(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
19 June 2008 (19.06.2008)

(10) International Publication Number
WO 2008/072229 A2

(51) International Patent Classification:
A61B 18/18 (2006.01)

(21) International Application Number:
PCT/IL2007/001527

(22) International Filing Date:
11 December 2007 (11.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/869,564 12 December 2006 (12.12.2006) US

(71) Applicant *(for all designated States except US):* **NANOPASS TECHNOLOGIES LTD.** [IL/IL]; 18 HaWeviim St., 31043 Haifa (IL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only):* **LEVIN, Yotam** [IL/IL]; Savion 5B, 74201 Ness Ziona (IL). **ALMAGOR, Yotam** [IL/IL]; 20 Hagdud Haïvri, 92345 Jerusalem (IL). **LAVI, Gilad** [IL/IL]; 71 Hameshoreret Rachel, 74750 Rishon Lezion (IL). **YESHURUN, Yehoshua** [IL/IL]; 17 Avshalom St., 34403 Haifa (IL). **WOLLOCH, Lior** [IL/IL]; 2 Keren Kayemet Lelsrael, 26367 Kiriyat Motzkin (IL).

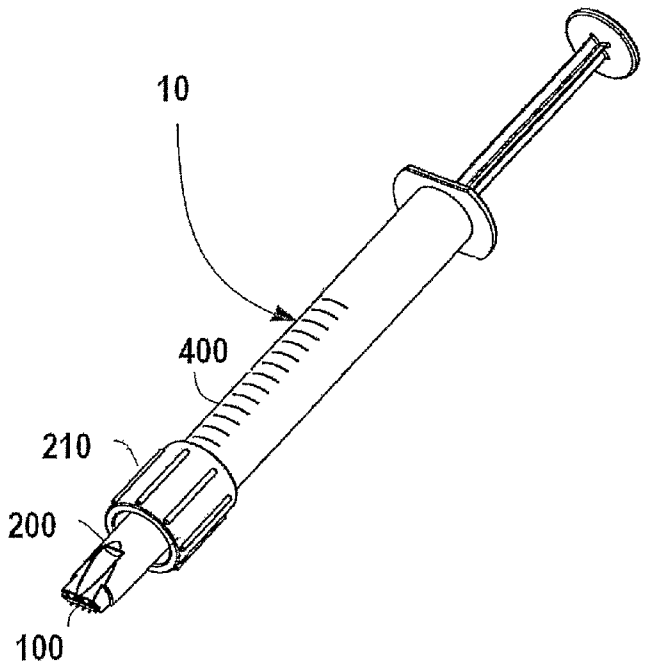
(74) Agent: **FRIEDMAN, Mark;** Moshe Aviv Tower, 54th Floor, 7 Jabotinsky Street, 52520 Ramat Gan (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(54) Title: METHODS FOR DERMAL FILLING USING MICRONEEDLES



(57) Abstract: A device and method for dermal filling using microneedles is disclosed. A microneedle device including at least two hollow microneedles arranged in at least one row, the row defining a treatment vector of the device, is used to intradermally inject a dermal filler composition into the skin of a subject along a pre-defined line in the skin where dermal filling, cosmetic repair or augmentation of tissue is desired. The device and method reduces or eliminates pain, and provides a safer, more effective administration method. The method also enables reduction in the required number of treatments (and re-treatments) due to an improved stability of the filler in these shallower depths within the skin; smoother contours due to a more even distribution of the filler within the skin; easier application for curved wrinkle lines (as opposed to hypodermic needles that are long and straight); and filling of very fine lines and wrinkles which are not accessible with regular needles.

WO 2008/072229 A2

METHODS FOR DERMAL FILLING USING MICRONEEDLES

This application claims the benefit of U.S. Provisional Application No. 60/869,564 filed on December 12, 2006, which is hereby incorporated by reference in its entirety.

FIELD AND BACKGROUND OF THE INVENTION

The invention relates generally to a device and methods for delivery of dermal filler compositions into the skin of a subject using a microneedle device. More particularly, the invention relates to a system and methods of deploying microneedles along a pre-defined line or wrinkle and injecting a quantity of dermal filler composition through the microneedles to a specific depth.

It is often desired to improve skin contour anomalies and deficiencies. A variety of different materials have been used to repair or augment skin deficiencies or to contour abnormalities caused by facial defects, trauma, aging, environmental exposure to the sun and other elements, disease such as acne and cancer, and surgery. These fillers are typically injected subcutaneously in a manner that enables filling and thus smoothing out skin contour irregularities such as wrinkles and scars, although some are injected into the dermis.

The skin is composed of the outer layer of the epidermis and the underlying dermis. Below these layers lies the hypodermis, also commonly referred to as subcutaneous tissue. The outermost epidermis is made up of stratified squamous epithelium with an underlying basement membrane. It contains no blood vessels, and is nourished by diffusion from the dermis. This layer of skin is responsible for keeping water in the body and keeping harmful chemicals and pathogens out.

The dermis lies below the epidermis and contains a number of structures including blood vessels, nerves, hair follicles, smooth muscle, glands and lymphatic tissue. The dermis (or corium) is typically 0.6-3.0 mm thick and is the major component of human skin. It is composed of a network of connective tissue, predominantly collagen fibrils providing

support and elastic tissue providing flexibility. The main cell types are fibroblasts, adipocytes (fat storage) and macrophages. The hypodermis lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as to supply it with blood vessels and nerves. It is made up of loose connective tissue and elastin. The hypodermis contains 50% of body fat, which serves as padding and insulation for the body.

Facial aging occurs as the result of several factors: inherent changes within the skin, effects of gravity, facial muscles acting on the skin (dynamic lines), soft tissue loss or shift, bone loss and loss of tissue elasticity. The skin ages when the epidermis begins to thin, causing the junction with the dermis to flatten. Collagen decreases as a person ages and the bundles of collagen, which gives the skin turgor, become looser and lose strength. When the skin loses elasticity, it is less able to resist stretching. Coupled with gravity, muscle pull, and tissue changes, the skin begins to wrinkle. Water loss and breakdown of bonds between cells also reduces the barrier function of the skin, which can cause the skin's pore size to increase.

As a person ages, the face loses volume, soft tissue, and fat. The appearance of jowls and folds are usually caused by the drooping of facial tissues and the folding of areas where the muscles below are attached to the skin. As part of the reduction in soft tissue, the face gets more hollowed.

More specifically, in various facial areas, such as the forehead, eyes, nose, mid-face and lower face, changes relating to aging have been well documented. In the forehead area, the forehead and brow droop over time, which lowers the eyebrows and causes the upper eyelid skin to bunch. Forehead lines appear when one tries to hold the brows and eyelids up to counteract these changes. It is well known that the eyes are often the first facial feature to show signs of aging. Skin changes around the eyes occur earlier than in the rest of the face since the skin is thinner around the eyes. The skin here contains fewer glands and is subjected to constant blinking, squinting, rubbing, and pulling. The mid-face ages when the cheeks begin to droop, causing nasolabial folds. Nasolabial folds are the lines that run from the sides of the nose to the corners of the mouth. These folds have been treated with facial fillers. In the nose area, as a person ages, the nose elongates. Common causes of elongation

are thinning of the soft tissue and loss of elasticity, which causes "drooping of the tip" and unmasking of the bone, creating a new hump. In the lower face area, as the face ages, facial tissues descend. This results in the so-called "laugh lines". Folds and lines in this area have been treated with facial fillers. Further down on the face, the corners of the mouth may droop and descent of the jowls can create folds often-referred to as "marionette" lines. Furthermore, jowls form when the cheeks sag around a fixed point along the jaw where the facial muscles attach to the jawbone. The facial muscles continue down into the neck as a sheet called the platysma muscle. This muscle often gaps in the center of the neck, creating two bands. Wrinkles (rhytids) related to aging are also apparent in other areas of the body, including the Decolletage region.

Further, there are situations in which loss of tissue can leave an indentation in the skin. For example surgical removal of a dermal cyst, lipoatrophy or solid tumor can result in loss of tissue volume. In other cases, injuries, such as gunshot wounds, knife wounds, or other excavating injures may leave an indentation in the skin. Regardless of the cause, it can be desirable to provide a dermal filler that can increase the volume of tissue to provide a smoother or more even appearance.

Injections of dermal fillers are meant to correct congenital or acquired folds, wrinkles or depressions of skin, mostly (but not only) of facial skin. While tens and possibly hundreds of various fillers are available, they are all administered with conventional steel needles. Fillers intended for correction of relatively superficial or fine skin imperfections are usually injected intradermally (into the skin). Several injection techniques are commonly employed in order to perform intradermal injections with standard needles, but none of these allows optimal control over the precise depth and volume of delivery and all require extremely fine coordination from the person performing the injections. Also, due to the shear width of even the finest conventional needle, it is impractical to inject very small amounts of dermal fillers, or inject fillers to very shallow depths, partially due to back-leakage of the substance through the channel created by the needle. Furthermore, imperfections in the injection technique or accidental movements while injecting may result in injection of the filler into subcutaneous or muscular tissue or

even into blood vessels. This may result in reduced effect of the treatment, the formation of unwanted permanent or semi-permanent subcutaneous nodules and other complications and adverse reactions including necrosis.

Dermal fillers are used for a variety of indications, including, among others:

- Wrinkle filling for aesthetic medicine
- Tissue augmentation for aesthetic medicine (e.g. lip augmentation)
- Tissue augmentation and filling for aesthetic-reconstructive medicine (e.g. following trauma, diseases or congenital malformations that cause damage or depressions of the skin, subcutaneous tissue or bones).

