correspondingly sized microcuts/microslits in the skin. Upon piercing through the outermost layer (i.e., the stratum corneum) of the skin, the microprotrusions form pathways as shown in Figures 3 and 4 through which an agent such as a drug can be introduced, i.e., transdermally delivered. A principal advantage of the present invention is that the device
30 ensures uniform penetration, i.e., generates the same size and depth pathways, by the microprotrusions across the device. Furthermore, the present invention reproducibly provides uniformity in penetration from patient to patient and can form deeper penetrations with shorter microprotrusions.

The device of the present invention uses stretching elements which
35 engage the surface of the skin, such as with adhesive, and create opposing forces across the surface of the skin surface so as to create tension at the

5 skin surface between the skin stretching elements. When piercing the skin with very tiny microprotrusions, the degree of tension under which the skin is placed becomes much more critical compared to skin piercing using substantially larger skin piercing elements such as blood drawing lancets. In accordance with the present invention using microprotrusion piercing, the skin
10 is placed under a tension in the range of about 0.01 to about 10 M Pa, and preferably in the range of about 0.05 to about 2 M Pa (M Pa = megapascal = 1×10^6 pascals). Thus, the skin stretching/tensioning devices according to the present invention apply a predetermined amount of tension (i.e., stress) in the range from about 0.01 to about 10 M Pa, and preferably in the range of
15 about 0.05 to about 2 M Pa. The amount of skin strain resulting from a given tension varies between individuals depending upon skin characteristics, such as the age of the patient, the location on the patient's body and the tensioning direction. Therefore, in order to adapt to individual characteristics and improve penetration, the skin tensioning devices according to the present
20 invention preferably are designed to provide a given tension (stress) rather than a given strain. In general, for these stress or tension ranges, the applied skin strain is within about 5 to 60% and most preferably within about 10 to 50%. Strain is the amount of skin stretch per unit length of skin and is defined as the change in length of skin in an extended or stretched state
25 divided by the length of skin in a non-stretched state. The strain can be expressed mathematically by the following equation:

$$\text{Strain} = (l_{\text{ext}} - l_{\text{non-ext}}) \div l_{\text{non-ext}}$$

wherein:

- 30 l_{ext} is the length of a sample of skin in a stretched state; and
 $l_{\text{non-ext}}$ is the length of the skin sample in a non-stretched state.

With the skin in tension, the skin is less compliant and less extensible, resulting in the microprotrusions being able to pierce the outermost layer of the skin without the skin conforming around or giving way to the
35 microprotrusions so easily. The stretched skin allows nearly complete penetration by all of the microprotrusions, so as to produce a substantial

5 number of agent pathways and electrical continuity (if electrotransport is used) with the skin for continued and reproducible agent flux through the skin. With the skin at the site of application being held taut by the stretching elements the surface of the skin itself is now exerting more resistance to the applied pressure by the points of the microprotrusions. This allows for more reproducible penetration from patient to patient, or from one site to another
10 on a patient, by making the underlying characteristics of the tissue layers under the stratum corneum less influential on penetration as the surface of the skin is exerting resistance to the applied pressure.

In one aspect of the invention, the apparatus comprises an expandable
15 device with skin engaging portions which in use stretches the patient's skin, and a skin penetrating device having a plurality of microprotrusions adapted to pierce the stratum corneum prior to transdermal agent delivery therethrough. One example of a suitable skin penetrating device includes a relatively thin, flexible sheet, which in use is adapted to be placed in
20 substantially parallel relation with the body surface to be pierced. The sheet has a plurality of microprotrusions extending perpendicularly from a body proximal side of the sheet and at least one opening therethrough, which allows the agent to pass between a reservoir associated with the sheet (and typically positioned on the body distal surface of the sheet) and the holes or
25 pathways pierced in the outermost layer of the body surface by the microprotrusions.

The device of the present invention can be used in connection with agent delivery, and in particular, transdermal drug delivery. Delivery devices for use with the present invention include, but are not limited to,
30 electrotransport devices, passive devices, osmotic devices, and pressure-driven devices.

BRIEF DESCRIPTION OF THE DRAWINGS

35 Many objects and advantages of the present invention will be apparent to those skilled in the art when this specification is read in conjunction with

5 the attached drawings, wherein like reference numerals are applied to like elements, and wherein:

Figure 1 is an enlarged diagrammatic view of microprotrusions being applied to unstretched skin as was done in the prior art;

Figure 2 is an enlarged diagrammatic view of microprotrusions after
10 penetrating unstretched skin as was done in the prior art;

Figure 3 is an enlarged diagrammatic view of microprotrusions being applied to stretched skin in accordance with the present invention;

Figure 4 is an enlarged diagrammatic view of microprotrusions after penetrating stretched skin in accordance with the present invention;

15 Figure 5 is a perspective view of a device in accordance with the present invention;

Figures 6-8 illustrate operation of the device shown in Figure 5;

Figure 9 is an enlarged perspective view of a portion of the device shown in Figures 5-8;

20 Figures 10-12 illustrate operation of a second device in accordance with the present invention;

Figures 13 and 14 illustrate operation of a third device in accordance with the present invention;

Figures 15 and 16 illustrate operation of a fourth device in accordance
25 with the present invention;

Figure 17 is an enlarged perspective view of a portion of the device shown in Figures 15 and 16;

Figure 18 is a perspective view of a fifth device in accordance with the invention;

30 Figure 19 illustrates the operation of the device shown in Figure 18;

Figure 20 is an enlarged perspective view of a portion of the device shown in Figures 18 and 19;

Figure 21 is a schematic side view of a sixth device in accordance with the present invention;

35 Figure 22 is a side cross sectional view of a seventh device in accordance with the present invention;

5 Figure 23 is a side cross sectional view of an eighth device in accordance with the present invention;

 Figure 24 is an alternate embodiment for the microprotrusions of the present invention;

 Figure 25 is a graph of tension or force applied versus skin strain;

10 Figure 26 illustrates the effect of skin stretching on skin extensibility in humans;

 Figure 27 illustrates the effect of skin stretching on passive lisinopril flux;

 Figure 28 illustrates the effect of skin stretching on electrically assisted
15 insulin flux;

 Figure 29 is a section view of a microblade array having a single row of blades adapted to be dragged across the skin surface;

 Figure 30 is a sectional view of one of the microblades illustrated in Figure 29, taking along line 130-130;

20 Figure 31 is a perspective view of one embodiment of a hand held device which incorporates the microblade array of Figure 29; and

 Figure 32 is a perspective view of the device shown in Figure 30 after dragging the microblade array across the skin.

25 **MODES FOR CARRYING OUT THE INVENTION**

 As shown in Figures 3 and 4, the present invention, comprises stretching the skin 30 during piercing of the skin by microprotrusions 34. The stretching constrains the skin motion (i.e., conformability) relative to the
30 penetrating action of the microprotrusions 34 so as to make the depth of penetration 35 by the microprotrusions 34 into the skin 30 more reliable and uniform.

 The present invention involves stretching a body surface (e.g., skin) just prior to and during piercing with the microprotrusions of the
35 aforementioned size to create a plurality of microcuts/microslits therein. The microcuts/microslits can be formed by any suitable body surface penetrating

5 device as the invention is not limited in this respect except with respect to the size of the microprotrusions. Thus, the present invention can be used with any known skin piercing or skin cutting microprotrusions, for example, those described in U.S. Patent Nos. 5,279,544; 3,964,482; 5,250,023; Reissue 25,637; 5,312,456 and those disclosed in PCT Publication Nos. WO 97/48440, WO 96/37256, WO 97/03718, WO 98/11937, and WO 98/00193. One particularly preferred type of microprotrusion device is shown in Figures 9, 17 and 20 and is comprised of a plurality of microprotrusions 34 extending outwardly from one surface of a thin, compliant member or sheet 36 with its main surface 37 oriented parallel to the patient's body surface 30.

15 A particularly preferred configuration for the microprotrusion device is illustrated in Figure 24 and comprises a plurality of individual sheet members 36 stacked together to form the device 2. Each thin sheet 36 in use is oriented perpendicular to the patient's body surface 30. The sheets 36 each have a plurality of microprotrusions 34 in the same plane as the sheet 36 and which extend outward from a body proximal edge 38 of the sheet 36 for penetrating the body surface 30. Each of the sheet members 36 has a pair of holes 12, 13 through which bolts 15 are inserted. Spacers (e.g., tubes) 17 are positioned between each adjacent pair of sheet members 36 to form voids 27 therebetween. The spaced sheet members 36 are held together as a unit by passing the bolts 15 through the sheet members and spacers 17 and securing nuts 14 on the ends of the bolts, or using other known fasteners. The voids 27 can be filled with a reservoir matrix material (e.g., a gel) adapted to contain the beneficial agent to be delivered. Those skilled in the art will appreciate that spacers 17 having other than tube-like configurations (e.g., square or rectangular blocks) can also be used to provide voids 27 between the agent reservoir 42 (i.e., the agent reservoir contained in the voids 27) and the skin. Furthermore, more than two sets of bolts 15, or other fastening pins, may be used to secure the sheet members 36 and spacers 17 together.

35 In either the Figure 9 or the Figure 24 embodiments, the sheet members 36 are generally compliant and flexible because of their relatively

5 thin thickness, for example, about 5 μm to about 100 μm , preferably about 25 μm to about 50 μm .

As used herein, "stretching" means applying a tension in the range of about 0.01 to about 10 M Pa, and preferably about 0.05 to about 2 M Pa, to the skin at the time of puncturing the skin with the microprotrusions. As used
10 herein, the term "unilateral stretching" means tensioning the skin in one direction. As used herein, "bilateral stretching" means tensioning the skin in two directions. As used herein, the term "shear puncturing" means the microprotrusions are moved parallel to the surface of the skin. As used herein, the term "normal puncturing" means the microprotrusions are moved
15 normal to the surface of the skin. As used herein, the term "longitudinal shearing" means shear loading that is oriented parallel to the direction that the skin is stretched. As used herein, the term "transverse shearing" means shear loading that is oriented orthogonal to the direction that the skin is stretched. As used herein, the term "global puncturing" refers to
20 microprotrusions that all move as a single unit rather than relative to one another during insertion. As used herein, the term "local puncturing" refers to microprotrusions which move relative to one another, usually in opposite directions, during insertion.

Figure 25 illustrates the typical stress-strain curve for an in vitro tensile
25 test on excised mammalian skin. In phase I there is rapid extension of skin under low load. In phase II there is rapid stiffening of skin followed by phase III in which the skin has stiff behavior. If the skin is tensioned to a degree that reaches phase IV skin tearing and rupture occurs. For effective skin stretching according to the present invention, it is desirable to tension to a
30 degree that results in phase II or III strain but not phase IV strain. Figure 25 illustrates the typical stress-strain curve for unpierced skin, however, the curve may vary somewhat for skin which has been pierced by an array of microprotrusions.

The device of the present invention is for use in the percutaneous
35 administration of an agent. The terms "substance", "agent", and "drug" can be used interchangeably and broadly include physiologically or

5 pharmacologically active substances for producing a localized or systemic effect or effects in mammals, including humans and primates, avians, valuable domestic household, sport, or farm animals, or for administering to laboratory animals such as mice, rats, guinea pigs, and the like.

The major barrier properties of the skin, such as resistance to agent permeation, reside with the outermost layer of the skin, i.e., stratum corneum. 10 The inner division, i.e., the underlying layers, of the epidermis generally comprise three layers commonly identified as stratum granulosum, stratum malpighii, and stratum germinativum. There is essentially little or no resistance to transport or to absorption of an agent through these layers.

15 Therefore, for enhancing transdermal flux the microprotrusions used to create pathways in the body surface in accordance with the present invention need only penetrate through the stratum corneum in order for the agent to be transdermally delivered with little or no resistance through the skin.

The devices shown in Figures 5-12, utilize microprotrusions that pierce 20 the body surface by global, normal puncturing. That is, all of the microprotrusions move as a single unit normal to the skin during the piercing process. With each of these devices, the skin is stretched during puncturing, and the load used to puncture is applied normal to the skin. The stretching of the skin can be transverse to the microprotrusions as shown in Figure 9, or 25 the array of microprotrusions can be rotated 90° such that the stretching occurs in line with each of the microprotrusions 34 as shown in Figure 8. After penetration by the plurality of microprotrusions 34, the skin optionally remains under tension created by the skin stretching portions of the devices. Most of the embodiments of the present invention utilize unidirectional stretching of the skin. However, bi-directional stretching can be used as well 30 as shown in Figures 15-16. In addition, impact insertion of the microprotrusions may also be employed in any of the embodiments by bringing the microprotrusions into contact with the skin at a predetermined impact velocity which causes the microprotrusions to penetrate the skin.

