Title: MICRONEEDLE ARRAYS

Abstract: A microneedle array (10) is provided. The microneedle array (10) includes a plurality of solid or hollow microneedles (14) which are designed for delivery of an agent into skin for treating skin contour irregularities or skin disorders.
FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a device, system and method for delivering agents intradermally and, more particularly, to a microneedle array which is designed for cosmetic and dermatologic tissue remodeling.

The skin is a protective tissue-layered stratum that encases the body and guards it from potentially harmful intruders. It is the body's first defense against pathogens such as fungi, viruses and bacteria. The constituent components of the skin perform a second major skin function of equal importance, sensation. Encapsulated and free nerve endings, corpuscles (e.g., Meissner's corpuscle), and sensory receptors for touch and pressure found in the dermal layer of skin communicate tactile information to the brain.

Skin is made up of two primary layers the epidermis (outermost layer) and its sublayers, and the dermis; below the dermis there is subcutaneous tissue, or the hypodermis which is mainly composed of fat and connective tissue. The two layers are further differentiated by their respective amounts of hair follicle, pigmentation, cell formation, gland makeup, and blood supply. Moreover, these layers are present in the two general types of skin, thin and hairy, and thick and hairless. The former is more prevalent on the body, while the latter is found on parts of the body that are used heavily and experience extreme friction, like the palm and the heel.

The epidermis, the outermost layer of skin, is thin but complex. Melanin, which is responsible for skin pigmentation, is found throughout the epidermis. The epidermis also keratinizes to produce nails, hair, sweat, and to regenerate. It is the foremost initiator of cell death and regeneration, the final boundary between body and environment. The epidermis is a stratified squamous epithelium consisting of five keratinocyte layers at various stages of differentiation, the stratum germinativum, stratum spinosum, stratum granulosum, and stratum corneum. The stratum germinativum or basal layer is immediately superficial to the dermal-epidermal junction. This single cell layer of keratinocytes is attached to the basement membrane via hemidesmosomes.
Keratinization, the maturation and migration of skin cells, begins in the innermost layer of the epidermis, the stratum germinativum. Keratinocytes, accumulate and move outward toward the next epidermis layer, the stratum spinosum, where they become dense. As they move into the stratum granulosum, skin cells pick up granules that contain lipids. Lipids assist in the formation of water barriers among the cells of the skin, which, in turn, help to ensure body moisturization. At this point, the cell also becomes flattened, or horny, and the nucleus disappears; what remains is keratin. In the next layer, the stratum lucidum, the cell is prepared to move into its final sublayer with the addition of melanin granules. Then, sudden changes in enzyme function cause cell death. The products of this ongoing process form the stratum corneum, which is the outermost epidural layer consisting of neatly packed dead horny cells. When new cells reach the surface, their upward and outward force causes the dead cells to break apart and slough away, a process known as desquamation. It can take anywhere from six to 10 weeks for a cell to mature and journey through the layers of epidermis to its death and expulsion.

The stratum corneum may be as thin as a few cells, or as thick as 50 or more cells, again depending on its location on the body. The corneum of the scalp, for instance, may be very thin, perhaps five cells thick, while that of the elbow is more likely to be upwards of 50 cells thick. So the body provides for high-contact areas by maintaining a thicker and, therefore, more durable layer of protection.

The second, larger layer of skin is called the dermis. Its main roles are to regulate temperature and to supply the epidermis with nutrient-saturated blood. The dermis is made up of fibroblasts, which produce collagen connective tissues and which lend elasticity and support to the skin. It is the seat of hair follicles, nerve endings, and pressure receptors. Furthermore, the dermis defends the body against infectious invaders that can pass through the thin epidermis, the first defense against disease.

The dermis is also subdivided into two divisions, the papillary dermis, and the reticular layer. The papillary dermis supplies nutrients to select layers of the epidermis and regulates temperature. The reticular layer is much denser than the papillary dermis; it strengthens the skin, providing structure and elasticity. As a foundation, it supports other components of the skin, such as hair follicles, sweat glands, and sebaceous glands.
Aging (both photo- and chronological aging) decreases skin function and causes degenerative clinical changes such as wrinkling, color changes (yellowish, patches, pigmentation), and a loss of elasticity and skin thickness.

Skin wrinkling is due to a gradual, age-related depletion of collagen and elastin fibers. While skin characterized by decreased content of collagen and elastin contributes to the formation of fine wrinkles, muscles situated below such skin further contribute to the formation of deep wrinkles.

Four types of skin depressions can be defined according to their depth: folds, permanent wrinkles, reducible wrinkles and skin micro-relief.