While most dermal filling is currently indicated for the face, additional skin sites may benefit from dermal filling, tissue augmentation and the like. This includes, as an example only, dermal filling of wrinkles of the arms, neck, and the Decolletage regions. internal tissue augmentation of sphincters and like, and body organs. Many compositions used for dermal filling are also used for soft tissue augmentation other than dermal filling, including soft tissue filling for the treatment of gastro-esophageal reflux disease (Heartburn) and urinary stress incontinence, and intra-articular injections (injections into joints) for treatment of various conditions that destroy joint structures.

Various injectable dermal filler compositions have been used for restoring tissue loss. Since the 1980s, injectable collagen has been used as a soft-tissue filler to fill wrinkles, lines and scars on the face. Collagen is a naturally occurring protein that supports various parts of the body including skin, tendons and ligaments. Fat injections have been used for years to add volume, fill wrinkles and lines and enhance the lips. Fat injections involve taking fat from one part of the patient's body (abdomen, thighs or buttocks) and re¬ injecting it beneath the facial skin.

One of most commonly used cosmetic dermal fillers is Hyaluronic acid ("HA"), which adds volume to minimize wrinkles and lines. Hyaluronic acid is a linear polysaccharide that exists naturally in all living organisms and is a universal component of the extra-cellular spaces of body tissues. The identical structure of hyaluronic acid in all species and tissues makes this polysaccharide an ideal substance for use as a bio-material in

health and medicine. Hyaluronic acid, present in many places in the human body, gives volume to the skin, shape to the eyes and elasticity to the joints. The highest concentrations are found in connective tissues, and most hyaluronic acid (about 56%) is found in the skin.

Various forms of hyaluronic acid are provided commercially by a number of manufacturers. The most commonly used hyaluronic acid is the non-animal stabilized hyaluronic acid (NASHA) in a clear gel form, produced by bacterial fermentation from streptococci bacteria. Different from animal derived hyaluronic acid, the non-animal derived hyaluronic acid is free from animal proteins. This limits the risk of animal based disease transmissions or development of allergic reactions to animal proteins.

Techniques and devices have been developed to improve the ability to administer dermal filler injections. For example, U.S. Patent No. 4,393,870 to Wagner discloses a suction injector that comprises a suction cup and an exchangeable cannula inserted into the cup for injecting a liquid medicine under human skin by the action of a piston movable in a cylinder. The suction cup is formed with an outer chamber that accumulates negative pressure and an inner chamber closed with a membrane that is placed over the skin to be treated. The device enables stretching of the wrinkle and controlled injection beneath it.

U.S. Patent No. 5,211,644 to VanBeek et al. discloses a process and apparatus for an autologous dermal graft transfer for placement of dermal grafts during plastic surgery, typically for the filling of wrinkles or scars.

U.S. Patent No. 6,200,291 to Di Pietro discloses an adapter for controlling the penetration depth of a needle, for application to an injection syringe. The adapter also provides lateral skin extension.

U.S. Patent No. 6,766,202 to Underwood et al. discloses systems and methods for intradermal collagen stimulation by selectively applying energy to the dermis tissue to generate the growth of new collagen in this tissue.

U.S. Patent No. 6,730,318 to Quan et al. discloses transdermal delivery devices containing polydiorganosiloxane polymers to regulate adhesive properties.

U.S. Patent No. 6,616,642 to Jensen et al. discloses a wrinkle-resistant dressing for use with ostomy devices, the dressing having wrinkle resistant edges allowing the dressing to be used in areas of the body having high mobility.

U.S. Patent No. 6,565,532 to Yuzhakov et al. discloses matrices (non linear) of symmetrical microneedles in perpendicular approach that are blunt and thus piercing the skin for delivering tattoo markings, cosmetic compounds or skin structure modifiers.

U.S. Patent No. 6,228,078 to Eggers et al. and U.S. Patent No. 6,210,402 to Olsen et al. disclose methods for electrosurgical dermatological treatment by applying high frequency (RP) electrical energy to one or more electrode terminals adjacent an external body surface, such as the outer surface of the skin, to remove and/or modify the structure of tissue structures within the skin

U.S. Patent No. 6,001,367 to Bazin et al. discloses an anti-wrinkle composition containing a dispersion of a polymer system and use of this system as a tensioning agent in a cosmetic or dermatological composition.

U.S. Patent No. 5,885,596 to Parab discloses methods and compositions for improving and reducing fine lines and/or wrinkles.

U.S. Patent No. 5,713,375 to McAllister discloses a skin-tightening device and method using an abrading tool to treat the wrinkle site (facial, back of palm) to allow better absorption of cream.

U.S. Patent Nos. 5,643,961; 5,643,963; 5,648,388; 5,648,391; 5,650,436; 5,650,437; 5,650,440; 5,652,267; 5,654,336; 5,654,340; 5,656,665; 5,656,666; 5,677,339; 5,670,542; 5,670,543; 5,674,899; 5,677,339; 5,677,340; and 6,574,903 disclose methods of using various materials including malic acid, isocitric acid, methyllactic acid, galacturonic acid or galacturonolactone, galactonic acid or galactonolactone, benzilic acid, citramalic acid, saccharic acid or saccharolactone, glycolic acid, gulonic acid or gulonolactone, quinic acid or quinolactone, ribonic acid or ribonolactone, glucuronic acid or glucronolactone, pantoic acid or pantolactone, lactic acid, citric acid, mandelic acid, and glyconic acid or gluconolactone for treating wrinkles.

U.S. Patent No. 5,614,215 to Rïbier et al. discloses cosmetic compositions for the simultaneous treatment of the surface and deep layers of the skin, compr sing. dispersions of lipid vesicles.

U.S. Patent Publication No. 20030093032 to Py et al. discloses an intradermal delivery device and method comprising a pre-filled injecting tool that enables perpendicular penetration for a preset depth for multiple needle insertion using the same pre-filled syringe.

U.S. Patent Publication No. 20030199822 to Alchas et al. discloses an intradermal needle with pre-set penetration depth control.

U.S. Patent Publication No. 20030208167 to Prausnitz discloses a microneedle drug delivery device.

U.S. Patent Publication No. 20040225276 to Burgess discloses methods of administering a material (including polylactic acid, hyaluronic acid, hydrogel, and/or collagen or other suitable materials) to a patient for dermal enhancement and/or as soft tissue fillers and to methods of molding the material after administration to a patient to achieve a desired orientation of the material in the patient.

U.S. Patent Publication No. 20040147901 to Py et al. discloses an intradermal delivery device and method for intradermal delivery using a vacuum-assisted tool that stretches the skin and enables inclined penetration of a regular needle attached to a pre-filled syringe. The device is used for cosmetic intradermal applications such as dermal filling.

U.S. Patent Publication No. 20060035861 to Berg et al. discloses compositions of polyacids and polyethers and methods for their use as dermal fillers.

U.S. Patent Publication No. 20060073178 to Giampapa discloses a method and composition which contains a growth factor and hyaluronic acid as a carrier for restoration of age related tissue loss in the face or selected areas of the body to stimulate collagen, elastin, or fat cell production.

U.S. Patent Publication No. 20060166928 to Moon et al. discloses a hyaluronic acid derivative gel, and a method for preparing it for use as a material for wrinkle treatment.

Dermal fillers are injected intradermally to restore age-related or other tissue loss in the face or selected areas of the body. Typically, conventional needles are used for injection into the epidermis and upper layer of the dermis. Below the dermis layer is subcutaneous tissue (also sometimes referred to as the hypodermis layer) and muscle tissue, in that order. Healthcare professionals require extensive training to deliver the fillers into the desired space in the dermis. There is considerable variation in the skin thickness both between individuals and within the same individual at different sites of the body. Generally, the outer skin layer, or the epidermis, has a thickness between 70-120 microns in most areas of the body, and the dermis, the inner and thicker layer of the skin, has a thickness between 0.6-3.0 mm. A needle cannula that penetrates the skin deeper than about 3.0 mm may potentially pass through the dermis layer of the skin and deliver the filler into the subcutaneous region, which can reduce the effectiveness of the injection, and possibly deliver the substance in a way not approved for delivery. Alternatively, the needle cannula may penetrate the skin at too shallow a depth to deliver the substance and result in what is commonly known as a "wet injection" because of reflux of the substance from the injection site.

Using a standard needle (i.e., one typically used for subcutaneous or intramuscular injections) to deliver an intradermal injection requires the healthcare professional to perform a complicated and at times difficult technique. The success of the injection depends upon the skill and experience of the healthcare professional. The needle has to be inserted into the dermis and then threaded for up to 10 to 12mm in the dermis along a fold or line to be filled. Incorrect placement of the needle cannula could lead to a failed filler injection. Placement of the needle tip deeper than about 3.0 mm potentially makes the injection into the subcutaneous region. The needle cannula may also penetrate the skin at too shallow a depth to deliver the substance in a way invisible from the outside. Intradermal injections performed by using the technique described above cause significant pain to the patient because of the angle at which the needle cannula is inserted into the skin.

There is a need, therefore, for improved devices and methods of administering dermal filling compositions in order to achieve a desired and consistent depth and orientation of

administered material, to improve overall safety of the injection device (restricting deeper tissue injection), to improve the ability to inject into various places in a fold, concurrently thereby improving usability for the doctor, and to reduce the dose required for injection (since shallow delivery requires less material to fill the gaps or folds).