35 The expandable device 100 shown in Figures 5-8 uses biasing members 46 and 47 (e.g., springs) housed in hollow cylindrical members 48

5 and 49 to initially stretch the body surface, and then biasing members or inclined surfaces 50 and 51 (Figure 8) or a combination of both to stretch the body surface 30. The expandable device 100 has an adhesive on the skin-contacting surface thereof, initially protected by a release liner 52 (Figure 5). A disposable retainer 54 holds the opposite ends 56 and 57 of the device
10 together such that the biasing members 46 and 47 located within the device are in compression. The patient removes the release liner 52 and applies the device 100 to a portion of the skin surface 30 such that the adhesive on the skin-contacting surface holds the device to the patient's skin surface 30. Then the disposable retainer 54 is removed from the top of the device 100 to
15 release the biasing members 46 and 47 which are in compression so that the device 100 expands a predetermined distance to stretch the skin in the aforementioned tension range. A snap-in cartridge housing 44 having a microprotrusion array on a skin-engaging surface and a reservoir 42 (Figure 8) therein is then snapped into the elongated opening left by the expansion of
20 the device 100 such that the protrusions 58 and 59 on each end of the housing 44 lock into the indentations 60 and 61. In an optional embodiment as illustrated, the ends 62 and 63 of the cartridge housing 44 form a wedge to match the inclined surfaces 50 and 51 so that when the cartridge is snapped into the expandable device 100, the opposite ends 56 and 57 stretch the skin
25 even farther. It is also within the scope of the present invention that the surfaces 50 and 51 and ends 62 and 63 are not inclined such that the stretching is done only by the biasing members 46 and 47. As seen in Figure 9, the stretching of the body surface transverse to the plane of the microprotrusion not only helps with the initial penetration but also holds the
30 pathways through the body surface 30 open during delivery or sampling.

A second embodiment of the invention is illustrated in Figures 10, 11, and 12. The expandable device 101 is manually actuated by the patient, but essentially retains the same characteristics of operation as described with respect to device 100, in that the skin is stretched under a predetermined
35 tension in the range of about 0.01 to about 10 M Pa and preferably about 0.05 to about 2 M Pa, at the time of puncturing and all of the microprotrusions

5 34 move normal to the skin as a single unit during the insertion process. With respect to this embodiment, the release liner 52 is removed to expose the adhesive on the skin-contacting surfaces of each of the ends 56 and 57 of the device 101, and the device is placed on the patient's body surface. The patient or another person then stretches the skin by spreading apart the ends
10 56 and 57 of the device as shown in Figure 11 to a position which provides a skin tension in the range of about 0.01 to about 10 M Pa, and preferably about 0.05 to about 2 M Pa, to improve penetration by the microprotrusions. The ratcheted sides 64 and 65 on the expandable device 101 allow the device to maintain its expanded position after the patient or another has
15 removed their hand from the device. The snap-in cartridge housing 44 is then pressed down with a load applied normal to the body surface 30 as described with respect to device 100, and if the snap-in cartridge housing 44 has the optional wedge shape, then the device 101 will stretch the body surface farther upon insertion of the cartridge housing 44 into the device 101.

20 A third embodiment of the invention is illustrated in Figures 13 and 14. Device 102 is operated with a rotational motion, rather than a translational motion as illustrated in devices 100 and 101, in order to move the opposing ends 56, 57 of the stretching device 102 a predetermined distance apart which achieves a skin tension in the range of about 0.01 to about 10 M Pa,
25 and preferably about 0.05 to about 2 M Pa. This embodiment of the invention has the entire device 102 as one integral unit, rather than having the agent reservoir and microprotrusion array in a separate cartridge housing 44. The patient or another person removes the release liner 52 from the skin-contacting side of the device 102 to expose the adhesive on each end of the
30 device, and places the device 102 on the patient's body surface. The reservoir housing 44 with the microprotrusion array on the underneath side is then rotated, and due to its elliptical shape, forces the ends 56 and 57 of the expandable device 102 apart. The housing 44 is pushed down with a load applied normal to the body surface to have the microprotrusions penetrate the
35 body surface. The housing 44 of the device 102 can also be rotated during or

5 after penetration by the microprotrusions to shear the body surface cutting elongated curved slits.

The fourth embodiment of the invention is illustrated in Figures 15-17. Device 103 utilizes global, shear puncturing rather than the global, normal puncturing described with respect to the devices 100, 101 and 102. The
10 global, shear puncturing is movement of all of the microprotrusions 34 in the plane of the skin 30 as a single unit during the insertion process as shown in Figure 17. According to this embodiment normal pressure is applied before and/or during the movement of the microprotrusions in the plane of the skin to perform shear puncturing.

15 In addition to shear puncturing, device 103 provides bi-directional stretching of the skin. The skin is stretched in one direction prior to cartridge housing 44 being inserted and in an orthogonal direction when the cartridge housing 44 is inserted. As shown in Figure 15, similar to those described with respect to device 102, the device 103 is manually actuated by the patient or
20 another, and a ratchet system along each side 64 and 65 holds the skin in the aforementioned tension range for improved skin penetration by the microprotrusions. Then a cartridge housing 44 containing the agent reservoir and a microprotrusion array is slid into the device 100 as shown in Figure 16 along a direction parallel to the direction of the first tensioning. The cartridge
25 housing 44 has a wedge configuration so that the skin is stretched orthogonal to the original tensioning direction so that the skin is then tensioned along two axes. The microprotrusion array can be oriented so that the plane of the microprotrusions 34 are oriented parallel to the direction that the skin is being stretched to provide longitudinal shearing, or the plane of each of the
30 microprotrusions 34 can be oriented perpendicular to the direction that the skin is being stretched to provide transverse shearing.

In some embodiments of the sheet member 36, the microprotrusions 34 are angled or slanted in the same direction. With this configuration, the cartridge housing 44 can be slid along the body surface in the direction of the
35 slanted microprotrusions while pressing down on the cartridge housing to facilitate better penetration against the elastic nature of the skin.

5 As one of ordinary skill in the art will recognize, it is also within the scope of the invention that the cartridge housing 44 could be pressed down normal to the plane of the skin with inclined surfaces and ends as described with respect to devices 100, 101, and 102, which would provide bi-directional stretching. In this way, rather than resulting in global, shear puncture as does
10 device 103, it would result in global, normal puncture.

 As an alternative, the portion of device 103 illustrated in Figure 15 can also be used with the hand held device 108 illustrated in Figures 29-32. The device 108 can be used to form a plurality of elongated microslits through at least the stratum corneum layer of the portion of the skin held in tension by
15 device 103. In this alternative embodiment, the cartridge housing 44 (Figure 15) does not have a microprotrusion array on its skin-contacting surface. Device 108 (Figures 29-30) is comprised of a head 120 and a handle 122. Mounted in the head 120 is a microprotrusion array 124 which is illustrated in greater detail in Figure 29. The microprotrusion array 124 is comprised of a
20 plurality of microprotrusions 126 mounted in a plastic member 128. Member 128 has a length substantially greater than its width as best shown in Figures 31 and 32 such that the microprotrusions 126 comprise a single row of microprotrusions arranged similarly to the tines on a rake. The microprotrusions 126 are preferably formed of a metal and are mounted in
25 the plastic member 128 using known micromolding techniques. Alternatively, the member 128 and the microprotrusions 126 can be one and the same member. For example, the member 128 can be a thin (e.g., 0.03 mm) metal plate having microprotrusions 126 which are photochemically etched and punched as in the processes used to make the microprotrusion arrays shown
30 in Figures 9, 17 and 20. The shape of the microprotrusions 126 is not important, although a particularly preferred shape and microprotrusion cross-sectional shape are shown in Figures 29 and 30, respectively. In operation, the head 120 of device 108 is placed on the surface of skin 30. As mentioned above, the skin is in a prestretched condition. Thus, for example,
35 the skin can be that portion of the skin 30 which is located in the center of device 103 shown in Figure 15. The device 108 is then pulled across the

5 surface of the skin in the direction of the arrows shown in Figures 29 and 31. This movement causes the microprotrusions 126 to cut through the skin forming a plurality of slits 134 therein. The depth of microprotrusion 126 penetration can be controlled by the length of the microprotrusions 126 which typically ranges from 50 to 400 μm . The depth of the microprotrusion 126 cut
10 is controlled by the skin contacting face 132 of member 128 which slides across the surface of skin 30 during the formation of the slits 134.

A fifth embodiment of the invention is illustrated in Figures 18-20. The device 104 provides local, shear puncturing. That is, the microprotrusions 34, or small sets of microprotrusions on a plurality of adjacent sheet members
15 36A and 36B, move in the plane of the skin relative to one another in opposite directions during the insertion process as shown in Figure 20. The expandable device 104 operates and is constructed essentially the same as device 100. The device 104 initially has biasing members (e.g., springs) 46 and 47 in compression which are held in place by a disposable retainer 54.
20 However, device 104 does differ from device 100 with respect to the microprotrusion array. Device 104 has a plurality of alternating sheet members 36A and 36B sheet members 36A are attached to end 56 of an internal expanding assembly 66 which sits in elongated track 68 of the device. Sheet members 36B are attached to the opposite end 57 of the
25 internal expanding assembly 66. Thus, as assembly 66 is caused to expand due to the biasing members 46 and 47 being released from their compressed state, the alternating sheet members 36A and 36B are pulled over the skin in opposite directions. The device 104 is shown partially in phantom view to show the internal expanding assembly and elongated track 68 more clearly.
30 In addition, the microprotrusion array is already in place in the device 104 prior to removing the disposable retainer 54 rather than being inserted after the stretching. As a result, when the release liner (not shown in Figures 18 and 19) is removed from the bottom of the device 104, and the device is adhered to the patient's body surface 30, each of the microprotrusions 34
35 comes into contact with the patient's skin prior to stretching and continues to contact the skin during stretching. However, due to the elasticity and

5 compliance of the patient's skin, many of the microprotrusions do not
puncture or penetrate the body surface initially. Penetration by the
microprotrusions does not occur until after the disposable retainer 54 is
removed, the skin is stretched a predetermined distance by the ends 56 and
57 of the internal expanding assembly 66 being moved apart by the biasing
10 members 46 and 47 thereby placing the skin under tension in the
aforementioned tension range. A force is preferably applied (e.g., by finger
pressure) to the skin distal side of device 104, in a direction with a component
which is normal to the skin surface so as to force the device 104 against the
skin as the skin is being stretched. While the microprotrusions 34 are
15 penetrating the body surface, further separation of the ends 56 and 57 results
in the microprotrusions 34 on the sheet members 36A being moved in
opposite direction from the microprotrusions 34 on the adjacent sheet
members 36B, so as to cause the microprotrusions to shear the body surface
as shown in Figure 20. As one of ordinary skill in the art will appreciate,
20 device 104 can be modified to include alternate (i.e., as an alternative to the
disposable retainer 54 and compressed biasing members 46 and 47 of
device 104) skin stretching means, such as the ratcheted sides 64, 65 of
device 101, the rotatable housing 44 of device 102 or the ratcheted sides 64,
65 in combination with the wedge-shaped housing 44 of device 103.

25 A sixth embodiment of the invention is illustrated in Figure 21. The
device 105 utilizes rotational members 70 for skin stretching. The skin
stretching device 105 includes an upper housing 72 having two or more
rotational skin stretching members 70 pivotally mounted thereon. A lower
housing 74 containing the agent to be delivered is positioned on a lower
30 surface of the upper housing 72. The lower housing 74 is provided with the
plurality of microprotrusions 34 for penetrating the skin surface. Although the
device 105 has been illustrated with two rotatable stretching members 70 for
unidirectional skin stretching, it should be understood that a plurality of such
members can be used for multidirectional skin stretching. As the skin
35 stretching device 105 is pressed onto the skin 30 of the patient, an adhesive
on curved surfaces 76 of the rotatable stretching members 70 adheres to the

5 skin on opposite sides of the microprotrusions 34 and pulls the skin 30 apart a predetermined distance, thereby stretching the skin (at a tension within the aforementioned tension range) at the site between the stretching members 70, for improved penetration of the skin 30 by the microprotrusions 34. According to one variation of the device 105, asymmetric shaped stretching
10 members 70 may be used to provide lateral movement for shear puncturing. The microprotrusions 34 of this device may be oriented either parallel to or transverse to the direction of skin stretching.