Of the various aesthetic alternatives for reducing wrinkles and rejuvenating appearance, invasive surgical procedures, such as cosmetic eyelid surgery, tummy tucks and facelifts, can create the most pronounced and currently available long-lasting changes in appearance. They are performed by plastic surgeons with the patient typically under general anesthesia. Due to the limitations inherent to invasive surgical procedures, alternative approaches which are less invasive and can be performed without the need for a surgical staff are constantly sought after.

One alternative approach to surgery involves Botulinum Toxin injections (e.g. Botox, Dysport) into muscle underlying wrinkles around the eyes, mouth and brows. Although this approach is effective in eliminating muscle-induced wrinkles, it is not effective in treating wrinkles which are caused solely by aging.

In wrinkles, changes in collagen type I, III, IV and VII at the dermal-epidermal junction (DEJ) have been observed. Reduced fibroblast concentrations and function result in a decrease of collagen and a loss of dermis density.

Since decreased collagen concentration leads to the formation of wrinkles, it has been suggested that replenishing skin with collagen can partly reverse skin aging and decrease wrinkles.

Approaches for increasing skin collagen content can be divided into two main categories, injection of exogenous collagen and induction of endogenous collagen formation.

Although injection of collagen (and other skin fillers) is widely practiced, the benefit of stimulating endogenous collagen production is that collagen is deposited in an orderly, structured manner and that there is no risk of allergy, immune reaction or
injection-induced infection. Furthermore, many agents useful in stimulating collagen synthesis are relatively inexpensive and safe.

Prior art studies have shown that agents such as glycolic acid, ascorbic acid and others are capable of stimulating collagen synthesis [Bernstein et al. Dermatol Surg. 2001 May;27(5):429-33; Farris, Dermatol Surg. 2005 Jul;31(7 Pt 2):814-7; discussion 818]. However, presently used approaches for delivering such agents are limited by both efficacy and accuracy of delivery.

Thus, it would be highly advantageous to have an approach for efficiently and accurately delivering agents such as glycolic acid and ascorbic acid into the skin for the purpose of treating and remodeling skin contour irregularities as well as treating skin disorders.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a microneedle array comprising a plurality of microneedles each having a stem region and a tip region, wherein the tip region comprises a substance being capable of promoting remodeling of skin tissue or for treating a dermal disorder.

According to further features in preferred embodiments of the invention described below, the stem region is devoid of the substance.

According to still further features in the described preferred embodiments the substance is formulated as slow release particles.

According to still further features in the described preferred embodiments the substance is selected from the group consisting of glycolic acid, lactic acid, combinations thereof and ascorbic acid.

According to still further features in the described preferred embodiments the tip region is composed of the substance.

According to still further features in the described preferred embodiments each of the microneedles further comprises a linker region between the tip region and the stem region, the linker region being designed for facilitating release of the tip region from the stem region following introduction of the microneedles into skin tissue.

According to still further features in the described preferred embodiments the linker region is composed of a biodegradable substance.
According to still further features in the described preferred embodiments the linker region is designed for mechanically detaching from the tip region and/or the stem region following introduction of the microneedles into skin tissue.

According to still further features in the described preferred embodiments a length of each of the microneedles is selected such that following introduction of the microneedles into skin tissue the tip region resides within a dermal skin layer or subcutaneous fat.

According to still further features in the described preferred embodiments the microneedles are attached to a support designed for application onto a surface of a skin region predisposed to, or being characterized by wrinkling.

According to still further features in the described preferred embodiments the support is fabricated from a material being compressible under load, wherein application of the microneedle array onto a skin region and loading of the material drives the microneedles into the skin region.

According to another aspect of the present invention there is provided a microneedle array comprising a plurality of microneedles each comprising a substance (e.g. in the form of particles) within a solid matrix, the substance being capable of promoting remodeling of skin tissue or for treating a dermal disorder.

According to still further features in the described preferred embodiments the particles are formulated for slow release.

According to still further features in the described preferred embodiments the solid matrix is biodegradable.

According to still further features in the described preferred embodiments the particles are composed of a substance selected from the group consisting of polyglycolic acid, poly-lactic acid, combinations thereof and ascorbic acid.

According to still further features in the described preferred embodiments the particles are embedded only within a tip region of the microneedles.

According to yet another aspect of the present invention there is provided a method of preventing or diminishing skin contour irregularities or treating dermal disorders comprising delivering an agent suitable for treatment of skin contour irregularities or dermal disorders under the stratum corneum using a microneedle array thereby preventing or diminishing skin contour irregularities or treating the dermal disorders.
According to still further features in the described preferred embodiments the microneedle array is capable of releasing glycolic acid, lactic acid or ascorbic acid.

According to still further features in the described preferred embodiments delivery is effected using an applicator capable of accelerating the microneedle array into skin.

According to still another aspect of the present invention there is provided a device for treating dermal disorders comprising: (a) an applicator head having a surface designed suitable for contacting skin, the surface including microneedles having a length selected capable of penetrating the stratum corneum when the surface contacts the skin; and (b) a mechanism for accelerating the microneedles through the stratum corneum.