Microneedle Devices

The term "microneedle" is used to refer to all shapes, materials, and fabrication methods used to form microneedles. Of particular relevance as background to the present invention are U.S. Patent Nos. 6,533,949; 6,558,361; 6,924,087, U.S. Patent Publication Nos. 2005/0029223; 2005/0165358; 2005/0209566, and U.S. Serial Nos. 10/362835, 10/506904, 11/134411 11/549,982 and 11/946,889, all commonly assigned with the present invention, which are hereby incorporated by reference in their entirety, among various pyramidal protrusions where the hole does not cross the tip or the cutting blade. These documents disclose microneedle structures, devices and methods for delivering fluid into a flexible biological barrier employing a microneedle structure wherein a final position of microneedles inserted into the biological barrier is generally sideways projecting from the delivery configuration instead of the conventional downwards projecting arrangement. This technique is referred to herein for convenience as "side insertion". A preferred microneedle design may be a structure similar to those disclosed in US Patent No. 6,533,949, which needles have a generally triangular cross-sectional shape including one or more upright wall intersecting with a sloped surface through which a fluid flow channel passes.

However, there is a lack of suitable devices and methods for delivery of dermal fillers of various kinds to the epidermal and dermal skin layers. Standard needles commonly used to inject dermal fillers are too large to accurately target these tissue layers when inserted into the skin and the delivery technique is difficult to perform, unreliable and painful to the subject. Thus, there is a need for devices and methods that will improve the efficacy, reliability and ease of delivery of dermal fillers to shallow layers of the skin, reduce adverse reactions (including inflammatory reactions), increase the effect duration, reduce the associated risks and better the overall effect of dermal filler injections,

substantially without pain to the patient. Furthermore, there is a need for devices and methods for dermal filling that offer the possibility to correct curved lines and very fine lines and wrinkles that are not correctable with currently available delivery methods.

SUMMARY OF THE INVENTION

In contrast to the conventional methods discussed above, the present invention is directed to an improved, safer, easier and more efficient device and methods for intradermally delivering a dermal filler composition into the dermal tissue of the skin of a subject at a pre-defined line in the skin where dermal filling, cosmetic repair or augmentation of tissue is desired, using a microneedle device. The dermal filler composition may comprise therapeutic dermal filler materials, cosmetic dermal filler materials and combinations thereof. Compared with the standard method of dermal filling, the method of the invention offers significant biological benefits for the patients in terms of safety (as the device cannot penetrate deeper than the dermis) and requires only minimal expertise in intradermal injections. The method of the invention improves the efficacy of dermal filling, reduces the required effective dose, improves the ease of delivery and reduces pain. Using the present invention, delivery of dermal fillers is more superficial and the filler is deposited in shallower layers where its resorption by the body is reduced and the cosmetic effect remains for a longer period of time. It is also possible to self-administer intradermal injections by the methods of the invention.

The present invention allows the reduction or elimination of pain, a safer administration method (that reduces the risk of deeper delivery, of abrupt movement by the user that results in trauma to the deeper tissues, and of bleeding, as well as easier handling and injection technique for caregivers); dose sparing (the reduction of the dose of filler that is required for a similar filling effect, i.e., the same end result is obtained with injections of smaller volumes of fillers), reduction of inflammation (as a result of shallower delivery); increased longevity (due to reduction of elimination by bodily mechanisms and cells that typically reside in deeper layers); reduction in the required number of treatments and re-treatments due to an improved stability of the filler in these shallower depths within the skin; smoother contours due to a more even distribution of the filler within the skin; easier

application for curved lines (as opposed to hypodermic needles that are long and straight), and filling of very fine lines and wrinkles which is not practical with regular needles.

The microneedle injection device and method of the invention allows excellent control over delivery depth: since the microneedles themselves are shorter than the skin's thickness, insertion of the microneedles completely into the skin enables injection to a known depth with extreme precision. Furthermore, this allows injection to particularly shallow depths within the skin since the microneedles are very short, and can be applied in a non-perpendicular manner, allowing injections to these depths. Injections as shallow as these are very hard to perform (if at all possible) with conventional needles, certainly with such standardization of the delivery depth. Injection to these shallow depths of skin typically offers one or more of the following advantages:

1. The shallow layers of the skin contain no pain-sensing nerves, and thus injections performed with the current invention cause minimal pain or no pain at all.
2. The shallow layers of the skin also contain a very thin network of blood vessels and cells, and thus clearing of the injected material may be much slower, resulting in a longer-lasting cosmetic effect of the treatment. This allows a significant reduction in the required dose and in the number of treatments required for any given effect.
3. Use of microneedle devices also eliminates the chances for accidental injections into subcutaneous tissue, muscle or blood vessels, all of which are located deeper than the maximal penetration depth of the microneedle devices. This also poses an advantage in cases of accidental injury from contaminated needles, due to the smaller risk of infection when no disruption of blood vessels occurs.

The use of the present invention for injection of dermal fillers also possesses advantages related to other aspects of the microneedle devices:

1. The method of the invention allows multiple injections of dermal fillers to a curved line, and to extremely fine lines and wrinkles that are difficult to correct with even the smallest of standard needles.

2. The injection technique of the invention is simpler to master than current injection techniques, requires less expertise on behalf of the performer, and produces results of similar quality with a reduced dependence on the performer's expertise.

According to the teachings of the present invention there is provided a method for dermal filling, comprising the steps of (a) providing a dermal filler composition to be intradermally injected into the skin of a subject at a pre-defined line in the skin where dermal filling, cosmetic repair or augmentation of tissue is desired; (b) providing a microneedle device including at least two hollow microneedles arranged in at least one row, the row defining a treatment vector of the device; (c) orienting and inserting the device such that the microneedles pierce at least the stratum comeum of the skin of the subject at a first injection site along the pre-defined line to be treated and are anchored into the pre-defined line in the skin; and (d) injecting a quantity of the composition through the microneedles into the dermal tissue such that the composition is intradermally delivered into the skin at the pre-defined line where dermal filling is desired, thereby at least partially filling, cosmetically repairing or augmenting the tissue.

According to a further feature of the present invention, steps (c) —(d) are repeated at least one additional time at one or more injection sites along the pre-defined line until the desired dermal filling, cosmetic repair or augmentation of the tissue is achieved.

According to another feature of the present invention, the pre-defined line is selected from the group of skin contour deficiencies consisting of a wrinkle, a subcutaneous defect, a depression, a fold, a stretch mark, a curved line, a fine skin line, a fine wrinkle line, and a superficial skin imperfection.

According to a further feature of the present invention, the microneedles have a base end and a tip, with at least one hollow pathway disposed between the base end and the tip, a substrate to which the base ends of the microneedles are attached or integrated, and a reservoir in fluid communication with the base ends of the microneedles, wherein the reservoir contains the composition to be delivered.

According to a further feature of the present invention, the method further comprises before the orienting step, the step of stretching the dermal tissue of the subject at the pre-defined line.

According to a further feature of the present invention, the microneedles have a length between 50μm and 1000 μm.

According to a further feature of the present invention, the microneedles have a length between 450μm and 750 μm.

According to a further feature of the present invention, the row of microneedles includes at least three microneedles aligned along the pre-defined line.

According to a further feature of the present invention, the row of microneedles includes at least four microneedles aligned along the pre-defined line.

According to a further feature of the present invention, the method further comprises after the orienting and inserting step the step of rotating the microneedle device while pushing the device forward towards the distal side of the pre-defined line, the inserted tips of the microneedles stretching the tissue along the direction of insertion, the microneedles projecting from the microneedle device in a direction having a major component parallel to the initial plane of the pre-defined line.

According to a further feature of the present invention, the dermal filler composition is selected from the group consisting of therapeutic dermal filler materials, cosmetic dermal filler materials, muscular activity reduction agents, and combinations thereof.

According to a further feature of the present invention, the composition comprises at least one material selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, cultured human fibroblasts, fat, polylactic acid, botox, fascia tissue, synthetic or natural polymers, and microspheres.

According to a further feature of the present invention, the microspheres are selected from the group consisting of Calcium Hydroxylapatite microspheres, DEAE Sephadex particles (Dextran), PLLA (Poly-L-lactic acid) microspheres, PMMA (Polymethylmethacrylate) microspheres, PAAG (Polyacrylamide / Poly (acrylamide-co-

DADMA)) microspheres, and formulations comprising microspheres in combination with fillers selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, synthetic polymers, and combinations thereof.

According to a further feature of the present invention, the synthetic or natural polymers are selected from the group consisting of silicone gels, carboxyrnethylcellulose, polyethylene oxide, polyvinyl alcohol, and combinations thereof.

According to a further feature of the present invention, the dermal filling is for treatment of skin contour deficiencies caused by trauma, disease, aging, environmental exposure, weight loss, surgery, congenital malformation or combinations thereof.

According to a further feature of the present invention, the dermal filling is used for a procedure to fill, repair or augment facial dermal tissue selected from the group consisting of camouflaging scars, filling depressions, smoothing out irregularities, correcting asymmetry in facial hemiatrophy, second bronchial arch syndrome, facial lipodystrophy, camouflaging wrinkles, lip augmentation, providing facial contouring and augmenting facial eminences.

According to a further feature of the present invention, the at least one microneedle penetrates the skin at a pre-selected depth of from about 0.05 mm to about 1.0 mm.

According to a further feature of the present invention, a comparable filler effect is induced using a lesser dose of the composition as compared to when the same composition is delivered via a standard injection.

According to a further feature of the present invention, the dermal filler composition is deposited in shallower layers of the dermal tissue thereby reducing resorption by the body and increasing cosmetic longevity as compared to when the same composition is delivered via a standard injection.