A seventh embodiment of the invention is illustrated in Figure 22. In this embodiment, the device 106 includes a suction member 80 of a
15 rectangular, square, circular, or other shape in plan view connected to a tube 82 for drawing a suction. The suction member 80 has a suction channel 84. For multi-directional stretching, the suction channel 84 may be a continuous or substantially continuous channel having a rectangular, circular, oval, or other shape in plan view. For uni-directional stretching, two opposed suction
20 channels 84 may be provided. An outer edge of the suction member 80 includes a lower surface 86 which grips the skin by having a high friction coefficient with respect to the skin. A lower surface 88 of an inner edge of the channel 84 is preferably provided with a low friction surface which allows the skin to slide over the surface. The non-slip surface 86 may be an
25 adhesive, while the slip surface 88 may be coated with a lubricant. When a suction is applied to the suction tube 82 a low pressure area is provided within the channel 84 which draws the skin 30 into the channel as shown in Figure 22, stretching the skin within the opposing surfaces 88. The amount of suction applied within channel 84 will vary depending on the size of device
30 104. Those persons of ordinary skill in the art can determine the level of suction needed to achieve a skin tension in the range of about 0.01 to about 10 M Pa, and preferably about 0.05 to about 2 M Pa. An array of microprotrusions 34 are then applied to the stretched skin in the center of the device 106.

35 An eighth embodiment of the invention is illustrated in Figure 23. The device 107 includes a tubular member 90 having a lower, edge 92 which is

5 pressed into the skin surface 30 causing skin in a center of the tubular member to form a dome shape and become tensioned. The amount of skin stretching or tensioning may be controlled by the amount of pressure applied to the tubular member 90. Manually applied pressure is not recommended in this embodiment since the amount of skin tension achieved through manually
10 applied downward pressure applied to member 90 will be variable and hence difficult to ensure a skin tension in the range of about 0.01 to about 10 M Pa. Thus, with this embodiment, a device (not shown) for applying a predetermined downward (i.e., toward the skin) force to the tubular member 90 is recommended. To prevent slippage between the skin and the lower
15 edge 92 of the tubular member 90, a non-slip surface, such as an adhesive may be employed. The array of microprotrusions 34 are then applied to the tensioned skin within the tubular member 90. The device 107 as shown in Figure 23 may be cylindrical, square, rectangular, or any other shape in plan view.

20 In the preferred embodiments, the microprotrusions 34 are microprotrusions as shown in Figures 9, 17, 20, and 22. In the embodiments shown in Figures 9, 17, and 20, the sheet member 36 is formed with a plurality of openings 40 adjacent the microprotrusions 34 to permit the transport of agent from an agent reservoir 42 located within housing 44. In
25 this embodiment, the openings 40 correspond to the portion of the sheet member 36 occupied by each of the microprotrusions 34 prior to the microprotrusions being bent into a position which is substantially perpendicular to the plane of the sheet member 36 as shown.

The preferred configurations for the array of microprotrusions and a
30 connecting medium for delivering agents between the reservoir 42 and the body surface are described in detail in WO 97/48440; WO 97/48441; WO 97/48442; and WO 98/28037.

The array of microprotrusions 34 in the various embodiments of the present invention may take on different shapes. The present invention can
35 be used with any known delivery device and is not limited to any particular device. It will be appreciated by those working in the field that the present

5 invention can be used in conjunction with a wide variety of electrotransport systems, as the invention is not limited in any way in this regard. For example, the apparatus of the present invention can be used with the electrotransport systems disclosed in U.S. Patent Nos. 5,147,296; 5,080,646; 5,169,382; 5,423,739; 5,385,543; 5,310,404; and 5,169,383; and PCT
10 Publication No. WO 97/48440. Similarly, any known passive transdermal delivery device can be used with the present invention, as the invention is not limited in this regard. For example, the apparatus of the present invention can be used with the passive systems disclosed in U.S. Patent Nos. 4,379,454; 4,588,580; 4,832,953; 4,698,062; 4,867,982; and 5,268,209; and
15 PCT Publication No. WO 97/48440. It will be appreciated by those working in the field that the present invention can also be used in conjunction with a wide variety of osmotic and pressure driven systems, as the invention is not limited to a particular device in this regard. For example, the apparatus of the present invention can be used with the osmotic and pressure driven systems
20 disclosed in U.S. Patent Nos. 4,340,480; 4,655,766; 4,753,651; 5,279,544; 4,655,766; 5,242,406; and 4,753,651.

Example 1

To determine the effect of stretching the skin during application of a
25 transdermal delivery device having skin piercing microprotrusions along a skin-contacting surface of the device, the following experiment was performed.

Excised hairless guinea pig skin was pierced, under stretched and unstretched conditions, using a microprotrusion array having a configuration
30 similar to that shown in Figure 9. The sheet 36 was stainless steel having a thickness of 25 μm . The microprotrusions 34 had a length of 300 μm , a width of 190 μm and were triangularly shaped, with the tip of each microprotrusion having an angle of 35°. The microprotrusion density was 73 microprotrusions/cm². The stretched samples were manually stretched bi-
35 directionally (\leftrightarrow and \updownarrow) and pinned on cork. The bi-directional stretching was estimated to achieve a skin tension of between 0.1 and 1 M Pa. The

5 microprotrusion array was then applied and removed. The treated sites were then covered with an agent reservoir containing a model drug in the form of a dye. The model drug was comprised of a 1% aqueous solution of methylene blue, with 2% hydroxyethyl cellulose added as a gelling agent to create a hydrogel agent reservoir. The reservoirs were placed on the pierced skin
10 samples and the methylene blue was allowed to passively diffuse from the reservoirs into the skin over a treatment period of 15 minutes. The skin was then tape stripped to remove any dye that still remained on the skin surface. The methylene blue diffused into the microcuts made by the microprotrusions, thereby causing selective staining of the microcuts, making them clearly
15 visible to the eye. Polaroid pictures were taken of each site. These photos showed the length of the microcuts made by the microprojections.

Sample 1: 1 kg/cm² normal pressure was applied manually for 30 seconds, with no skin stretching.

20

Sample 2: 1 kg/cm² normal pressure was applied manually for 30 seconds on manually stretched skin.

The microcuts on sample 1 were smaller than those on sample 2.
25 When the methylene blue was allowed to diffuse in via the microcuts, more dye was found in the larger microcuts of sample 2. This is qualitative data based only on the relative sizes of the dye spots.

Example 2

30 Skin Extensibility Evaluation:

Skin extensibility was evaluated in humans using a CUTOMETER SEM 575® (COURAGE + KAHZAKA electronic, GmbH, Köln, Germany) which is conventionally used for measuring skin elasticity in dermatological applications. The CUTOMETER probe (a metal cylinder having a length of
35 about 10 cm, an outside diameter of 3 cm and an inside diameter of 6 mm) was applied on the ventral forearm of four female and four male volunteers

ages 26 to 42 years to measure skin extensibility (E). The CUTOMETER applies a negative pressure of 0.5 bar through the inner (6 mm diameter) opening of the probe which is pressed against the skin. The negative pressure causes the skin to be drawn into the probe opening. The CUTOMETER measures the distance the skin is drawn into the probe and provides a skin extensibility (E) measurement in units of distance (mm). Skin extensibility was measured in a normal (i.e., non-stretched) condition as well as under bi-directional (\leftrightarrow and \updownarrow) manual stretching of the same skin site. The bi-directional stretching was estimated to achieve a skin tension of between 0.1 and 1 M Pa. Figure 26 shows that similar results were obtained in males and in females. As expected, stretching significantly reduced skin extensibility. Surprisingly, stretching appears to reduce variability of the data as demonstrated by the reduction in the standard deviation values of the data.

Penetration of the microprotrusion array is dependent on the skin physical properties. Reduction of the skin extensibility by stretching indicates that stretching of the skin facilitates penetration of the microprotrusion array for a given force. In addition, it was discovered that stretching of the skin made extensibility of the skin more uniform from subject to subject. This indicates that skin stretching will result in a more uniform application/penetration of the microprotrusion array.

Example 3

Effect of Skin Stretching on Transdermal Lisinopril Flux:

The drug lisinopril does not penetrate the skin significantly without the use of penetration enhancers or physical disruption of the skin barrier. In this experiment, lisinopril was delivered by passive diffusion through pathways in the skin created by an array of microprotrusions. The purpose of the experiment was to show that stretching the skin prior to pretreatment with the microprotrusion array improved flux of the drug through the skin in vivo.

In one group of 12 hairless guinea pigs the skin of one flank was stretched manually bi-directionally (\leftrightarrow and \updownarrow) before application of a foam

5 double adhesive ring having a thickness of 0.8 mm (1/32 inch) with a 2 cm² hole in the middle which would later contain the drug. The bi-directional stretching was estimated to achieve a skin tension of between 0.1 and 1 M Pa. The adhesive ring served to keep the skin under the drug compartment in the stretched configuration. Next, a 2 cm² stainless steel microprotrusion
10 array having trapezoidal microprotrusions with microprotrusion lengths of 430 μ m and a microprotrusion density of 241 microprotrusions/cm² was applied to the skin beneath the drug compartment using an approximately 2 kg/cm² normal manual pressure. The microprotrusion array was held for a few seconds and then removed. A hydrogel containing ³H-lisinopril in water
15 (lisinopril 60 mg/mL, pH 5.2, 3% hydroxyethyl cellulose) was dispensed into the drug compartment and a plastic cover was applied to the adhesive outer surface of the ring to seal the system.

A second group of 12 hairless guinea pigs were treated in the same way, except that the skin was not stretched. At 12, 24, and 48 hours after
20 application four systems from each group were removed and residual drug was washed from the skin. The amount of drug penetrated during these time intervals was determined by measuring urinary excretion of tritium (previous studies has shown that in hairless guinea pigs 80% of the tritium derived from ³H-lisinopril injected intravenously is excreted in urine). The results shown in
25 Figure 27, show that penetration of drug during the first twelve hours was significantly enhanced by skin stretching; after 12 hours there was no drug flux in either group. In particular, Figure 27 shows that the amount of lisinopril delivered transdermally tripled with skin stretching.

30

Example 4

Effect of Skin Stretching on Transdermal Iontophoretic Insulin Flux:

This study examined the effect of skin stretching applied before and maintained during application of a microprotrusion array on the electrically assisted insulin flux in the hairless guinea pig.

35

Hairless guinea pigs were divided randomly into two groups of four animals. One group of animals received the microprotrusion array delivery

5 system without skin stretching, and the other, received the microprotrusion blade array with skin stretching during application. In the group undergoing skin stretching, the skin of one flank was stretched manually bi-directionally (\leftrightarrow and \updownarrow) before application of a thin (0.8 mm or 1/32") foam double adhesive ring with a 2 cm² hole in the middle which would later contain the
10 drug. The bi-directional stretching was estimated to achieve a skin tension of between 0.1 and 1 M Pa. The adhesive ring served to keep the skin under the drug compartment in the stretched configuration. Prior to application of this ring, a 2 cm² microprotrusion array of stainless steel having trapezoidal microprotrusions with lengths of 430 μ m and 241 microprojections/cm² was
15 attached on the side of the foam contacting the skin across the hole. After application of the ring, an approximately 2 kg/cm² normal manual pressure was applied on the microprotrusion array and held for a few seconds.

A hydrogel containing Humulin R-500 (Eli Lilly, Indianapolis, IN) supplemented with a final concentration of 25 mM L-histidine (base) and 2%
20 (w/v) hydroxylethyl cellulose, was dispensed into the drug compartment. The remainder of the iontophoretic system was added to this construction. The drug-containing formulation was separated from the cathode electrode by a Nafion ion exchange membrane. A gel containing 0.15M sodium chloride was placed between the cathode and the ionic exchange membrane. The
25 system also comprised an anode compartment which comprised a skin-contacting gel containing a saline hydrogel and an anode electrode. The current was preset to 100 μ A/cm². The system was maintained on the animal skin for 2 hours. Blood samples were also collected at 0.5, 1, 2, 3, and 4 hours after system removal. Plasma was then prepared from these blood
30 samples and insulin was analyzed by radioimmunoassay.

The results shown in Figure 28, show a significant enhancement effect of skin stretching on plasma insulin concentrations found in the blood samples. As can be seen in Figure 28, the skin stretching doubled the amount of insulin delivered transdermally. The average flux (mean \pm sem)
35 extrapolated from these data using pharmacokinetic analysis was 26 ± 9

- 5 $\mu\text{g}/\text{cm}^2\text{h}$ in the unstretched group, versus $53 \pm 13 \mu\text{g}/\text{cm}^2\text{h}$ in the stretched group.