According to still further features in the described preferred embodiments the device further comprises (c) a reservoir containing at least one agent useful for treating a dermal disorder, the reservoir being in fluid communication with the microneedles.

According to still further features in the described preferred embodiments the microneedles are hollow microneedles.

According to still further features in the described preferred embodiments the microneedles are solid microneedles.

According to still another aspect of the present invention there is provided a microneedle array comprising a plurality of microneedles each composed of a biodegradable region attached to a non-biodegradable region, wherein the biodegradable region comprises a substance being capable of promoting remodeling of skin tissue or for treating a dermal disorder.

According to still further features in the described preferred embodiments the substance is provided as microparticles.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a device system and method which can be used to accurately and consistently deliver active agents to a discrete tissue layer of skin, thereby enabling prevention or reduction in skin contour irregularities and treatment of skin disorders.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which
this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1-2 illustrate several embodiments of the microneedle array of the present invention.

FIGs. 3a-b illustrate a microneedle array having a compressible support in a non-compressed (Figure 3a) and compressed (Figure 3b) states.

FIG. 4 illustrates an applicator device for applying the microneedle array of the present invention to skin regions using a vibrating tamper.

FIG. 5a-b illustrate treatment of periorbital skin regions using the present system.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a microneedle array which can be used for delivering skin tissue remodeling agents into the skin. Specifically, the present invention can be used to prevent or reduce wrinkling of skin.

The principles and operation of the present invention may be better understood with reference to the drawings and accompanying descriptions.
Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Although the issue of whether currently available wrinkle-reducing topical formulations are effective is still being debated, scientists are in agreement that active agents used in such formulations are capable of promoting skin tissue remodeling and thus are capable of reducing wrinkles. Thus, the effectiveness of such active agents is not being questioned, rather it is the mode of delivery.

The effectiveness of skin tissue remodeling agent formulations largely depends on skin permeability, site of delivery and the delivered dose. Due to the low permeability of the stratum corneum, active agents such as vitamin C are typically formulated in skin permeabilizing carriers which decrease the effective dose of the active agent. With some active agents such as glycolic acid, the local dose required for a tissue remodeling effect is relatively high while tissue penetration is relatively low and thus they cannot be effectively delivered via topical formulations.

Due to its limited skin permeability, glycolic/lactic acid is injected into the skin in the form of biodegradable poly-glycolic acid microparticles (see U.S. Pat. No. 6,716,251 or U.S. Pat. Application No. 10/186183). One commercial example of injectable lactic acid microparticles is Sculptra/NewFill™ which is a suspension of 40-60 μm diameter irregularly shaped PLLA particles. Since it is difficult to control the depth of delivery using a syringe, Sculptra/NewFill™ is injected subcutaneously in a matrix pattern. Due to the depth of injection, lidocaine is typically applied prior to injection to reduce patient discomfort and pain.

Although injection of PLLA overcomes dose/penetration limitations, injection thereof requires a high degree of skill for accurate deposition at the proper skin depth. One complication of inaccurate delivery of such agents is irregular skin remodeling resulting in bumps nodules which form contour irregularities. The use of poly lactic acid (PLA) or poly-L-lactic (PLLA) as filler agents is reviewed in Simamora et al Journal of Drugs in Dermatology 2006 May; 5(5): 436-440.
While reducing the present invention to practice, the present inventors have set out to design a device which enables accurate and efficient delivery of skin tissue remodeling agents such as glycolic/lactic acid in a convenient and easy manner.

The present device enables intradermal delivery of accurate doses of such agents in a controlled and repeatable manner thereby overcoming the limitations of prior art delivery approaches.

Thus, according to one aspect of the present invention there are provided microneedle arrays which can be used for reducing the formation or severity of skin contour irregularities or for treating skin disorders.

As used herein, the phrase "skin contour irregularities" refers to fine or deep wrinkles, stretch marks, scars or cellulite of any skin region of a mammal, and in particular a skin region covering the face, neck, hands, arms, legs, abdomen or buttocks of a human. Skin contour irregularities can also result from lipoatrophy (e.g. HIV lipoatrophy), especially in the facial regions.

Skin disorders include, but are not limited to, solar elastosis effects, hyperpigmentation, acne, scarring due to acne, dyschromias, melasma, stria distensae, actinic keratosis, acanthosis nigricans, dermatitis, psoriasis and any other disorders of the skin.

The microneedle array of the present invention includes a plurality of microneedles. Such microneedles can be needle-shaped microneedles, pyramid-shaped microneedles, prong-shaped microneedles, and the like. A review of some of the various microneedle designs is provided by Prausnitz [Adv Drug Deliv Rev. 2004 Mar 27;56(5):581-7].