According to a further feature of the present invention, there is provided an injection device for performing dermal filling comprising (a) a microneedle device including at least two hollow microneedles arranged in at least one row, the row defining a treatment vector of the device, and a reservoir in fluid communication with said row of microneedles; and (b) a dermal filler composition contained in said reservoir to be intradermally injected into

the skin of a subject at a pre-defined line in the skin where dermal filling is desired, the dermal filler composition comprising at least one material selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, cultured human fibroblasts, fat, polylactic acid, botox, fascia tissue, synthetic or natural polymers, and microspheres.

BRIEF DESCRIPTION OF THEDRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

FIG. 1 is an isometric view of a microneedle device used to implement the method of the invention;

FIG. 2 is an enlarged view of the distal end of the device of Fig. 1 showing a top perspective view of the delivery adapter;

FIG. 3 is an enlarged bottom perspective view of the delivery adapter of the device of Fig. 1;

FIG. 4 is an isometric view of the device of Fig. 1 combining a pre-filled syringe with a microneedle delivery configuration protected by a cover;

FIG. 5 is an exploded view of the device of Fig. 4 prior to engagement of the pre-filled syringe with the adapter that is protected by the cover;

FIG. 6 is an enlarged partial side view of the device of Fig. 1 prior to penetration into a pre-defined line;

FIG. 7 is an enlarged, partial cross-sectional view taken through the device, similar to Fig. 6, prior to penetration;

FIG. 8 is an enlarged, partial side view of the device of Fig. 1 after insertion into a pre-defined line;

FIG. 9 is an enlarged, partial side view of the device of Fig. 1 following injection of a dermal filler composition;

FIG. 10 is a histological slide of rat's skin following injection of hyaluronic acid using the microneedle device of Fig. 1;

FIG. H A is a histological slide of rat's skin following injection of hyaluronic acid using a regular #30 needle; and

Fig. 1IB is a magnified view of Fig. 1IA showing dye infiltrating muscle.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is a device and method for intradermal delivery of dermal filler compositions into the dermal tissue of a subject using a microneedle device. In accordance with the method of the invention, microneedles are deployed along a pre-defined line or wrinkle where dermal filling, cosmetic repair or augmentation of tissue is desired and a quantity of dermal filler composition is injected through the microneedles to a specific depth. The principles and operation of the device and methods according to the present invention may be better understood with reference to the drawings and the accompanying description.

Referring now to the drawings, FIGS. 1 to 5 illustrate an example of a microneedle dermal filler delivery device for delivery of a dermal filling composition to intradermal layers of the skin of a mammalian subject that can be used to practice the methods of the present invention.

Referring now to the drawings, Figs. 1-5 shows an implementation of a microneedle device, generally designated 10, constructed and operative according to the teachings of the present invention. In the case illustrated here, microneedle device **10** is formed primarily from a molded block that provides the various external surfaces and internal channels described herein. The microneedle-skin interface of device **10** includes a delivery adapter 200 having at its distal end a linear array of microneedles **100** arranged in at least one row projecting from a substrate **140** attached to a relief surface **160** adjacent to a skin contact surface 180, and where the relief surface and skin contact surface are roughly orthogonal. The adapter **200** terminates in a luer connector **210** at its proximal end applied with luer lock wings for use with an external reservoir or fluid supply device such as a syringe **400.** A primary flow channel **220** is in fluid connection to bores passing through the microneedles and extends rearwards through the device for connecting to a syringe **400.** The rear portion of the flow channel may be formed with a slightly conical diverging shape configured to provide a standard female luer connector for engagement on a syringe tip. It should be noted, however, that the invention is not limited to such an implementation, and

may instead be implemented, for example, as an integral part of a self-contained fluid delivery device such as a prefilled or disposable syringe. When engaged with the filler container, such as a pre-filled syringe, the microneedles 100 are protected by cover 300.

Turning now to the injection method of the present invention, this is described below in more detail with reference to Figures 6-9. The invention provides a method for intradermally delivering a dermal filler composition into the dermal tissue of a subject at a pre-defined line in the skin where dermal filling, cosmetic repair or augmentation of tissue is desired. The pre-defined line is a treatment line that may be selected from the group of skin contour deficiencies consisting of a wrinkle, a subcutaneous defect, a depression, a fold, a stretch mark, a curved line, a fine skin line, a fine wrinkle line, and a superficial skin imperfection.

In general terms, the method employs a microneedle device such as device 10 described above, including at least two hollow microneedles arranged in at least one row. The row defines a treatment vector of the device. The user first orients the microneedle device such that the tips of the microneedles assume a deployed position at a first injection site along the pre-defined line such that the axis of the microneedle device is substantially parallel to the pre-defined line. The device is then inserted into the subject's skin so that the microneedles pierce at least the stratum corneum of the skin and are anchored into the pre-defined line in the skin. A quantity of the composition is injected through the microneedles into the dermal tissue such that the composition is intradermally delivered into the dermal layer of the skin at the pre-defined line where dermal filling is desired, thereby at least partially filling, cosmetically repairing or augmenting the tissue. The microneedle device is then removed from the subject. The method may be repeated at least one additional time at one or more injection sites spaced horizontally or longitudinally along the pre-defined line until the desired dermal filling, cosmetic repair or augmentation of the tissue is achieved. Further details of the method and its various advantages will be more fully described below.

Definitions

Before addressing the features of various specific implementations of the present invention in more detail, it is helpful to define certain terminology as used herein in the description and claims.

Firstly, the invention is primarily intended for delivery of a dermal filler composition into layers of the skin of a mammalian subject, and in particular, for intradermal or intra-epidermal delivery of a dermal filler composition into the skin of a human subject.

The term "dermal filler" is used to refer to any composition which is used for dermal filling and is able to flow, or can be induced to flow under working conditions of the device. Thus defined, "filler" includes, but is not limited to, any and all types of liquid, gel, hydro-gel, suspension or fluidized powder. Preferred examples include, but are not limited to, therapeutic dermal filler materials, cosmetic dermal filler materials, muscular activity reduction agents such as botox, and combinations thereof. It is contemplated that local anesthetic agents may be combined, incorporated, co-injected or formulated in the dermal filler formulation in order to reduce the pain associated with the injection.

The term "intradermal" is used generally herein to include every layer of the skin, including stratum comeum, epidermis and dermis.

The term "dermal tissue" is used generally to refer to the epidermal and dermal layers of the skin.

The term "dermal filling" is used to refer to any medical, cosmetic, aesthetic, therapeutic, or reconstructive procedure used to treat various dermatological conditions and skin contour anomalies or deficiencies in the skin of a subject and to restore tissue loss that may be caused by trauma, disease, aging, environmental exposure, child bearing, weight loss, surgery, congenital malformation, or combinations thereof. The disease may be acne, skin cancer or other diseases associated with or presented in, the skin. The skin contour anomalies or deficiencies may comprise one or more of the group consisting of frown lines, worry lines, wrinkles, rhytids, crow's feet, marionette lines, stretch marks, cutaneous depressions of non-traumatic origin, and internal or external scars resulted from traumas such as injury, wound, surgery, bites, cuts, or accident, non-traumas, or other procedures that result in fissures, openings, depressions, wounds, and the like, in the skin. Dermal

filling involves shallow delivery of bio-actives to fill scars, depressions and wrinkles to temporarily augment the dermis to correct the surface contour of the skin, without producing an unacceptable inflammatory reaction, hypersensitivity reaction or foreign body reaction that causes pain, redness or excessive scar formation for a period of time. Dermal filling includes methods of skin augmentation, reshaping, and reconstruction, plastic surgery, and anti-aging procedures to treat dermatological conditions in a subject.

"Tissue augmentation" in the context of the present invention refers to a change of the natural state of a subject's skin and related areas due to external acts. As used herein, "augmentation" or "augment" refers to filling, bulking, supporting, enlarging, extending, or increasing the size or mass of body tissue.

"Skin contour deficiencies," and "skin contour anomalies" are used interchangeably in the present invention to refer to skin conditions that are either abnormal or undesirable due to various internal or external conditions such as aging, environmental exposure to the sun and other elements, weight loss, child bearing, disease such as acne and cancer, surgery, wounds, accidents, bites, cuts, etc.

The term "pre-defined line" is used to refer generally to any area or site of a skin contour deficiency or anomaly, of any size, form, shape, configuration, cause, origin, reason or etiology, that may be treated by dermal filling to effect cosmetic repair or tissue augmentation. The pre-defined line may be selected from the group of skin contour deficiencies consisting of a wrinkle, a subcutaneous defect, a depression, a congenital or acquired fold (such as a nasolabial fold), a stretch mark, a curved line, a fine skin line, a fine wrinkle line, and a superficial skin imperfection. The device is oriented and inserted into the skin so that the microneedles pierce at least the stratum corneum of the skin of the subject at a first injection site along the pre-defined line to be treated and the microneedles are anchored into the pre-defined line in the skin. The pre-defined line to be treated may include a characterizable treatment line in which case the microneedles are oriented and inserted at spaced locations along the treatment line, the row of microneedles defining a treatment vector of the device. Alternatively, the pre-defined line may comprise a curve, in which case the microneedles are inserted along the tangent line for the curve, i.e., the best

straight-line approximation to the curve at that point. Where the pre-defined line comprises a more irregular or diffuse contour deficiency, multiple, incremental injections may be made at one or more subsequent injection sites along the pre-defined line to be treated, whether serially or non-serially, to achieve dermal filling of the contour deficiency. Subsequent injections may be made side by side to the initial injection site or sequentially in a line, so long as they are made at spaced locations along the treatment line.

Reference is also made to geometrical relations to the surface of the skin. For the purpose of the present description and the appended claims, all geometrical relations to the "surface" of the skin are defined in relation to a plane approximating to the surface of the skin in an initial state of rest of the skin, i.e., prior to any deformation of the skin caused by insertion of the microneedle device. As a more technical definition, particularly important in the case of a region of skin that has considerable curvature, this surface is defined as the plane containing two orthogonal tangents to the flexible biological barrier surface at the location of interest.