Example 5

Effect of skin stretching on microprotrusion penetration depth:

- 10 This experiment measured the effect of skin stretching on microprotrusion penetration depth using excised hairless guinea pig skin. Two hairless guinea pigs were used in the experiment. Before sacrifice, the skin extensibility (E) of each of the animals was measured using the CUTOMETER described in Example 2. A CUTOMETER probe having an
15 inside diameter of 8 mm was used to measure skin extensibility in this experiment. Six measurements were taken on each side of the animals; three in a natural (i.e., non-stretched) condition and three using manual bi-directional (\leftrightarrow and \updownarrow) stretching. The bi-directional stretching was estimated to achieve a skin tension of between 0.1 and 1 M Pa. The measured skin
20 extensibilities for non-stretched skin on the live guinea pigs ranged from 2.5 to 3.0 mm while the skin extensibility measurements for the stretched skin ranged from 1.5 to 2.0 mm.

- Following these measurements, the animals were sacrificed and skinned from the neck through hind leg region using a scalpel blade. Excess
25 fat under the skin was then removed. The skins were then cleaned with isopropyl alcohol swabs and dried with gauze. The excised skins were then placed over a thin silicone sheet (thickness of 0.3 cm) mounted over a thin piece (thickness of 0.3 cm) of cork board. The excised skins were placed over the silicone and stapled along their perimeter to secure the skins thereto.
30 Skin extensibility measurements were taken with the CUTOMETER and the skin stretch was adjusted (i.e., by removing staples and then restapling) in order to match the extensibility measurements of the live animals. Once the mounted skins had extensibility measurements which matched those of the live animal, the skin tension was assumed to be the same as that achieved
35 through bi-directional stretching of the live animal's skin, and experiments were conducted to measure microprotrusion penetration depth. The

5 microprotrusions used in the experiment were in the form of the metal sheet having a thickness of 0.025 mm (1 mil) having a multiplicity of openings (190 openings/cm²), each opening having one trapezoidally shaped microblade bent at an angle of about 90° to the surface of the sheet. The microprotrusion arrays had a skin-contact area of 2 cm² and had several
10 shapes, materials, and configurations. The microprotrusion arrays were made from both stainless steel and titanium. The arrays included blade widths of 140 microns and 280 microns. The leading angle of the blade tips were 35° and 55°. Blade lengths ranged between 435 and 486 microns. The skin samples were pierced by mounting the microprotrusion arrays on the
15 head of a spring-loaded impactor which drove the microprotrusion arrays into the skin. In spite of the variety of microprotrusion parameters and impact speeds, the experiments were run such that the non-stretched skin samples were tested using the same variety and number of microprotrusion arrays and impact speeds as the stretched skin samples. Thus, any influence in
20 microprotrusion design, blade width, tip angle, microprotrusion materials and impact speed was eliminated from the study results.

After impact penetration by the microprotrusion array, the skin site was rubbed with india ink both horizontally and vertically for about 15 seconds. Thereafter, the site was cleaned with gauze and water until the surface ink
25 was removed. Each treatment site was then labeled and photographed in order to determine the amount of microslits across the impacted site and the number of microslits/cm².

The skin samples were then wrapped in foil and sealed in a plastic bag and placed in a freezer overnight. Upon removal from the freezer, three 6
30 mm cryotomed biopsies were taken from each skin site. The slices were placed on a glass slide in order of increasing depth. When the cryotoming was completed, the india ink stains in each slice were counted at each depth and recorded to determine the penetration of the projections at each depth. The photographs taken prior to cryotoming were used to count the number of
35 penetrations at the surface of each of the sites. For each biopsy, the number of projections that penetrated to, but not yet beyond, each slice was

5 calculated. This data was used to determine mean microprotrusion
penetration depths, which are as follows:

Non-stretched mean penetration depth: 54 microns.

Stretched mean penetration depth: 85 microns.

Thus, stretching the skin increased the mean microprotrusion penetration by
10 57%.

It will be appreciated by those of ordinary skill in the art that the
invention can be embodied in other specific forms without departing from the
spirit or essential character thereof. The presently disclosed embodiments
are therefore considered in all respects to be illustrative and not restrictive.
15 The scope of the invention as indicated by the appended claims rather than
the foregoing description, and all changes which come within the meaning
and range of equivalence thereof are intended to be embraced therein.

5 Claims:

1. An apparatus for delivering an agent through a body surface (30) including a plurality of microprotrusions (34) for piercing and forming a plurality of micropathways through the body surface (30) and an agent-containing reservoir (42) in agent-transmitting relation with the micropathways, the apparatus being characterized by:
 - a stretching device (100, 101, 102, 103, 104, 105, 106, 107) for applying a tension of about 0.01 to about 10 M Pa to a body surface site during penetration thereof by the microprotrusions (34).
2. The apparatus of claim 1, wherein the stretching device (100, 101, 102, 103, 104) comprises a body surface engaging first portion (56) and a body surface engaging second portion (57) which stretch the body surface site when the device (100, 101, 102, 103, 104) is expanded.
3. The apparatus of claim 1, wherein the stretching device (106, 107) includes a suction chamber (84) which engages the body surface (30) surrounding the site.
4. The apparatus of claim 3, wherein the microprotrusions (34) are mounted on a member which is movable within the suction chamber to puncture the site.
5. The apparatus of claim 3, wherein the suction chamber comprises an interior space of a tubular member (90) which is provided with a negative pressure for drawing the skin into the tubular member (90).
6. The apparatus of claim 1, wherein the skin stretching device (106) includes
 - at least one channel (84) having an opening which engages the body surface (30) surrounding the site; and

5 means (82) for applying a suction to the channel (84) to draw the body surface (30) into the channel (84) and stretch the site.

7. The apparatus of claim 6, wherein the channel (84) has an annular shape.

10

8. The apparatus of claim 2, wherein the agent reservoir (42) has an array of microprotrusions (34) for puncturing the body surface (30), wherein the expandable device is configured to stretch body surface (30) and maintain stretching during penetration of the body surface (30) by the microprotrusions
15 (34).

9. The apparatus of claim 2, wherein the agent-containing reservoir (42) is located between the body surface engaging portions (56, 57).

20 10. The apparatus of claim 9, wherein the reservoir (42) is located in a housing (44) having the plurality of microprotrusions (34) extending from a body surface proximal side of the housing (44).

11. The apparatus of claim 10, wherein the housing (44) is wedge-shaped
25 and contacts surfaces (50, 51) on the first portion (56) and the second portion (57) to expand the device (101) when the housing (44) is inserted between the first portion (56) and the second portion (57) of the expandable device (101).

30 12. The apparatus of claim 10, wherein the housing (44) is shaped to expand the device (102) when the housing (44) is rotated in a space between the first portion (56) and the second portion (57) of the expandable device (102).

35

5 13. The apparatus of claim 2, further comprising:

a retainer (54) which initially holds the first portion (56) and the second portion (57) in a first position; and

a biasing member (46, 47) for urging the first portion (56) away from the second portion (57) when the retainer (54) is removed.

10

14. The apparatus of claim 2, further comprising means (64, 65) for holding the device (101, 103) in an expanded state after the device (101, 103) has been expanded.

15 15. The apparatus of claim 14, wherein the holding means (64, 65) holds the device (103) in the expanded state in a first direction and the housing (44) is wedge-shaped and contacts surfaces on the first portion (56) and the second portion (57) to expand the device (103) in a second direction.

20 16. The apparatus of claim 1, wherein the plurality of microprotrusions (34) comprise a first sheet member (36) having a plurality of microprotrusions (34) extending outward therefrom.

17. The apparatus of claim 2, wherein the body engaging first portion (70) and body engaging second portion (70) are rotatable members pivotally
25 mounted on a base (72).

18. The apparatus of claim 1, wherein the plurality of microprotrusions (34) are arranged in a row (124) and are adapted to be moved over the body site
30 to form a plurality of elongated slits therein.

19. The apparatus of claim 18, wherein the body surface engaging portions (56, 57) stretch the site in a direction transverse to the elongated slits.

35

5 20. The apparatus of claim 1, wherein the stretching device (100, 101, 102, 103, 104, 105, 106, 107) applies a stress of about 0.05 M Pa to about 2 M Pa to the site.

21. The apparatus of claim 1, wherein the stretching device (100, 101,
10 102, 103, 104, 105, 106, 107) stretches the site by about 5 to 60%.