According to one embodiment of the present invention, each microneedle of the array includes a stem region and a tip region wherein at least the tip region includes a substance which is capable of promoting remodeling of skin tissue. Although both the stem and tip regions of the microneedles can include the substance, restriction thereof to the tip region is preferred since it enables accurate localized delivery to a discrete tissue layer.

Figure 1 illustrates the microneedle array of this aspect of the present invention. The microneedle array which is referred to herein as array 10 includes a support 12 with attached microneedles 14, each including a tip 16 and stem 18 regions.
The microneedle array of the present invention preferably includes 10-1000 needles/cm² each having a length of about 50 to about 4,500 microns, preferably 200-800 microns, most preferably 300-600 microns; a width (at the base) of about 20 to about 500 microns, preferably 40-300 microns, and a tapered tip angle of 5-45°. The length of the tip region of each microneedle can be 5-50% of the overall length of the microneedle. The stem region is attached to a planar support (fabricated from polymer, metal etc) or co-molded therewith. The stem and tip region can be fabricated from the same material or from different materials in which case they are reversibly or irreversibly attached (further detail provided hereinbelow). For example, a PDMS mold can be filled with molten PLA that contains a solvent. Upon cooling and solvent evaporation, the PLA tip region shrinks and space is left in the mold above the PLA tip for the molding of a CMC stem and support.

The surface area of the array, the number and size of microneedles and spacing thereof are selected according to the intended use of the array.

For example, a circular or triangular array 0.5-2 cm in diameter with a microneedle density of 50-500 microneedles/cm² and a microneedle length of 500 microns can be utilized for treating orbital wrinkles; whereas, one or more square arrays with a total area coverage of 25-36 cm², a microneedle density of 200-1000 microneedles/cm² and a microneedle length of about 800 microns can be utilized for treating hand wrinkles. In any case, array and microneedle sizes are determined according to parameters (e.g. coverage area, skin thickness) characterizing the specific skin condition and skin type treated.

Each skin region can benefit from a support and microneedle shape most suitable for application and precise coverage. Thus regions such as side of mouth to chin ("marionette lines"), labial folds from nose to side of mouth, skin around the upper or lower lip, bulking of the lips themselves, eyebrows, furrow between eyes, hands, chest, neck, abdomen and buttocks can be treated using dedicated array designs. The density and size of the microneedles can be uniform throughout the array or it can vary (e.g. gradient) in a manner that provides spatial dose control. For example, higher density of microneedles or bigger sized microneedles can be provided along the projected centerline of a wrinkle with lower density of microneedles along the periphery of a wrinkle.
The microneedles can be fabricated from any material suitable for use in perforating the stratum corneum. Examples of suitable materials include, metals such as, stainless steel, titanium, Nitinol, Nickel, polymers such as PMMA, lactic acid, glycolic acid and carbohydrates, calcium hydroxyl appetite, dextran, polyacrylimide, Teflon, as well as silicon. Microarrays made of a metal covered polymer material compatible for the present invention include, for example, the array described by Choi et al. (An Electrically Active Microneedle Array for Electroporation of Skin for Gene Delivery; 2005 Controlled Release Society 32nd Annual Meeting & Exposition TRANSACTIONS).

The array of the present invention can be fabricated using well known techniques such as etching, extrusion, casting and the like. Additional information regarding fabrication of such arrays can be found in McAllister et al. PNAS November 25, 2003 vol. 100 no. 24 13755–13760, Park et al. Journal of Controlled Release 104 (2005) 51–66, or Park et al. Pharmaceutical Research, Vol. 23, No. 5, May 2006.

As is further described below, the microneedles of the present invention are preferably fabricated from a combination of materials using single step or multi-step casting approaches.

The phrase "skin tissue remodeling" denotes reorganization of cells or matrix of one or more skin layers, preferably, the subcutaneous fat, dermis and epidermis. This includes deposition of new collagen (neocollagenesis), deposition of new elastin and recruitment and proliferation of various cell types including fibroblasts and keratinocytes.

Preferred substances include ascorbic acid (vitamin C) and alpha-hydroxy acids (glycolic acid, lactic acid, malic acid and the like); most preferred are ascorbic acid, and polymeric forms of glycolic acid and lactic acid and combinations thereof (e.g. PLA, PGA, PLGA).

Additional substances such as gentian violet, an antibacterial that also visually stains holes in the stratum corneum or other delivery markers which outline the region treated can also be delivered from some or all of the microneedles on the array.

Several approaches can be used to deliver such substances from the tip region of the microneedles.

The tip region of the microneedles can be coated with the substance (preferably dry coated) such that when delivered into skin, the substance dissolves off the tip.
Alternatively, the tip of the microneedles can be shaped with a reservoir (e.g. a cup) which can be used to deliver liquid or solid (e.g. particles) forms of the substance. In this embodiment, microneedles can capture particles of the substance prior delivered on the surface of the skin at the site of delivery and then push them through the stratum corneum into the epidermis and/or dermis.