For convenience, directions or positions further from the surface of the skin are referred to as "up", "above" or other similar terms, and directions or positions closer to, or deeper within, the skin are referred to as "down", "below" or other similar terms. It will be understood that this terminology is arbitrary in the sense that the skin surface itself may have any orientation in space.

Where reference is made to a direction of motion having a component parallel to the surface of the skin, this includes any motion that is not perpendicular to the skin surface. Preferably, the motion has a majority component parallel to the skin surface, i.e., at an angle shallower than 45 degrees. Most preferably, the part of the motion performed in contact with the skin is performed substantially parallel to the skin's surface, i.e., with a motion vector not more than about +15 degrees above or below the plane of the skin surface at rest.

With regard to angles relative to the plane of the skin, angles will be referred to relative to a vector parallel to the skin as zero degrees with angles pointing into the skin being positive and angles away (outwards) from the skin being designated negative. For

simplicity of presentation, use may be made of the term "upwards" or "up" to refer to directions outwards from the initial plane of the skin and "downwards" or "down" to refer to directions inwards or towards the initial plane of the skin.

Reference is also made to various physical states of the skin. The skin is described as "stretched" when a distance between points defined on the skin in at least one direction is greater than the distance between the same two points when the skin is released. The direction of maximum strain is referred to simply as the stretching direction. "Unstretched" denotes a state of the skin where no stretching is present parallel to the direction of stretching in an adjacent region of stretched skin. It will be appreciated that, where compression of skin tissue has lead to local bulging or folding of the tissue, a degree of stretching may occur perpendicular to the compression vector to accommodate the out-of-plane distortion of the tissue. Nevertheless, such tissue is referred to herein as "unstretched" since no elongation is present in the direction of stretching. Tissue for which the distance between points is reduced relative to the same two points when the skin is released is referred to as "relaxed" tissue since it exhibits lower surface tension than the skin when released.

The term "microneedle" is used herein to refer to a structure projecting from an underlying surface to a height of no more than 1 mm, and preferably having a length in the range of 50 to 1000 μm. The microneedles employed by the present invention are preferably hollow microneedles having a base end and a tip, with at least one hollow pathway or fluid flow channel disposed between the base end and the tip for delivery of fluid. The hollow pathway ranges in size from 30μm - 100 μm, and preferably 50 μm - 60 μm, and does not reach the tip. The microneedles penetrate the skin at a pre-selected depth of from about 0.05 mm to about 1.0 mm. The height or length of the microneedles is defined as the elevation of the microneedle tip measured perpendicularly from the plane of the underlying surface. The base ends of the microneedles are attached or integrated to a substrate, and a reservoir containing the composition to be delivered is in fluid communication with the base ends of the microneedles. The term "peripheral surface" is used to refer to any surface of the microneedle that is not parallel to the surrounding

substrate surface. The term "upright" surface is used to refer to any surface that stands roughly perpendicular to the surrounding substrate surface. The microneedle device includes at least two hollow microneedles arranged in at least one row, the row defining a treatment vector of the device. In another embodiment, the row of microneedles includes at least three microneedles aligned along the pre-defined line. In yet another embodiment, the row of microneedles includes at least four microneedles aligned along the pre-defined line.

As mentioned above, most preferred implementations of the present invention employ microneedles of a type similar to those disclosed in co-assigned US Patent No. 6,533,949, namely, formed with at least one wall standing substantially perpendicular to the underlying surface and deployed so as to define an open shape as viewed from above, the open shape having an included area, and an inclined surface inclined so as to intersect with the at least one wall, the intersection of the inclined surface with the at least one wall defining at least one cutting edge. The hollow pathway or fluid flow channel is preferably implemented as a bore intersecting with the inclined surface. The particular robustness of the aforementioned microneedle structure and its particular geometrical properties exhibit great synergy with the structures and insertion methods of the present invention, ensuring that the microneedles can withstand the applied shear forces and are optimally oriented for delivery of a dermal filling composition in to the dermal tissue of a subject. These advantages are detailed further below.

Reference is also made to various surfaces which may be provided by a "block of material". The term "block" is used herein to refer generically to any structure of one unitary element or plural elements cooperating to provide the recited surfaces in fixed mechanical relation. The "block" thus described includes, but is not limited to, a solid block, a hollow block, a thin sheet-like block and an open arrangement of surfaces mechanically interconnected to function together as a block. Part or all of the block may also be provided by a substrate upon which the microneedles are integrally formed. In certain preferred cases, a plurality of microneedles are deployed in a linear array, i.e., positioned spaced along a line.

Turning now to the injection method of the present invention in more detail, after an initial stage of disinfecting the region of skin to be injected, the user optionally stretches the skin at a first injection site along the pre-defined line or wrinkle 600 in the skin where dermal filling, cosmetic repair or tissue augmentation is desired. The microneedle device including at least two hollow microneedles arranged in at least one row is oriented such that the row of microneedles assumes a deployed position at a first injection site along the pre-defined line, the row defining a treatment vector of the device. In one embodiment, the axis of the microneedle device may be substantially parallel to the pre-defined line. The device is inserted by pressing it against the skin to cause the microneedles to pierce at least the stratum corneum of the skin of the subject. As shown in Fig. 6, the device is brought to an anchored state in which the microneedles 100 are anchored into the pre-defined line 600 in the skin. The axis of the linear array of microneedles is parallel to the pre-defined line, i.e., the skin crease or fold. The axis of the reservoir or syringe in relation to the skin usually includes a sharp angle (less than 90 degrees, and more preferably 45-60 degrees) for anchoring the needles into the skin). In a preferred embodiment, the reservoir or syringe is then flattened to lie closer to the skin, by narrowing the angle between the syringe axis and the skin surface.

If the pre-defined line is curved rather than straight, the microneedles are inserted and anchored along the tangent line for the curve, i.e., the best straight-line approximation to the curve at that point. The microneedle device is then rotated to its position in Fig. 8 while pushing the device forward towards the distal side of the pre-defined line. In one embodiment, penetration is done at about 60 degrees to the skin, and then the syringe is lowered to lie on the skin at an angle of about ±15 degrees. In another embodiment, not shown, the skin will actually be lifted with the device, so that there is no angle. The rotation action results in the inserted tips of the microneedles stretching the tissue along the direction of insertion. The microneedles project from the microneedle device in a direction having a major component parallel to the initial plane of the pre-defined line. Once the microneedle penetrates, the operator has visual control to check if it is placed correctly. Anchoring of the microneedles may be visually verified by manipulating the device. A

quantity of the composition is injected through the microneedles into the skin such that the composition is intradermally delivered into the skin at the pre-defined line where dermal filling is desired by advancing the plunger of the syringe, thereby at least partially filling, cosmetically repairing or augmenting the tissue. Injection is controlled and there is no need to move the device during the sequence of delivery, as is the case when using a regular needle. Verification of successful completion of the injection is visible immediately by formation of a bleb 500 from the very shallow intradermal delivery of the dermal filler, as shown in Fig. 9. The method ensures constant minimal depth of delivery and minimizes the volume of dermal filler in use. The method also provides a flexible solution to follow curved lines and wrinkles. The microneedles are then gently withdrawn and the device removed from the skin of the subject. The bleb disappears over a few minutes after completion of the injection as the fluid disperses, filling the adjacent tissue. Optionally, the medical practitioner may then "sculpt" the material into place, as desired.

The procedure is repeated at least one additional time at one or more injection sites along the pre-defined line or wrinkle, or multiple times as required until the desired dermal filling, cosmetic repair or augmentation of the tissue is achieved. Thus, unlike the common method of using a regular needle for dermal filling (i.e., deep insertion along the wrinkle and continuous injection followed by withdrawal of the needle), the device and method of the invention involves making a number of small dose injections along the pre-defined line or wrinkle 600. The microneedles are inserted and anchored at incremental positions along the pre-defined line or wrinkle, whether adjacent to the initial injection side or sequentially along the pre-defined line, so long as the injection is made at spaced locations along the pre-defined line. This may reduce the number of actual injection sequences required, thereby reducing pain associated with the procedure and improving patient comfort. Preferably, the microneedles project from the microneedle device in a direction having a major component parallel to the initial or subsequent planes of the pre-defined line. Where the pre-defined line has a curved rather than straight configuration, the microneedles are inserted and anchored along the tangent line for the curve, i.e., the best straight-line approximation to the curve at that point. The at least one row of microneedles

is inserted into the skin so that the microneedles are attached to and anchored in the skin along the pre-defined line or wrinkle line. The dermal filler composition is then injected through the microneedles into a specific depth within the skin depending on the specific microneedle length, which may range from 50μm and lOOOμm. Preferably, the microneedles have a length between 450 μm and 750 μm.

Accordingly, the method of the present invention may be used to intradermally deliver a dermal filler composition selected from the group consisting of therapeutic dermal filler materials, cosmetic dermal filler materials, muscular activity reduction agents, and combinations thereof to fill, cosmetically repair or augment tissue. In this way, by targeting the dermal space, the bioavailability of the dermal filler is improved, which can result in a reduction in the amount of the necessary dose of the dermal filler to be delivered.