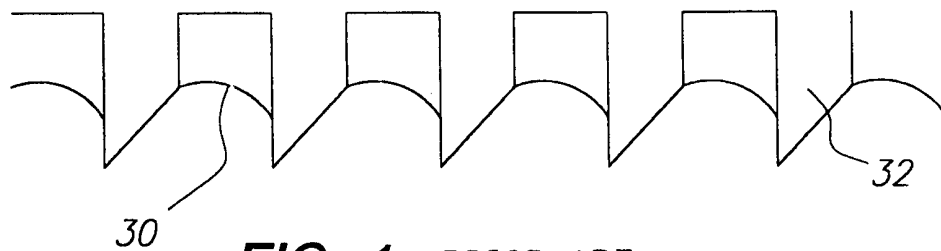


FIG. 1 PRIOR ART

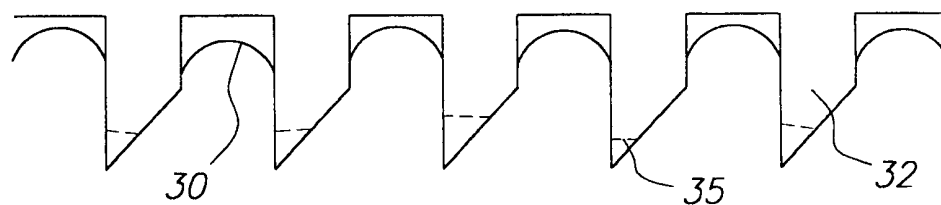


FIG. 2 PRIOR ART

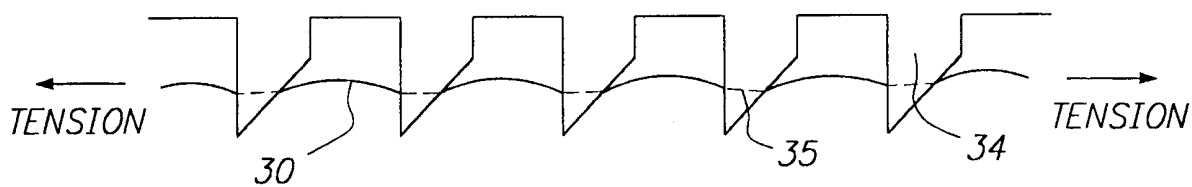


FIG. 3

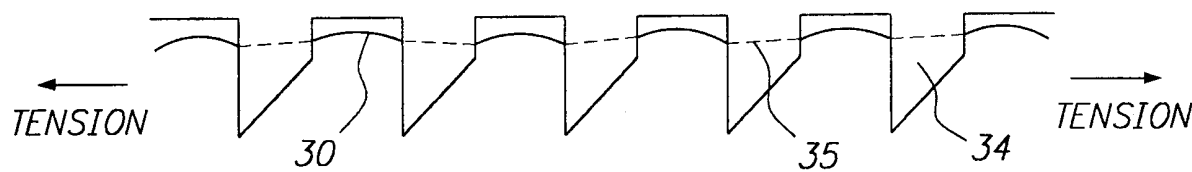


FIG. 4

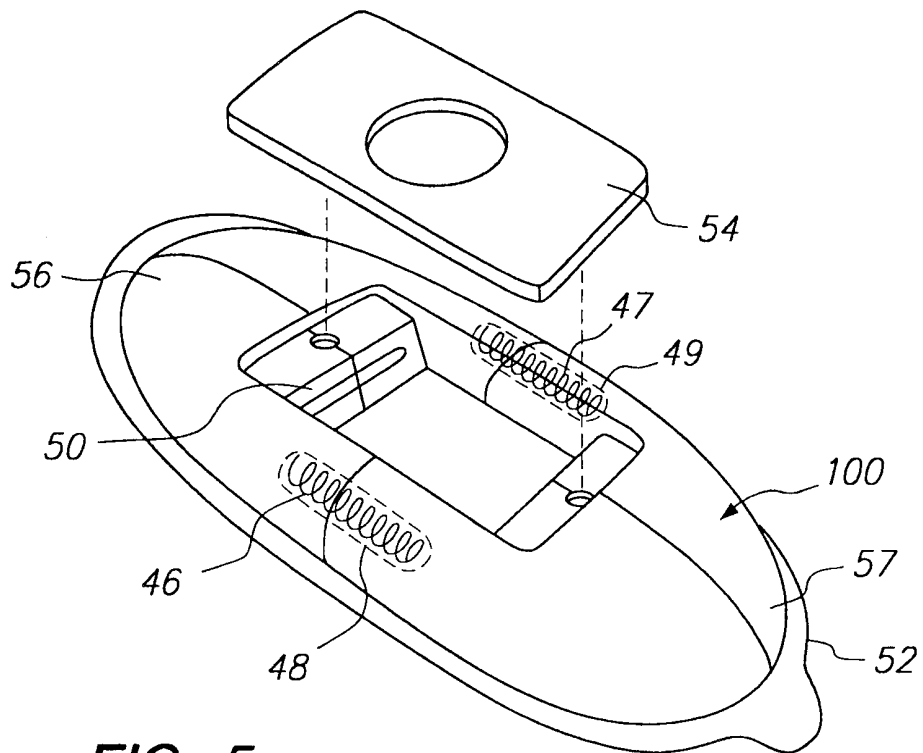


FIG. 5

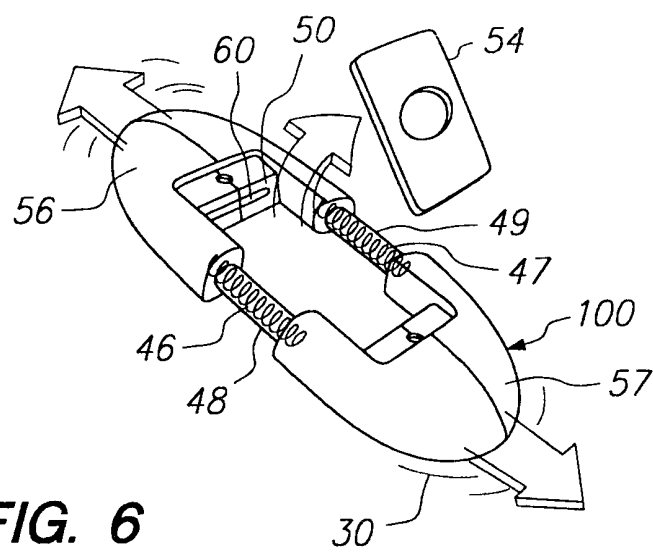


FIG. 6

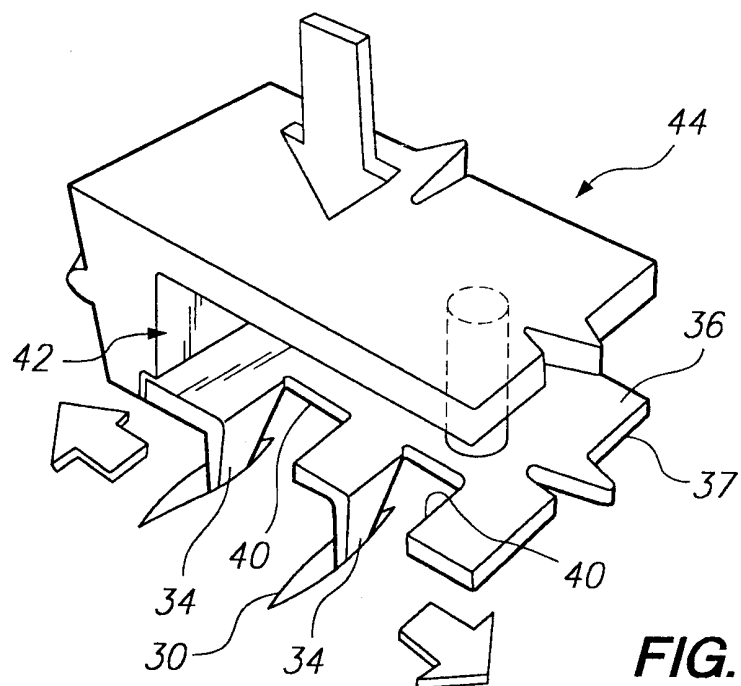
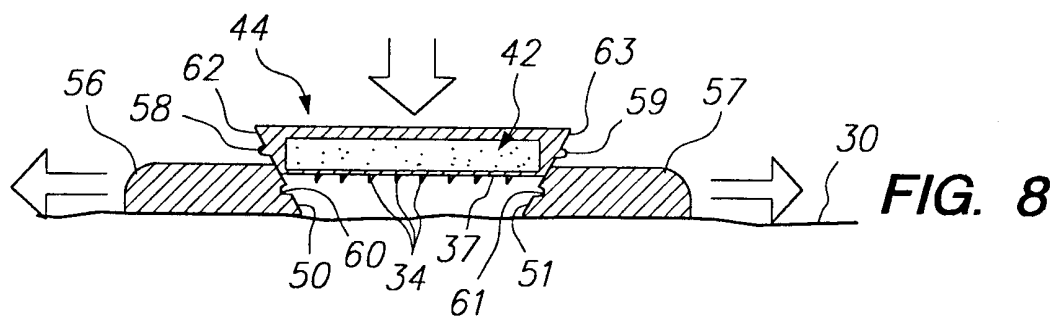
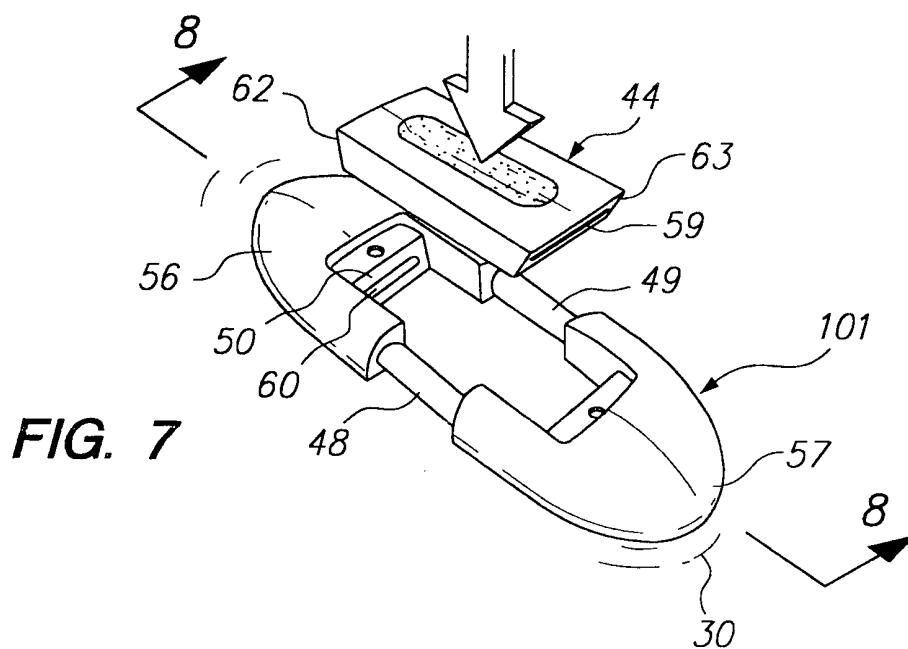


FIG. 10

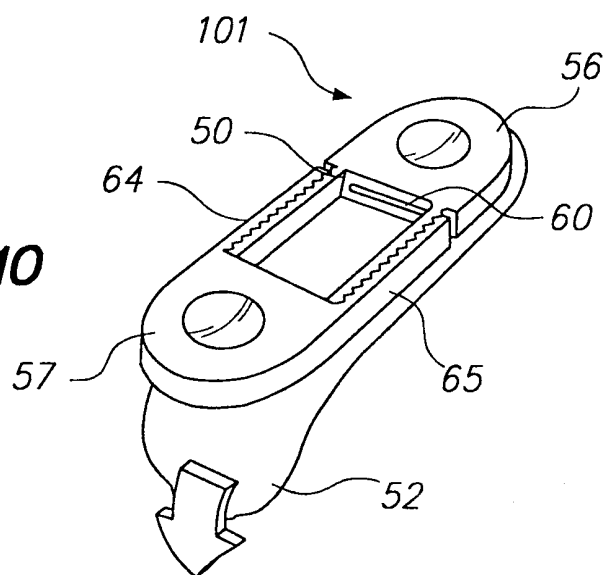


FIG. 11

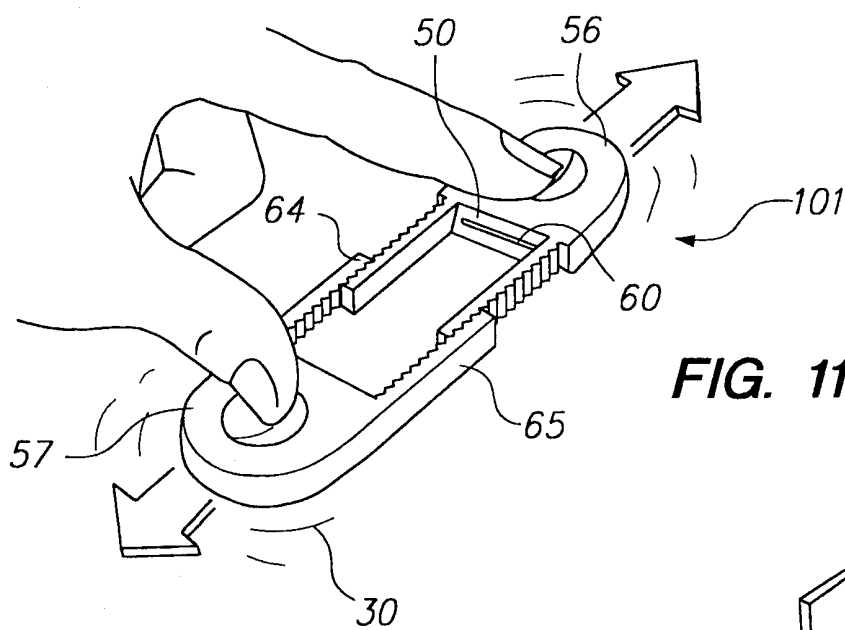
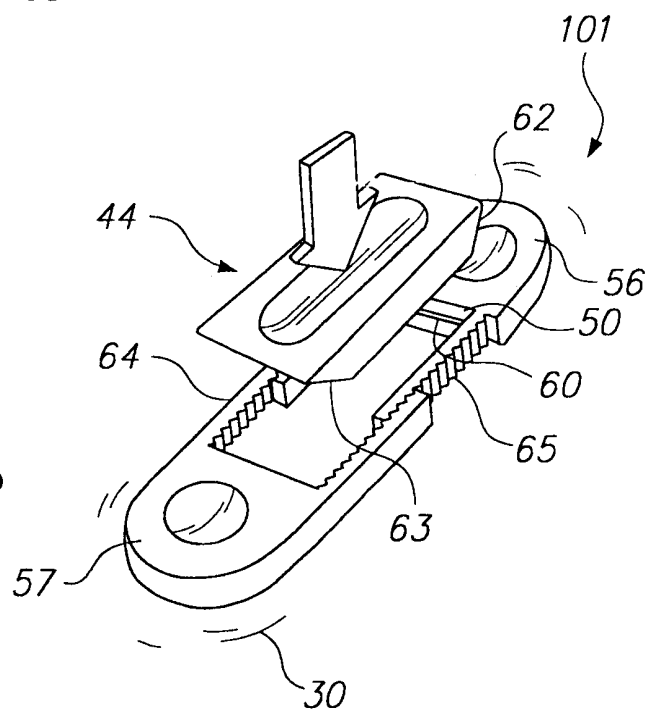