Presently preferred are delivery strategies which utilized biodegradable components. As used herein, the term biodegradable encompasses materials which dissolve or degrade in tissue.

Thus, according to one preferred approach, the entire microneedle or its tip region is fabricated from a biodegradable/dissolvable matrix which releases the substance following introduction of the microneedle into skin tissue. Two configurations can be used to facilitate such release, entrapment of the substance within a biodegradable/dissolvable microneedle, or fabrication of a tip region or of microparticles embedded within a dissolvable matrix from a biodegradable/dissolvable form of the substance, e.g. a microneedle tip which is composed solely from a biodegradable/dissolvable substance (e.g. PLGA) with no additional biologically active agents or substances.

When entrapped within a biodegradable/dissolvable matrix (which can form the entire microneedle, or only the tip), the substance can be dissolved directly into the matrix material or formulated as microparticles, having a diameter of 1-100 μm. For example, microparticles of vitamin C or glycolic acid (in the form of PLGA) can be encapsulated within a carboxymethyl cellulose (CMC), polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), ice or maltose matrix in the shape of a microneedle/tip. The matrix serves to provide structure to the encapsulated microparticles facilitating their penetration into the skin. Following administration, the microneedle/tip would dissolve to release the microparticles at the site of delivery. The substance can be formulated as part of a slow or timed release composition. Preferred forms of slow release formulation include nano or micro sized particles fabricated from poly-Lactic acid or Poly Glycolic acid or combinations thereof. Examples of particles include liposomes [Mantripragada, Prog Lipid Res. 2002 Sep;41(5):392-406], PLA/PGA particles [Tom and Debenedetti, Biotechnol Prog. 1991 Sep-Oct;7(5):403-11]. Long release profiles of drugs from a carrier particle delivered intradermally would be useful in many dermal disorders, for example in an anti-acne drug where the drug
would be released over 2-3 days and then the drug would be depleted and the biodegradable drug carrier particle would fully dissolve.

By way of example, a microneedle mold made from PDMS with pyramidal needles 800 microns long and 400 microns at their base was filled via centrifugation at 3000 rpm at a radius of 16 cm with PLLA microspheres 30-60 microns in diameter made of PLLA with an inherent viscosity of around 0.3-0.6 dL/g (Brookwood Pharma). Four distinct methods are given by way of example to construct the microneedles.

In the first step, the tip of an ultrasonic horn is pressed against the microparticles with a force of 1 kg and the particles were welded together using 20 pulses of ultrasonic energy at a pulse length of 1 s, duty cycle of 50%, and pulse power of 125 W using a 20-kHz ultrasonic device (Vibracell VC 505, Sonics & Materials, Danbury, CT). The sample is cooled to room temperature and removed from the mold. Such porous microneedle structures are relatively weak as compared to solid microneedles, but strong enough to survive a single accelerated plunge through the skin where they will break off and the welded particles disassociate from one another. Ultrasonic welding can also be used to connect microneedles to a thin flexible polymer base.

Other techniques utilize flowable and dissolvable matrix material. In the first such example, PEG powder (30,000 Dalton Sigma Aldrich) is mixed with PLLA microspheres or irregularly shaped microparticles approximately 50 microns in diameter and then heated in a vacuum oven to 80 degrees Celsius. The combined PEG/PLLA flows into the micromolds. Upon cooling, the PEG/PLLA microneedles are removed from the mold and packaged for use. It will be appreciated that microneedles composed of a relatively soft matrix can include coated delivery tips (e.g. coated with PLLA) to facilitate their penetration into tissue.

A similar approach can utilize maltose powder which is brought to 140 degrees C in a vacuum to make the maltose flowable and then spun in a centrifuge to pack it into the mold.

The matrix material can also be a monomer solution of 1-Vinyl-2-pyrrolidone with a thermal initiator of 0.5% benzoyl peroxide which flows into the space between the PLLA particles in a vacuum oven and when heated to 80 degrees C for one hour is
thermally polymerized to form a stiff gel. An alternative method is to UV cross link the 1-Vinyl-2-pyrrolidone using an initiator such as 2,2-Dimethoxy-2-phenylacetophenone under an intense UV light source for one hour.

In the case of slow release particles, the particles can range in size from 1-5 microns (similar in size to the colored pigments in tattoo inks) or larger. Much like tattoo pigments, which are on the order of 5 microns in diameter, the slow release particles of similar size ranges can agglomerate and form larger particles of hundreds of microns in diameter and therefore evade being removed from the site of injection by macrophages and the like. Preferably, particles of about 50 microns in diameter are used so that they are not taken up by macrophages and removed from the area of injection.