The device and method of the invention may be used in a variety of soft tissue repair, augmentation, reshaping, and reconstruction procedures to repair or augment depressions in or damage to dermal tissue, or other skin contour anomalies in a subject, caused by trauma, disease, age or congenital malformation. As a non-limiting example, such procedures may include facial tissue repair, augmentation or reconstruction including but not limited to procedures selected from the group consisting of camouflaging scars, filling depressions, smoothing out irregularities, correcting asymmetry in facial hemiatrophy, second bronchial arch syndrome, facial lipodystrophy, camouflaging wrinkles, lip augmentation, providing facial contouring and augmenting facial eminences (lips, brow, etc.).

Surgical applications for the device and method of the invention include, but are not limited to facial contouring (frown or glabellar line, acne scars, cheek depressions, vertical or perioral lip lines, marionette lines or oral commissures, worry or forehead lines, crow's feet or periorbital lines, deep smile lines or nasolabial folds, smile lines, facial scars, lips and the like). While most dermal filling is currently indicated for the face, additional skin sites may benefit from dermal filling, tissue augmentation and the like. This includes, as an example only, dermal filling of wrinkles of the arms, neck, and the Decolletage regions. Surgical specialists who would use the device and method of the invention include, but are

not limited to, plastic and reconstructive surgeons; dermatologists; facial plastic surgeons, cosmetic surgeons, otolaryngologists, and any other qualified physician.

Dermal Filler Compositions

The dermal filler composition may comprise at least one material selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, cultured human fibroblasts, fat, polylactic acid, botox, fascia tissue, synthetic or natural polymers, and microspheres.

Microspheres may be selected from the group consisting of Calcium Hydroxylapatite microspheres, DEAE Sephadex particles (Dextran), PLLA (Poly-L-lactic acid) microspheres, PMMA (Polymethylmethacrylate) microspheres, PAAG (Polyacrylamide / Poly (acrylamide-co-DADMA)) microspheres, and formulations comprising microspheres in combination with fillers selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, synthetic polymers, and combinations thereof.

The synthetic or natural polymers may be selected from the group consisting of silicone gels, carboxymethylcellulose, polyethylene oxide, polyvinyl alcohol, and combinations thereof.

The muscular activity reduction agent is preferably botox.

Specifically, dermal filler compositions include, among others, the following compounds and applications:

HA - The term "hyaluronic acid" ("HA") means an anionic polysaccharide composed of repeat disaccharide units of N-acetylglucosamine and glucuronic acid. HA is a natural component of the extracellular matrix in connective tissue. It includes cross and non-crosslinked HA, with various linkers and bonds, formulations, and additives. Sources include bacterial fermentation, avian sources, and other animal sources as well as synthetic analogues. HA may be mixed with other fillers (such as polysaccharides, for example GAGs (glucose amino glycans) including chondroitin sulphate, chitosan, etc.), and prepared in various chemistries (various birds, matrices, etc.). Preferred hyaluronic acid derivatives include Restylene and Hyaloform.

Collagen —in a variety of forms and formulations such as bovine, human, porcine origin or bio-engineered, with or without the addition of anesthetics agents. The filler may be native, cross-linked with different agents to reduce their dissolution time or immunological reactions, or contain additives such as local anesthetics. Some collagen dermal fillers are specially processed in order to minimize possible allergic reactions.

Cultured human fibroblasts —the patient's own fibroblast cells are cultured and processed to create an injectable filler.

Fascia tissue - processed fascia tissue from cadavers.

Autologous fat can also be taken from a donor site by liposuction and then injected in the targeted facial tissue.

Microspheres - these include CaHA (Calcium Hydroxylapatite) microspheres, DEAE Sephadex particles (Dextran), PLLA (Poly-L-lactic acid) microspheres, PMMA (Polymethylmethacrylate) microspheres, PAAG (Polyacrylamide / Poly (acrylamide-co-DADMA)) gels or microspheres, and formulations comprising such microspheres with collagen, HA, synthetic polymers or other additives.

Synthetic or natural polymers —these include Silicone gels, CMC (carboxymethylcellulose), PEO (polyethylene oxide), polyvinyl alcohol, and a combination of such materials with microspheres or other additives.

Botulinum toxin is a muscular activity reducing agent used to paralyze the small facial muscles around dynamic wrinkles in the forehead and around the eyes.

EXAMPLE 1

To demonstrate the shallower delivery achieved by use of the microneedle device and method for dermal filling of the invention as compared to use of a regular #30 needle and regular methodology for dermal filling, a dermal filler composition was intradermally injected by both the microneedle device of Fig. 1 (see Fig. 10) and a regular #30 needle (see Figs. 1IA and 1IB). The dermal filler composition used was hyaluronic acid (Restylene Vital™).

Fig. 10 is a slide providing a histological, microscopic view of rat's skin following injection of hyaluronic acid using the microneedle delivery device of Fig. 1. The

hyaluronic acid is marked with a biological dye. As evident in Fig. 10, the colored filler is concentrated in the epidermis.

Fig 1IA is slide providing a histological, microscopic view of rat's skin following injection using a regular #30 intradermal needle using the regular methodology. It can be seen that dye marked hyaluronic acid appears to infiltrate deep levels of the skin, involving the muscle layer. Fig 1IB is a magnified view of Fig. 1IA showing dye infiltrating muscle.

As demonstrated in Figs. 10-1 1, use of the microneedle device and method of the invention achieved shallower delivery of a dermal filler composition in comparison to regular intradermal injection using a standard #30 needle.

It will be appreciated that the above descriptions are intended only to serve as examples, and that many other embodiments are possible within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A method for dermal filling, comprising the steps of:

(a) providing a dermal filler composition to be intradermally injected into the skin of a subject at a pre-defined line in the skin where dermal filling, cosmetic repair or augmentation of tissue is desired;

(b) providing a microneedle device including at least two hollow microneedles arranged in at least one row, the row defining a treatment vector of the device;

(c) orienting and inserting the device such that the microneedles pierce at least the stratum corneum of the skin of the subject at a first injection site along the pre-defined line to be treated and are anchored into the pre-defined line in the skin; and

(d) injecting a quantity of the composition through the microneedles into the dermal tissue such that the composition is intradermally delivered into the skin at the pre-defined line where dermal filling is desired, thereby at least partially filling, cosmetically repairing or augmenting the tissue.

2. The method of claim 1, further comprising repeating steps (c) - (d) at least one additional time at one or more injection sites along the pre-defined line until the desired dermal filling, cosmetic repair or augmentation of the tissue is achieved.

3. The method of claim I, wherein the pre-defined line is selected from the group of skin contour deficiencies consisting of a wrinkle, a subcutaneous defect, a depression, a fold, a stretch mark, a curved line, a fine skin line, a fine wrinkle line, and a superficial skin imperfection.

4. The method of claim I_5 wherein said microneedles have a base end and a tip, with at least one hollow pathway disposed between the base end and the tip, a substrate to which the base ends of the microneedles are attached or integrated, and a reservoir in fluid

communication with the base ends of the microneedles, wherein the reservoir contains the composition to be delivered.

5. The method of claim 1, further comprising before the orienting step, the step of stretching the dermal tissue of the subject at the pre-defined line.

6. The method of claim 1, wherein said microneedles have a length between 50 μm and 1000 μm.

7. The method of claim 1, wherein said microneedles have a length between 450 μm and 750 μm.

8. The method of claim 1, wherein the row of microneedles includes at least three microneedles aligned along the pre-defined line.

9. The method of claim 1, wherein the row of microneedles includes at least four microneedles aligned along the pre-defined line.

10. The method of claim 1 further comprising after the orienting and inserting step the step of rotating the microneedle device while pushing the device forward towards the distal side of the pre-defined line, the inserted tips of the microneedles stretching the tissue along the direction of insertion, the microneedles projecting from the microneedle device in a direction having a major component parallel to the initial plane of the pre-defined line.

11 The method of claim 1, wherein said dermal filler composition is selected from the group consisting of therapeutic dermal filler materials, cosmetic dermal filler materials, muscular activity reduction agents, and combinations thereof.

12 The method of claim 1, wherein said composition comprises at least one material selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, cultured human fibroblasts, fat, polylactic acid, botox, fascia tissue, synthetic or natural polymers, and microspheres.

13. The method of claim 11, wherein said microspheres are selected from the group consisting of Calcium Hydroxylapatite microspheres, DEAE Sephadex particles (Dextran), PLLA (Poly-L-lactic acid) microspheres, PMMA (Polymethylmethacrylate) microspheres, PAAG (Polyacrylamide / Poly (acrylamide-co-DADMA)) microspheres, and formulations comprising microspheres in combination with fillers selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, synthetic polymers, and combinations thereof.

14. The method of claim 11, wherein said synthetic or natural polymers are selected from the group consisting of silicone gels, carboxymethylcellulose, polyethylene oxide, polyvinyl alcohol, and combinations thereof.

15. The method of claim 1, wherein dermal filling is for treatment of skin contour deficiencies caused by trauma, disease, aging, environmental exposure, weight loss, surgery, congenital malformation or combinations thereof.

16. The method of claim 1, wherein dermal filling is used for a procedure to fill, repair or augment facial dermal tissue selected from the group consisting of camouflaging scars, filling depressions, smoothing out irregularities, correcting asymmetry in facial hemiatrophy, second bronchial arch syndrome, facial lipodystrophy, camouflaging wrinkles, lip augmentation, providing facial contouring and augmenting facial eminences.

17. The method of claim 1, wherein the at least one microneedle penetrates the skin at a pre-selected depth of from about 0.05 mm to about 1.0 mm.

18. The method of claim 1, wherein a comparable filler effect is induced using a lesser dose of the composition as compared to when the same composition is delivered via a standard injection.

19. The method of claim 1, wherein the dermal filler composition is deposited in shallower layers of the dermal tissue thereby reducing resorption by the body and increasing cosmetic longevity as compared to when the same composition is delivered via a standard injection.