FIG. 12



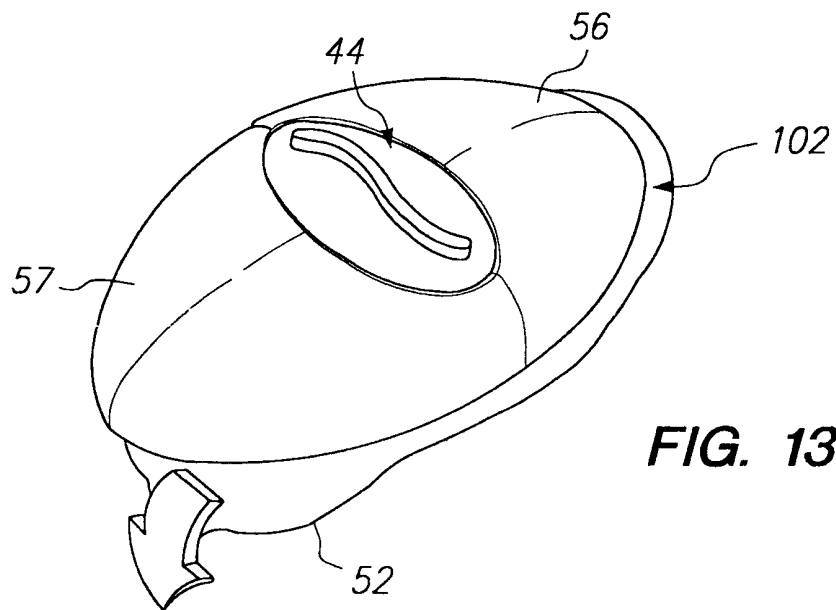


FIG. 13

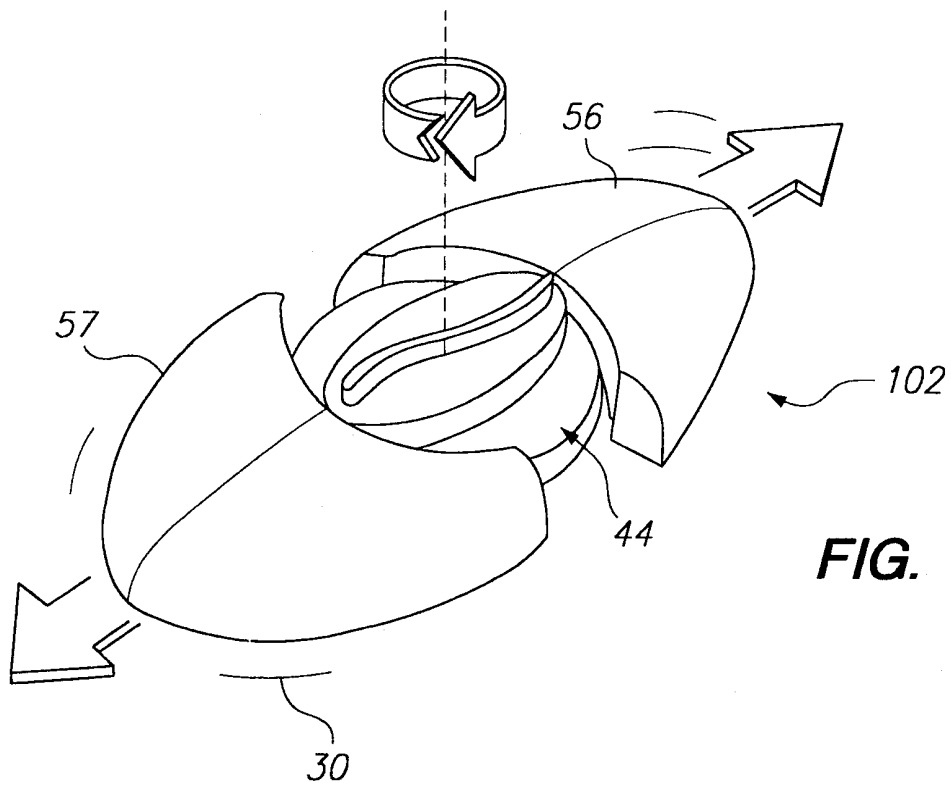


FIG. 14

FIG. 15

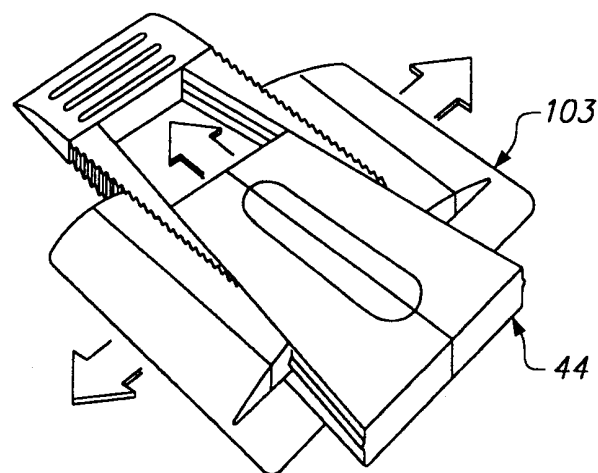
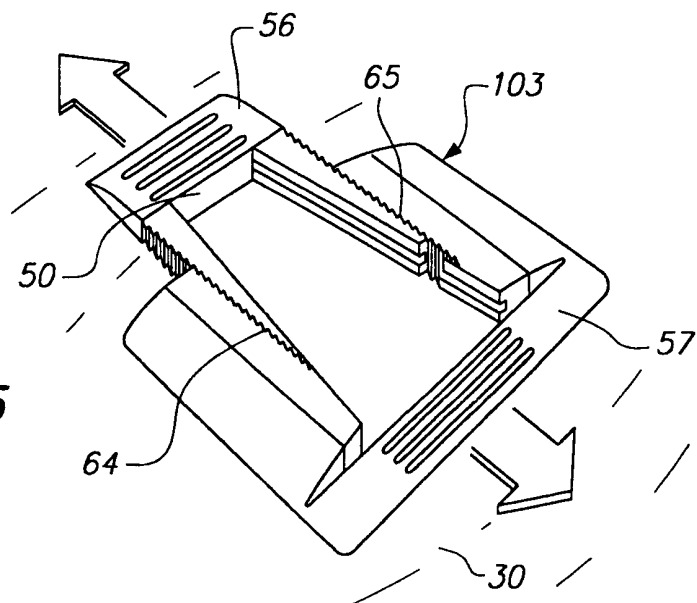


FIG. 16

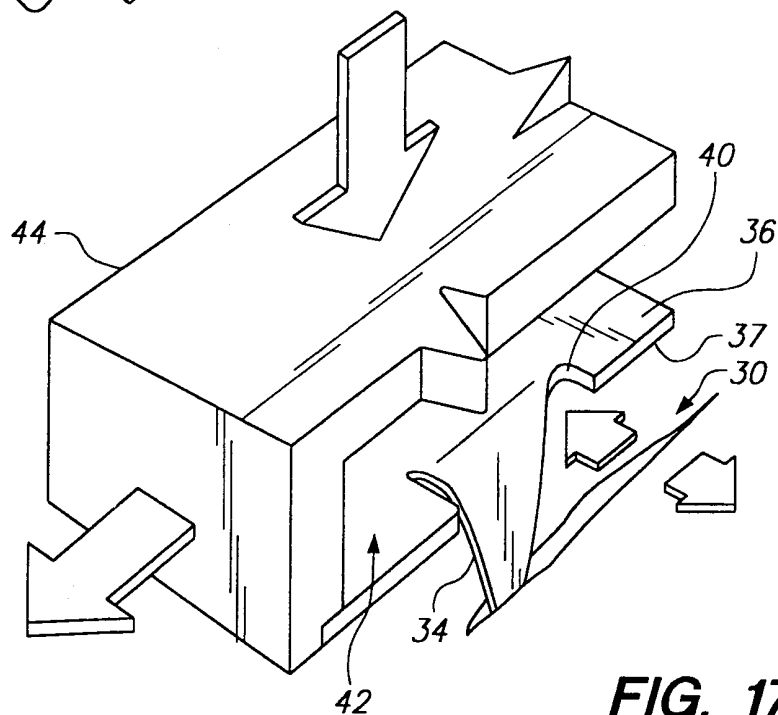