The second configuration is suitable for substances which can be formulated in biodegradable form. Such substances include glycolic acid and lactic acid which can be formulated as PLGA or agents which are dissolved in microneedles formed from ice (e.g. by freeze molding buffered agent solutions). PLGA or poly(lactic-co-glycolic acid) is a Food and Drug Administration (FDA) approved copolymer which is used in a host of therapeutic devices, owing to its biodegradability and biocompatibility. PLGA is synthesized by random ring-opening co-polymerization of various ratios of glycolic acid and lactic acid. PLGA degrades by hydrolysis of its ester linkages in the presence of water to yield glycolic acid and lactic acid. Thus, fabricating at least the tip region of the microneedles from PLGA would enable release of glycolic acid and lactic acid at the site of treatment. Examples of PLGA co-polymers include, PLGA 50/50 (1.2 dL/g high density) PLGA 50/50 (0.39 dL/g low density) various ratios of the two, low-molecular weight PLGA (Young’s modulus, E =1 GPa; yield strength, r =30 MPa), high-molecular weight PLGA (E =3 GPa; r =50 MPa), PLA (E =5 GPa; r =70 MPa) and PGA (E =10 GPa; r =90 MPa).

Since degradation of PLGA can take weeks to months (depending on the glycolic:lactic acid ratio), the microneedles of the array of the present invention can further comprise a mechanism for detaching the stem region from the tip region following administration of the microneedles into the skin. This enables removal of the array shortly following administration of the microneedles.

Such a mechanism can be realized through detachable coupling between the tip region and the stem region or stem and support or through the use of a linker region
which is designed for mechanical (e.g. controlled breakage) or chemical (e.g. biodegradable linker) detachment.

Coupling can alternatively be effected using a tip region fashioned as an arrowhead or barb and a stem region which slides into a bore configured within the tip region. Following administration of the microneedles, removal of the array (by pulling it out) forces the arrowheads or barbs to disconnect from the stem, leaving the tip region within the tissue to biodegrade over time.

Mechanical breakage can be effected using a linker region which supports loads through the longitudinal axis of the microneedle and yet collapses when loaded by a force which angles away from the longitudinal axis. Examples include a groove or notch which would concentrate a bending force and cause the microneedle to break off from the support at the application of a shear force. Furthermore, at a high enough aspect ratio, that is a relatively a tall and slender microneedle, shear stress will concentrate at the junction of the needle and the base and the microneedle will break naturally at the base upon application of a shear force without the need for a linker or special mechanical feature. Therefore the applicator can combine a sequence of downward motion to insert the microneedles, and then a sideways motion to break them off.

Figure 2 illustrates a microneedle array 10 having a detachable tip region 16 which is connected to stem region 18 through a linker 20 which is designed for mechanical breakage.

Chemical detachment can be effected using a carboxymethyl cellulose (CMC), Polyvinyl pyrrolidone (PVP), sugars such as maltose, maltodextrin or salts such as NaCl linker region. Other biocompatible materials that dissolve in tissue and yet have appropriate mechanical properties when dry can be used for this purpose. Alternatively, the detachment material can be doped into or layered between the same material as the tip, but only in the stem region, thereby weakening the stem sufficiently to enable it to preferentially disconnect at the stem.

The use of an array for delivery of solid preparations of a tissue remodeling substance provides several advantages over prior art delivery approaches. An array with breakable/dissolvable/biodegradable release mechanisms enables delivery of an accurate dose in a spatially controlled and consistent manner without requiring high operator skills. As opposed to PLA injections which are done by a doctor, such
microneedle arrays can be applied by a nurse, a technician, a cosmetician or by a person the treated individual. In addition, such an array can provide long term effects when used with biodegradable formulations of the substance delivered.

It will be appreciated that although the above described configurations preferably employ solid microneedles, the use of hollow microneedle configurations is also contemplated herein.

Thus according to another embodiment of the present invention, the microneedle array includes a plurality of hollow microneedles. Such hollow microneedles can be used to deliver an agent such as retinoic acid (and its derivatives), hyaluronic acid, collagen (as a solution/suspension), or glycolic/lactic acid (in the form of PLLA or PLGA) into skin tissue.

Such microneedles can be connected to a reservoir which can be activated to deliver the agent through the microneedles, or alternatively, the microneedles can be preloaded with the agent. For example, the microneedles can be preloaded with the agent (in liquid or solid form) prior to skin penetration and activated to eject the agent out of the microneedles and deliver it into the tissue following tissue penetration.