20. An injection device for performing dermal filling comprising:

(a) a microneedle device including at least two hollow microneedles arranged in at least one row, the row defining a treatment vector of the device, and a reservoir in fluid communication with said row of microneedles; and

(b) a dermal filler composition contained in said reservoir to be intradermally injected into the skin of a subject at a pre-defined line in the skin where dermal filling is desired, the dermal filler composition comprising at least one material selected from the group consisting of collagen, hyaluronic acid and derivatives thereof, cultured human fibroblasts, fat, polylactic acid, botox, fascia tissue, synthetic or natural polymers, and microspheres.

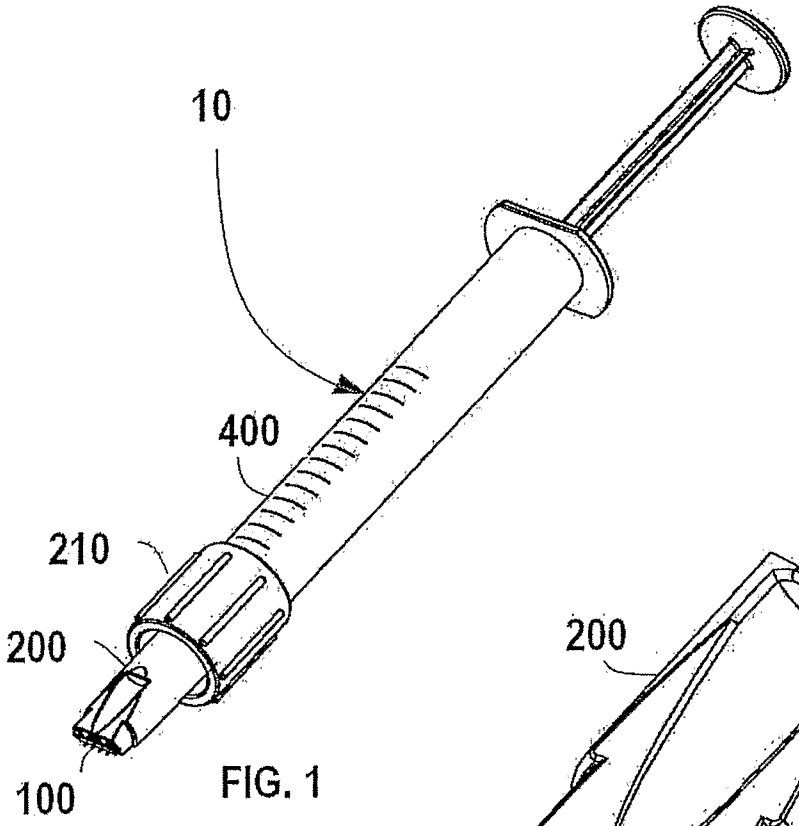


FIG. 1

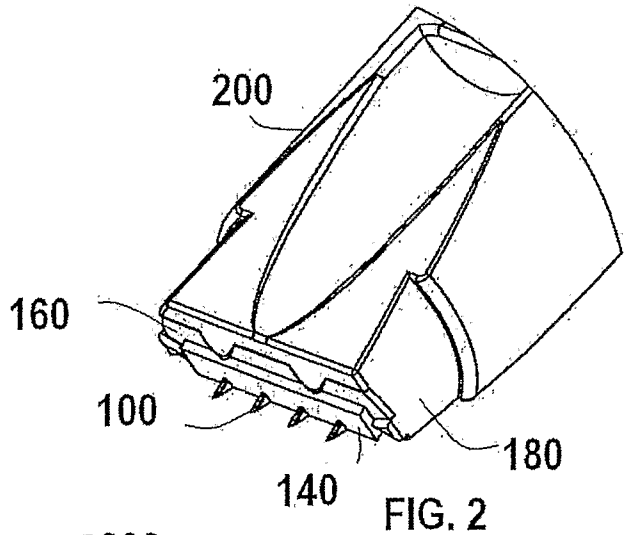


FIG. 2

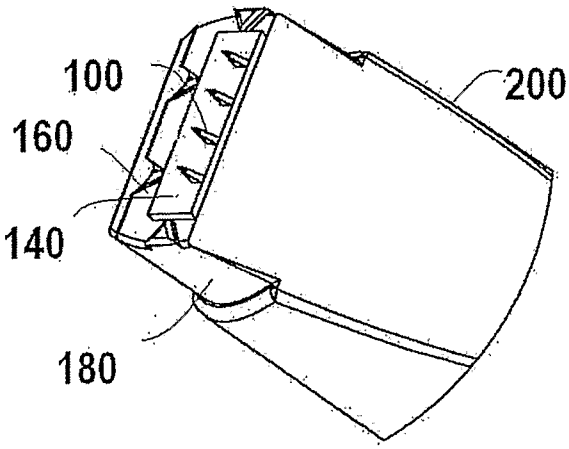


FIG. 3

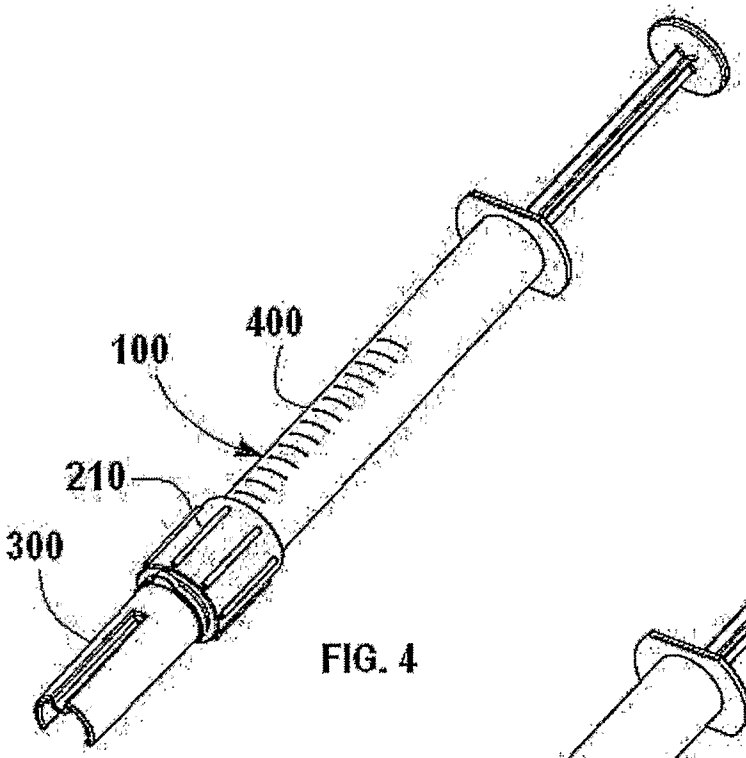


FIG. 4

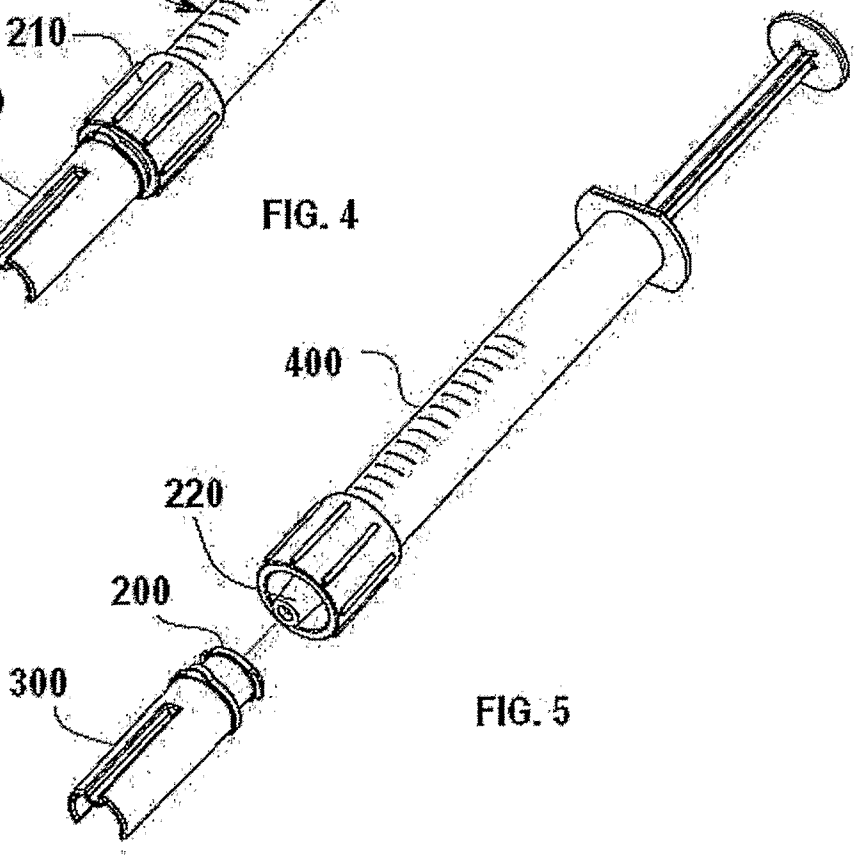


FIG. 5

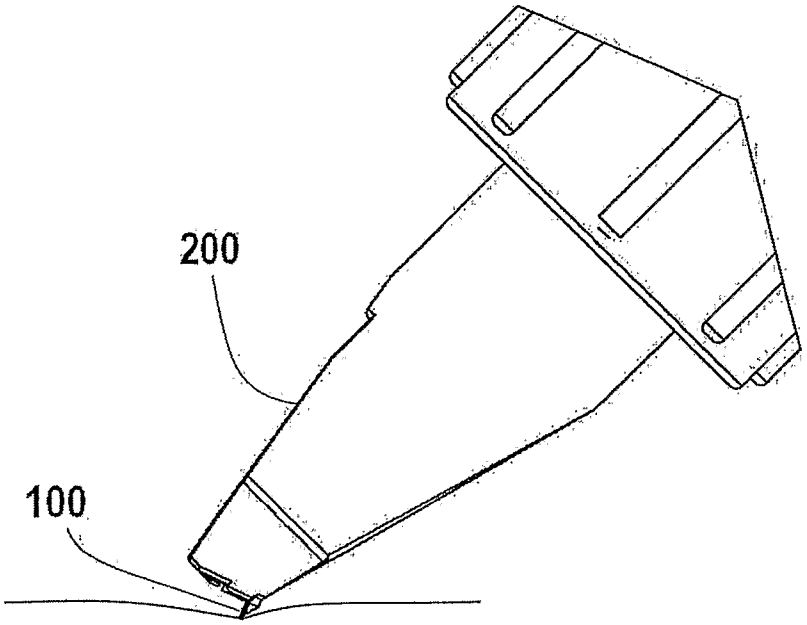


FIG. 6

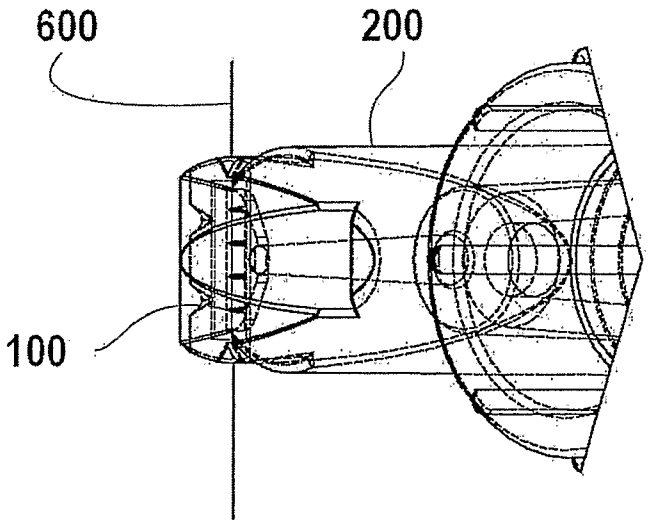


FIG. 7

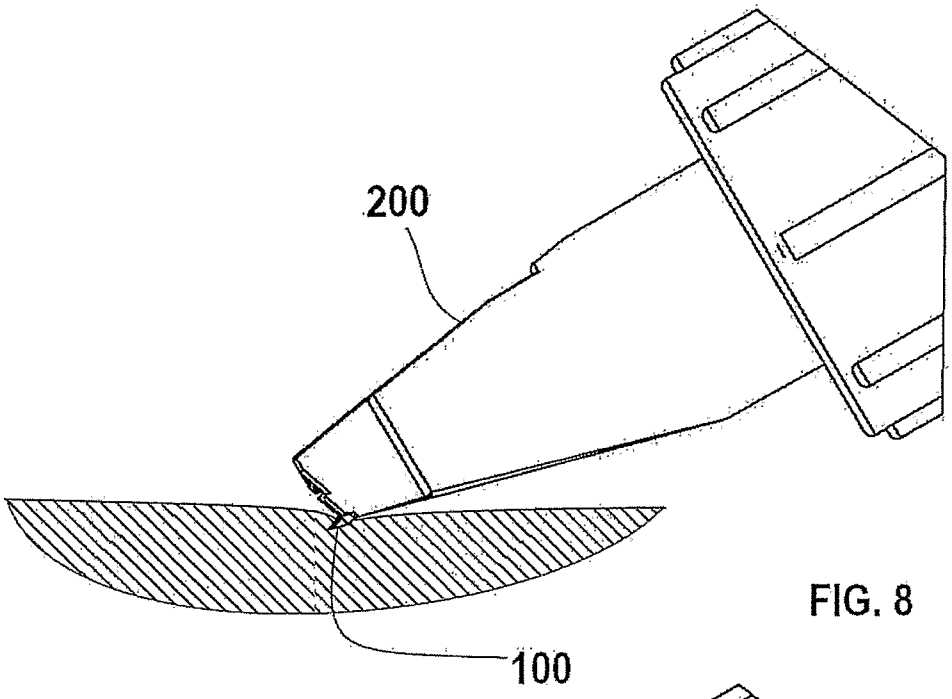


FIG. 8

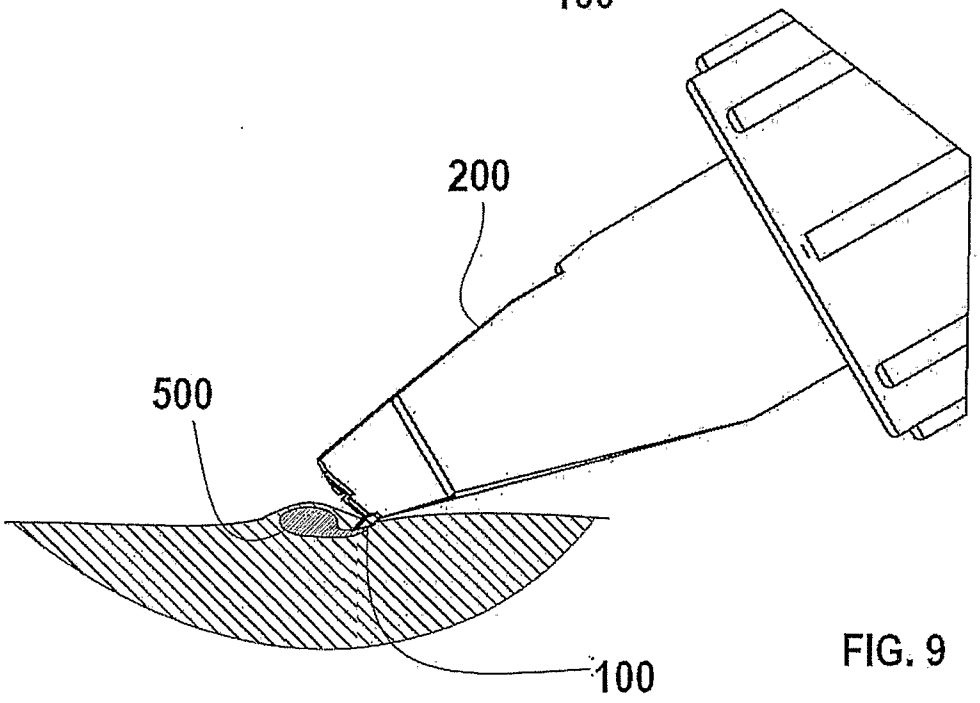


FIG. 9

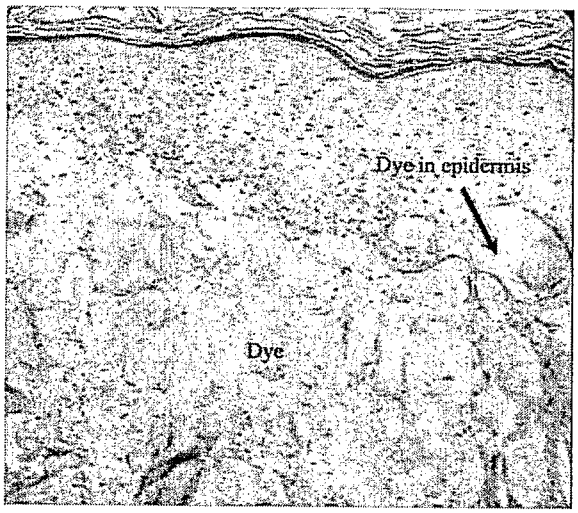


FIG. 10

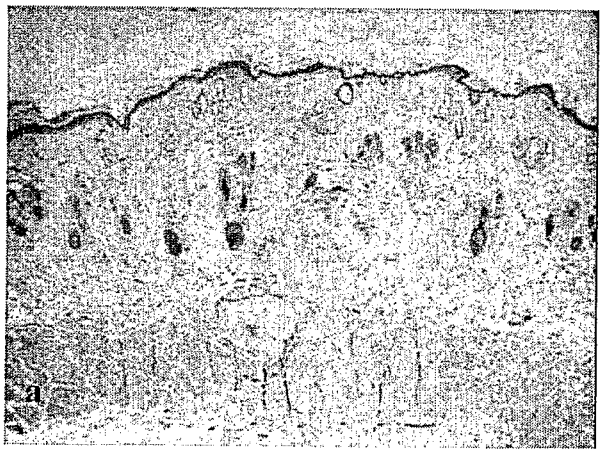


FIG.11A

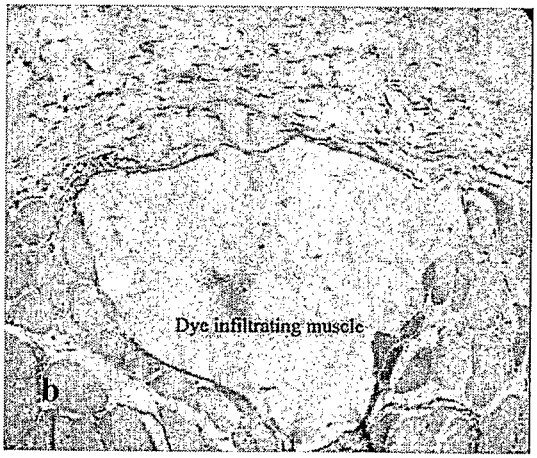


FIG. 11B