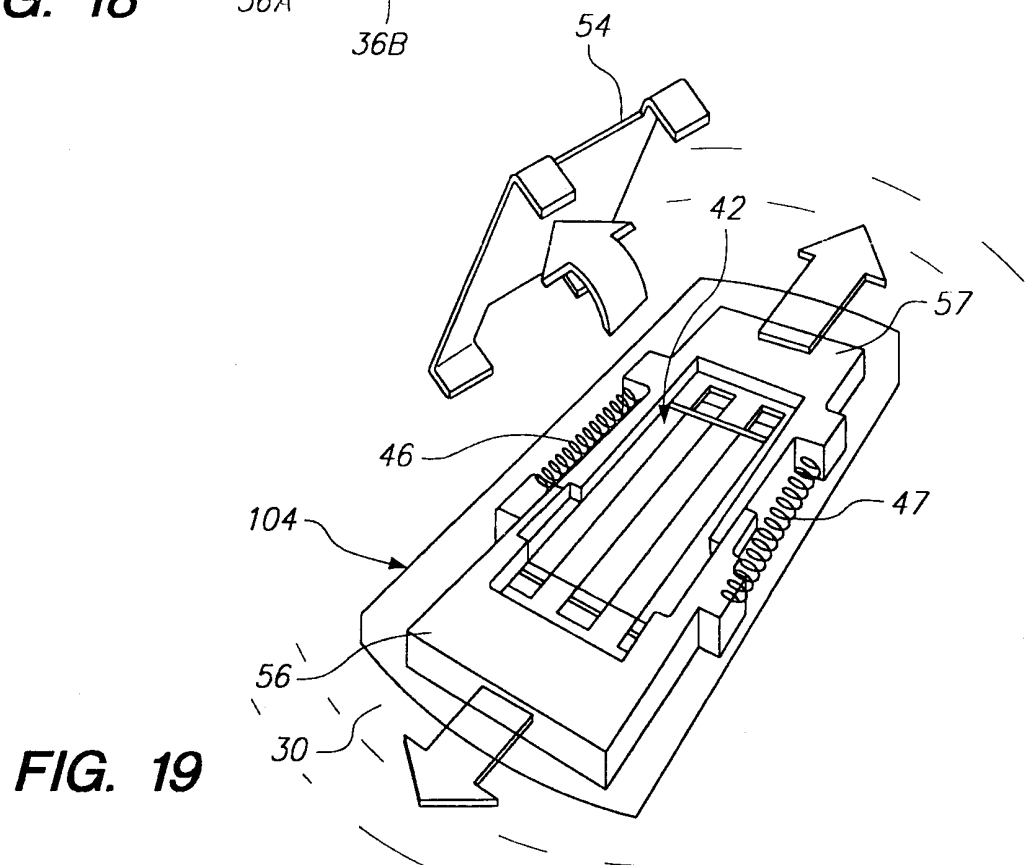
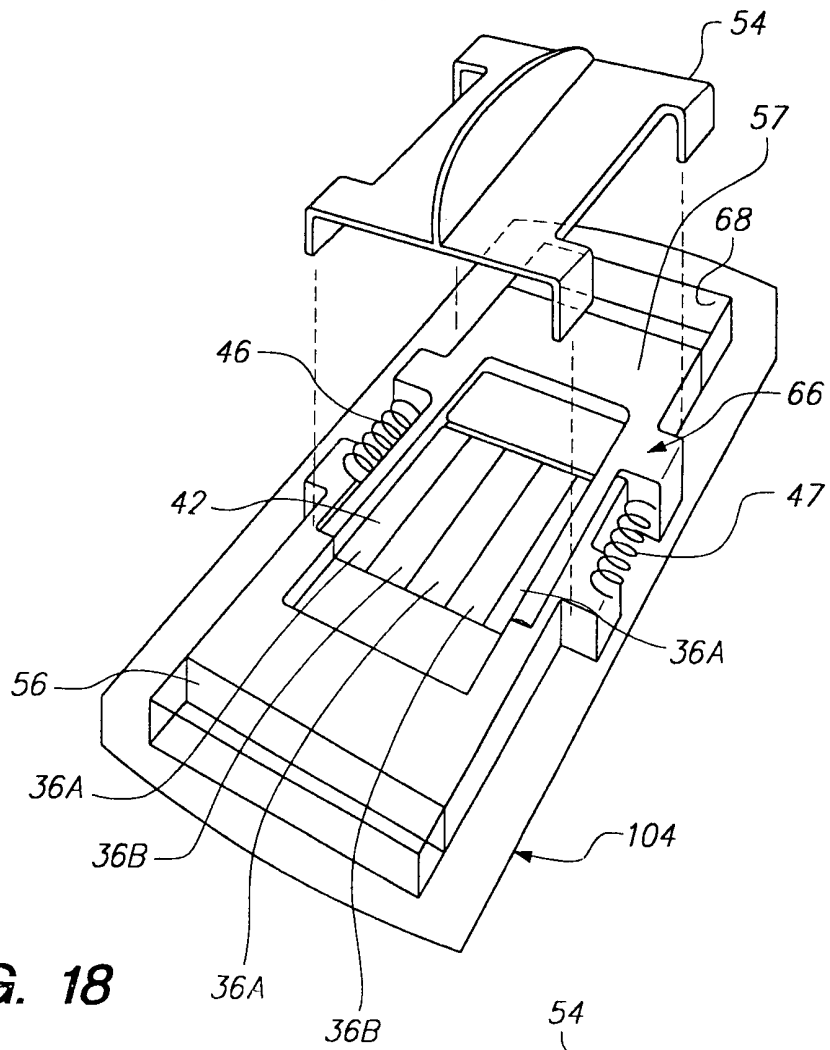
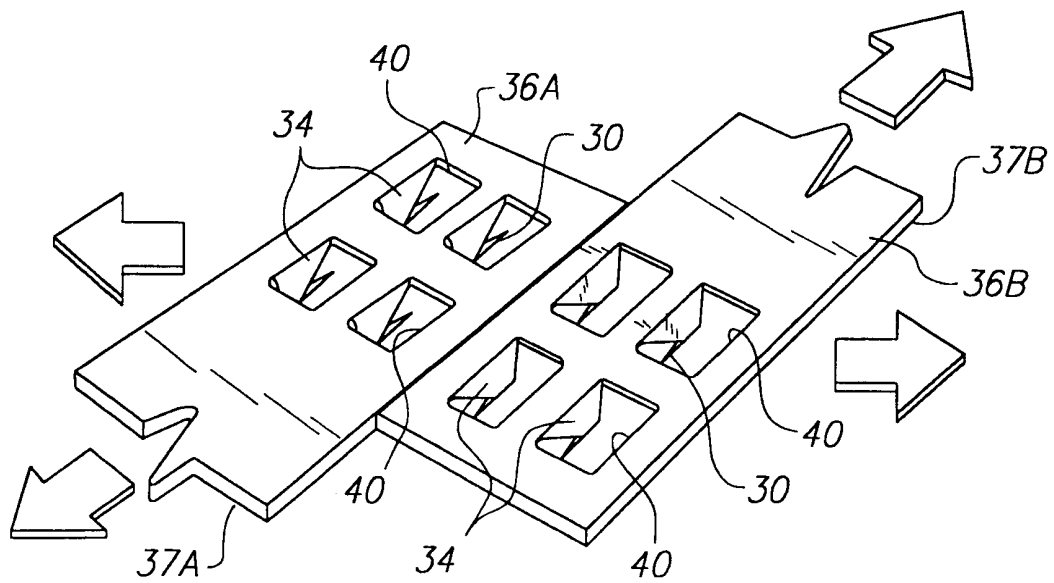
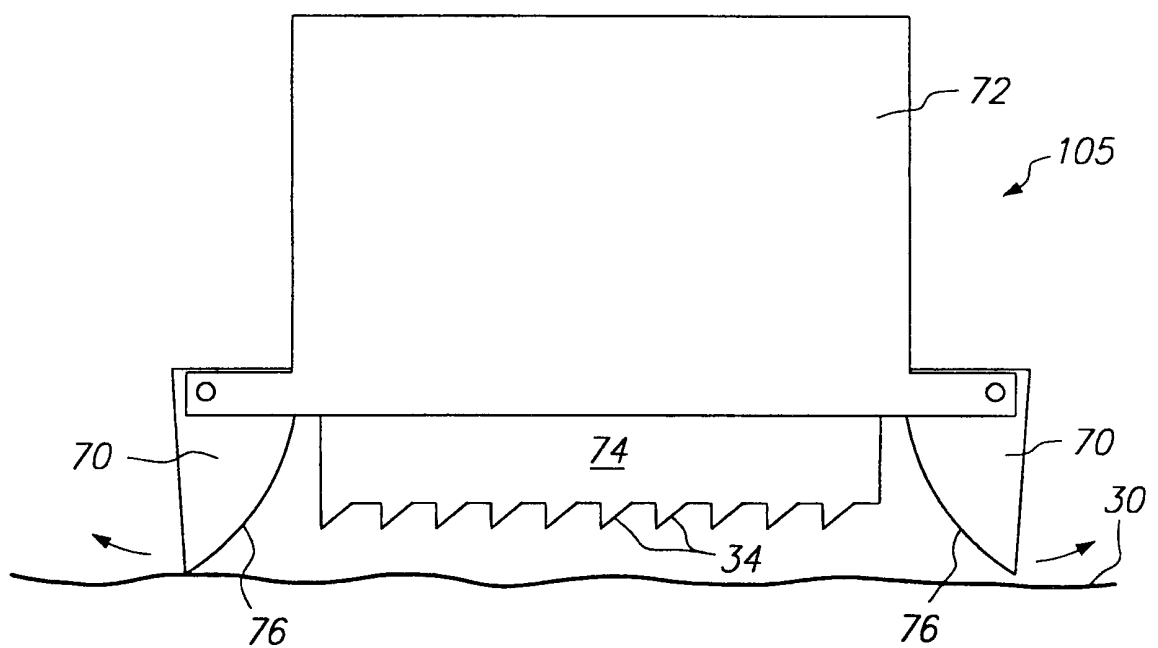
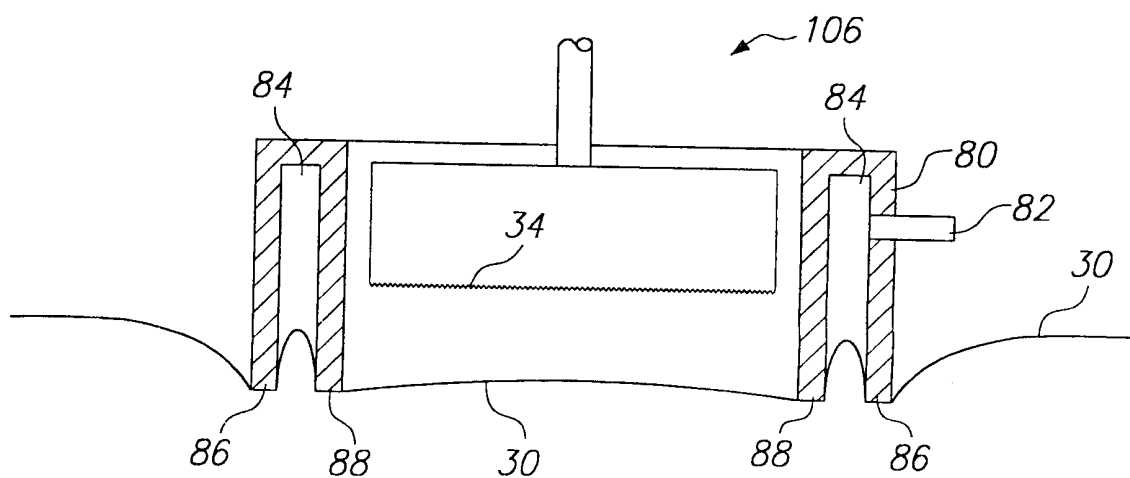
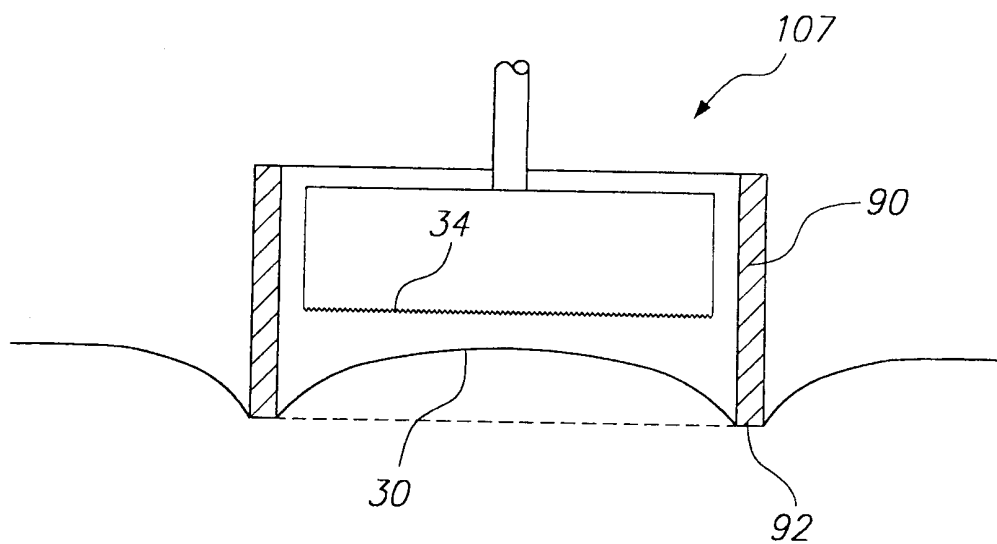