Delivery of a solid form of the agent from hollow microneedles can be effected via several approaches. For example, particles loaded with or composed from the agent (see description above) can be loaded directly into the microneedles. Alternatively, the agent can be (partially) molded into a shape that can be fitted within the microneedles or attached to a tip region thereof (e.g. arrowhead-shaped dose fitted into end of microneedles). In any case, once the solid dose is delivered into the tissue, the agent is released therein via one of the release mechanisms described hereinabove (e.g. dissolution, biodegradation). Alternatively, the solid agent can be suspended as particles in an appropriate matrix, such as CMC or PEG, that keeps the solid agent buoyant or flowable through a narrow bore of the microneedle. A positive displacement pump or plunger can be used to deliver precise doses of the active agent into the skin, since a passive pressure reservoir will likely cause a surge of material once the resistance to flow has been overcome, thereby making precise dosing difficult. Another embodiment can employ a microvalve in close proximity to the microneedle to prevent and material from surging out of the microneedle in an uncontrolled manner.
As is mentioned hereinabove, the microneedles of the array of the present invention can be attached to a planar support which can be elastic, plastic, semi-rigid or rigid in nature.

The support facilitates tissue penetration of the microneedles by directing a force applied thereto to the tops of the microneedles.

Although a simple microneedle array configuration having a polymer support mounted with microneedles will be capable of controlled and accurate delivery of the substance, in order to enhance microneedle penetration and preserve microneedle integrity during administration, especially in the configurations having a linker region which is susceptible to breakage, the present inventors have devised a microneedle array configuration which protects and guides microneedles during tissue penetration.

Thus, according to another aspect of the present invention there is provided a microneedle array which includes microneedles which are at least partially embedded within a support fabricated from a material being compressible under load. Such a support acts to reinforce the microneedles in the direction perpendicular to the axial load to help prevent buckling during the insertion.

The support is configured such that application of the microneedle array onto a skin region and loading of the material compresses the support axially and drives the microneedles into the skin region.

The support material can be an open cell foam (e.g. polyurethane or polyethylene foam), which is either plastic or elastic, or any material which demonstrates compression along the axis of load applied without substantial deformation in an axis perpendicular to the load. The latter trait is particularly important in that such deformation can lead to buckling of microneedles or deflection of microneedle paths and inefficient or incomplete delivery.

Figures 3a-b illustrate a microneedle array having a compressible support, which array is referred to herein as array 30.

In the non-activated (non-compressed) state, support 32 of array 30 includes embedded microneedles 34. Microneedles 34 can be any microneedles known in the art or the microneedles described herein. Support 32 also protects microneedles from breaking or scratching the skin during application and array handling.

When loaded (Figure 3b), support 32 compresses, exposing microneedles 34 and directing the path of the microneedles along the direction of the load. It will be
appreciated that although use of such a compressible support can negate the need for a rigid support (attached to the base of the microneedles), the above described configuration can also include a rigid planar support base for facilitating microneedle insertion and compression of the compressible support.

Delivery of any of the array configurations of the present invention can be effected manually, i.e. by applying a force using a finger, a hand, a roller device or the applicator device described hereinunder.

Presently known microneedle arrays of greater than a few square millimeter area, whether hollow or solid, are not optimized for penetrating the skin due to the so called “bed of nails effect”. The force of the array being pressed against the skin is divided by the collective area of all of the needles in the array, and so the force per needle can be below the threshold necessary to pierce the skin. The conventional means to overcome this effect include minimizing the number of needles or maximizing the force applied to the array, both of which have practical limitations.

Thus, the present inventors have devised an applicator device which can be used along with the microneedle arrays of the present invention in a system for treating skin contour irregularities.

Figure 4 illustrates the applicator device of the present system, which is referred to herein as device 40.

Device 40 includes an applicator head 42 which has a surface 44 designed for carrying a microneedle array and an element 46 (e.g. frame) for outlining an application site on the skin region.

Device 40 further includes a handle 48 which houses a power supply (not shown) and a mechanism 48 which is capable of accelerating microneedles 14 into the skin at a velocity of 4-16 m/s.

Mechanism 48 includes a free mass that can be accelerated and impacted to the backside of the microneedle array to transfer momentum to it, thereby accelerating the microneedles and causing them to penetrate the skin faster than the skin can move away. Mechanism 48 can include a mass, a return spring, a damper to prevent overshoot and can be driven using springs, solenoids, piezoelectric actuators or pneumatic actuators.
Applicator head 42 can also form an airtight seal around a skin region. Surface 54 which can be designed as a vacuum chuck for carrying a microneedle array with a porous base having a plurality of pores through which a vacuum can be applied.

Device 40 further includes a vacuum generating mechanism that generates vacuum from a manual, internal or external power supply (not shown). In operation, this configuration of device 40 is loaded with a microneedle array and placed in contact with a skin region. A vacuum is applied to stretch and pull the skin region up and in contact with the microneedle array thereby forcing the microneedles to penetrate into tissue of the skin region.