FIG. 17



**FIG. 20****FIG. 21**

**FIG. 22****FIG. 23**

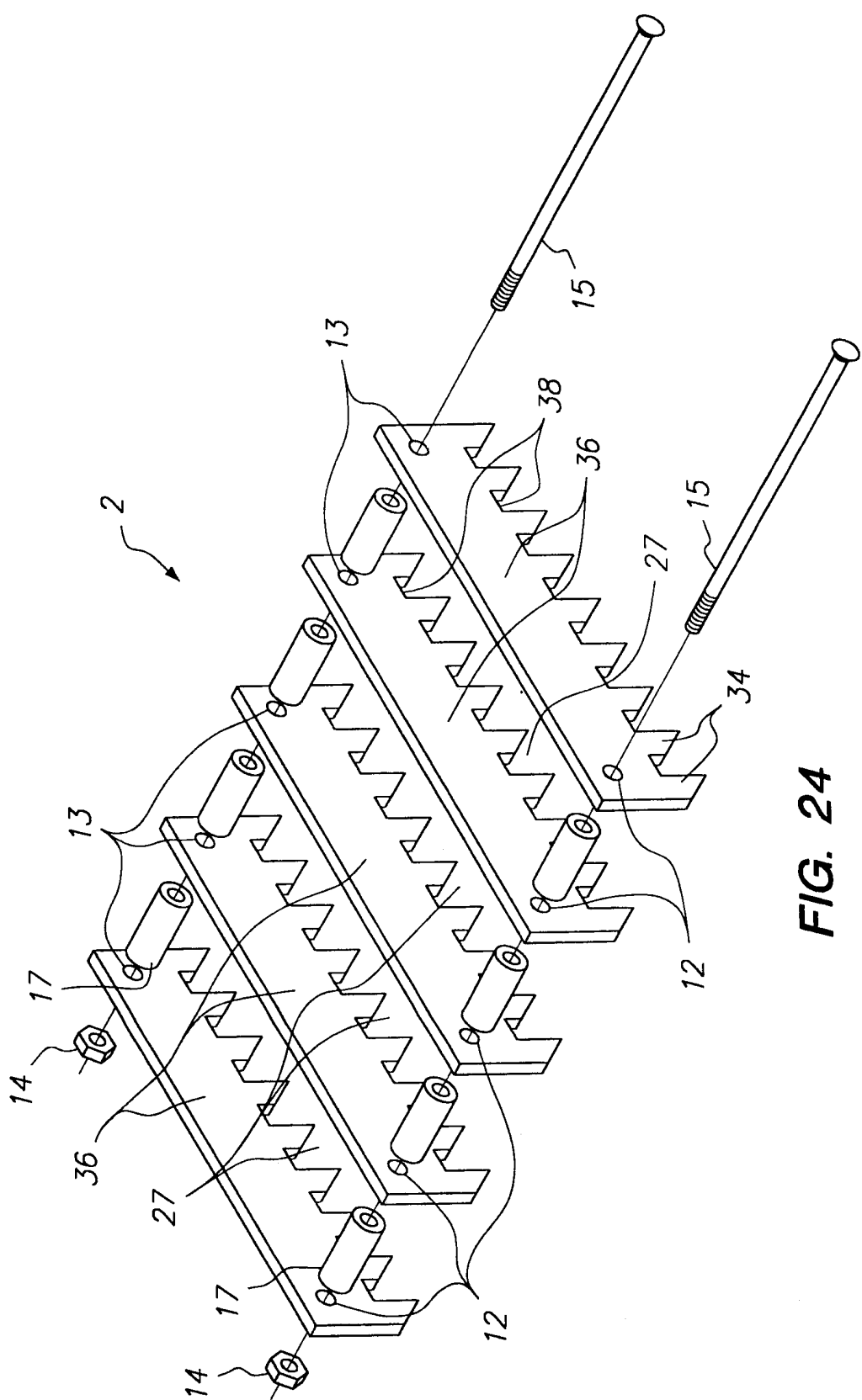
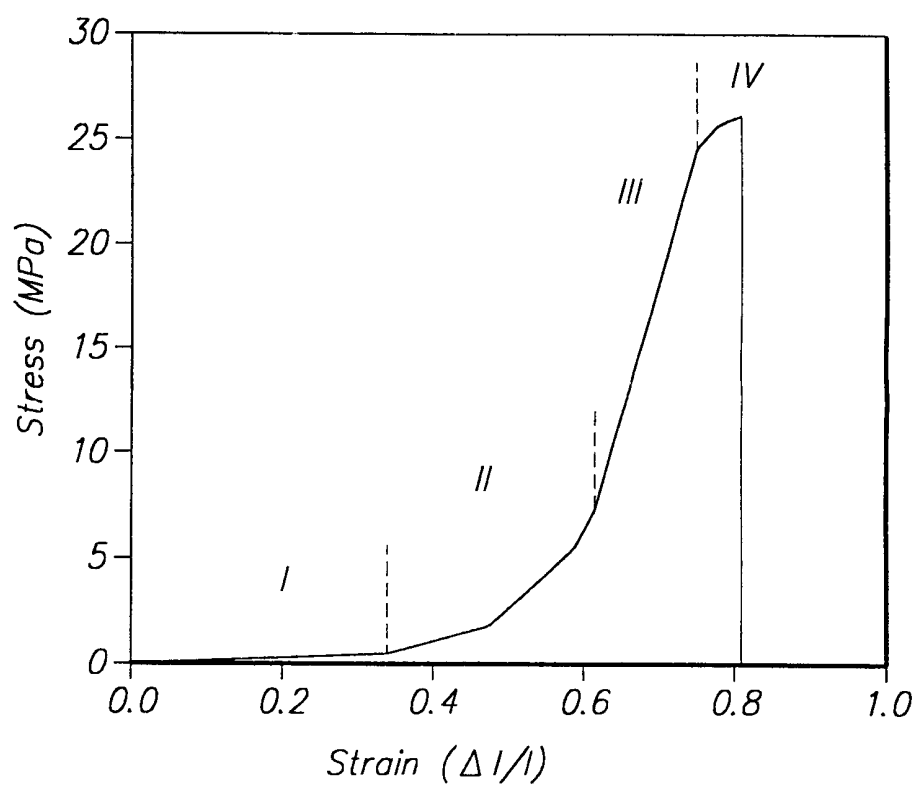
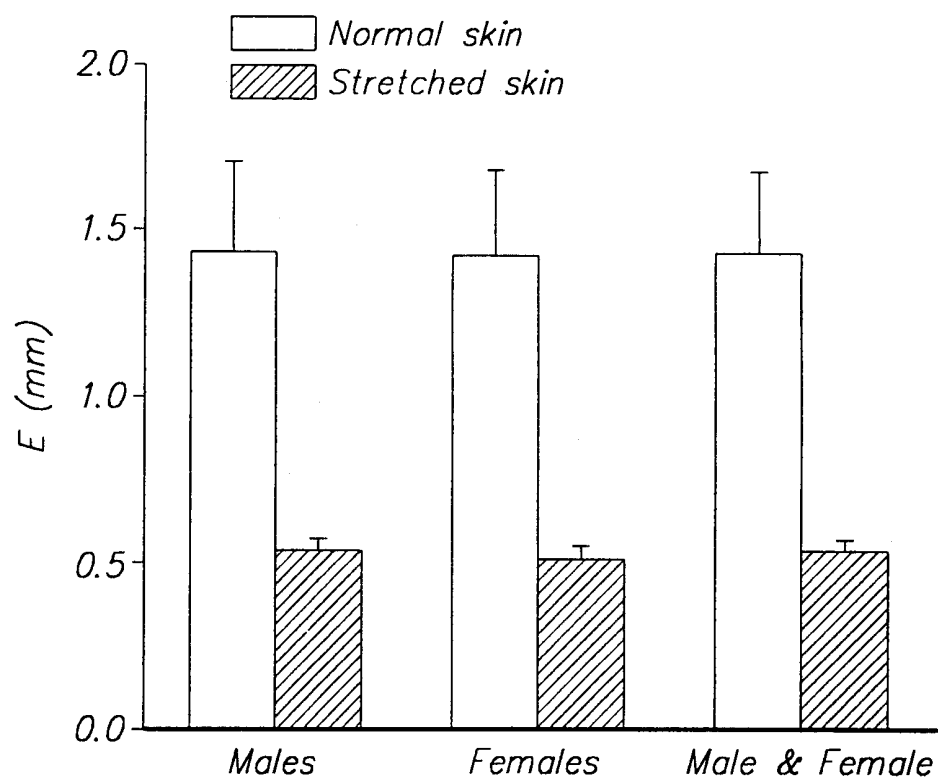
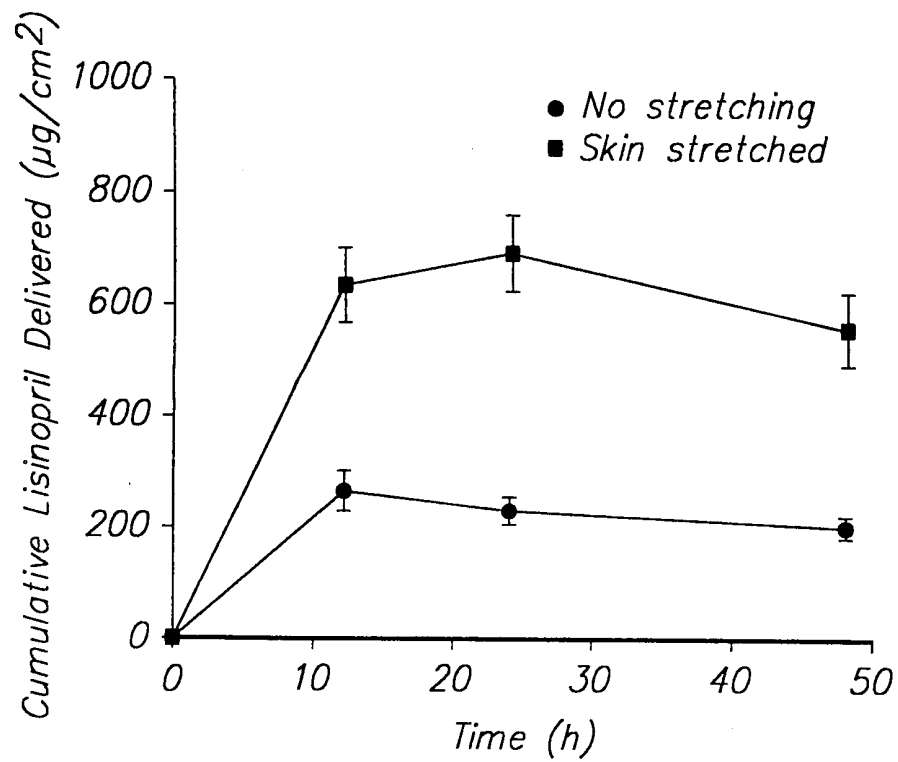
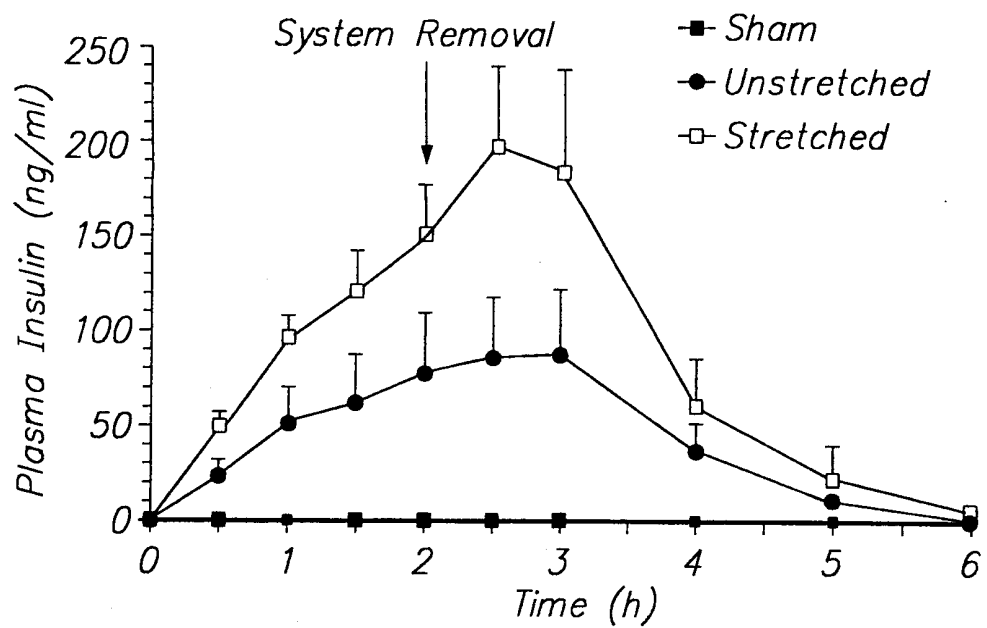


FIG. 24

**FIG. 25****FIG. 26**

**FIG. 27****FIG. 28**

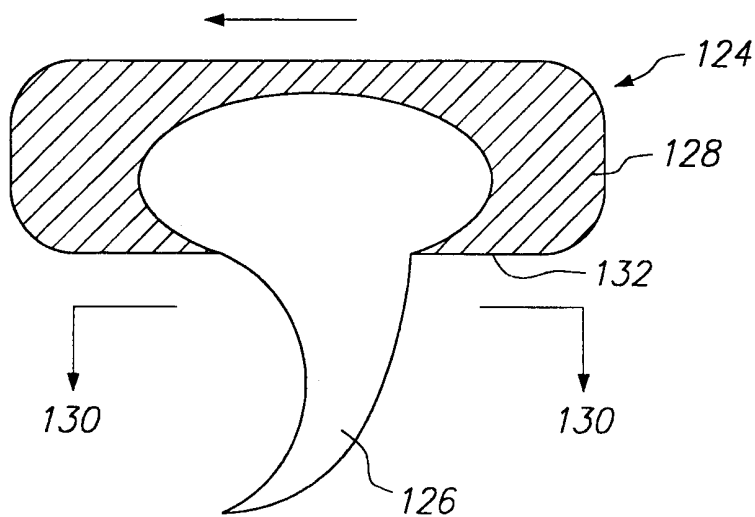


FIG. 29



FIG. 30

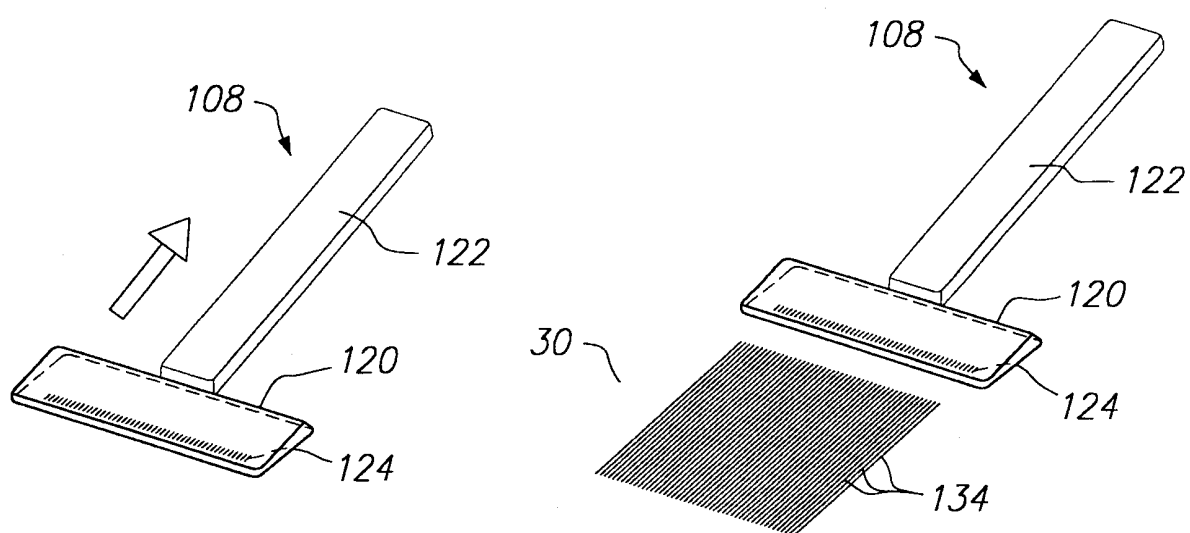


FIG. 31

FIG. 32

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 00/33318

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M37/00 A61M5/42

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)

IPC 7 A61M

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

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00 74763 A (GEORGIA TECH RES CORP) 14 December 2000 (2000-12-14) page 31, line 17 - line 29; figure 14B ---	1-16
X	AT 397 466 B (DIEM KARL) 25 April 1994 (1994-04-25) page 3, line 25 - line 39; figures 6,9 ---	1-10
A	WO 99 29365 A (ALZA CORP) 17 June 1999 (1999-06-17) page 10, line 23 - line 30; figure 10 ---	1
A	EP 0 132 940 A (RANGASWAMY AVVARI) 13 February 1985 (1985-02-13) figures 1,2 -----	1

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Patent family members are listed in annex.

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Date of the actual completion of the international search

30 March 2001

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/33318

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0074763	A	14-12-2000	NONE	
AT 397466	B	25-04-1994	AT 54392 A	15-09-1993
WO 9929365	A	17-06-1999	AU 1906899 A	28-06-1999
			AU 1997499 A	28-06-1999
			CN 1281375 T	24-01-2001
			CN 1281376 T	24-01-2001
			EP 1037686 A	27-09-2000
			EP 1037687 A	27-09-2000
			WO 9929298 A	17-06-1999
			US 6083196 A	04-07-2000
			AU 1997599 A	28-06-1999
			CN 1281377 T	24-01-2001
			EP 1035889 A	20-09-2000
			WO 9929364 A	17-06-1999
			US 6050988 A	18-04-2000
EP 0132940	A	13-02-1985	NONE	