The microneedle array can form a part of the surface of applicator head or it can be removably attached thereto through an adhesive layer, or a magnetic or mechanical coupling mechanism (e.g. a mechanical holder). Alternatively, microneedle array can be included in a multi-array cartridge which is carried by applicator device 40. The cartridge and device 40 can be configured for coordinated dispensing and delivery of microneedle arrays through applicator head 42. This enables repeated accurate delivery of arrays and large area coverage. Furthermore, the microneedle array can be presented to the applicator head in the form of a tape or cartridge or cassette to be laid down along a skin remodeling site. Applicator device 40 can be a tamper that hits the backside of the tape and plunges the microneedles in the skin. The tape can be porous and after application dampened with water to enhance the dissolution of the dissolvable link between the microneedles and the backing tape.

The examples section below illustrates use of such a delivery system for treating periorbital skin region wrinkles.

Applicator device 40 can also include a vibratory mechanism for vibrating the microneedles and causing breakage of the tip region from the stem region following tissue penetration. Applicator 40 can also incorporate a massaging mechanism, for example at 100 hertz, for distributing the deposited active agents, for example microparticles of PLLA, more uniformly in the skin. Such vibration can also be used for vibratory anesthesia. Applicator 40 can also direct electricity, light, heat or other forms of energy to melt and therefore detach the microneedles close to the base.

Applicator device 40 can also include a lock-out mechanism for preventing abuse of device 40. Such a lock out mechanism would prevent over-dosing of the substance by effectively prohibiting the user, especially when using the device without
medical supervision, from using the device too often. An example of one lock out mechanism is a lock out timer, while another can employ a sensing head which can lock out the device when it detect the presence of a co-administered dye which dissipates from the skin over a predetermined time period.

The above described applicator and delivery mechanisms can also be used in an applicator configuration which includes a reservoir and hollow microneedles or hollow microneedles preloaded with the agent.

For example, an applicator including a reservoir containing PLLA/PLGA microparticles suspended in a liquid carrier and a mechanism for accelerating the applicator head and attached hollow microneedles into skin can be utilized to efficiently and accurately to deliver such microparticles into the dermis or subcutaneous fat layers.

The microparticles can be suspended in any liquid carrier including glycerol, PEG, a sugar solution and the like. For example, a 25% PEG400-PBS solution can be used to maintain the particles suspended for delivery.

Delivery of an agent using the above described applicator configuration can be effected as follows.

A microneedle array which includes 100 hollow microneedles each having a height of 1000µm, a diameter (at the base) of 200 µm and a bore 20-100 µm in diameter is mounted by a user on the applicator head. The applicator includes a reservoir which is in fluid communication with the mounted microneedles and a mechanism for accelerating the applicator head and mounted microneedles into tissue.

Applicator head is applied onto a skin surface to be treated and the mechanism for accelerating the applicator head is activated to deliver the hollow microneedles tips into the dermal or subcutaneous fat layers. The reservoir is then activated to pump the agent through the microneedles and into the tissue optionally with concurrent manual or automatic (by reversing the mechanism) withdrawal of the microneedles from the tissue. Following delivery, the applicator head is removed from the skin, the microneedle array is replaced and a second delivery round is effected if so desired.

It will be appreciated that in cases where larger coverage is effected using several arrays, the skin region to be treated can be marked with a grid and the device can be repeatedly used within the grid to cover the area to be treated. Alternatively, a wrinkle of interest can be marked with a marker and an applicator device incorporating
a sensor can be used to identify the location of these markings on the skin and deliver the agent through hollow microneedles to the areas that are marked.

Applicator configurations of the present invention can further include cooling or heating mechanisms for providing local analgesia as well as facilitating delivery of the active agent. For example, an applicator head which incorporates a cooling element can be used to cool the skin region prior to microneedle delivery.

Examples agents which can be delivered using the microneedle arrays of the present invention include, but are not limited to, ascorbic acid and its derivatives, glycolic acid [Bernstein et al., Dermatol Surg. 2001 May;27(5):429-33], alpha-tocopherol [Ricciarelli et al. Free Rad Biol Med, 1999; 27: 729-37], phospholipid hydroperoxide glutathione peroxidase (PHGP) [Hoet et al., Free Rad Biol Med, 2000; 29:159-69], retinoic acid, ellagic acid derivatives [Zafirilla et al., J Agric Food Chem. 2001 Aug;49(8):3651-5], poly-1-lactic acid (PLLA), amino acids (as building blocks for collagen), copper peptides [copper is essential for collagen production, Malakyan et al., Inflammopharmacology. 2004;12(4):321-51], MMP (e.g. collagenase) inhibitors such as, doxycycline hyclate (Periostat), growth and trophic factors such as TGF-beta, FGF, PDGF, NGF, NTF [see Fitzpatrick, Dermatologic Surgery Volume 31 Page 827 - July 2005], an exemplary growth factor cocktail is a mixture of multiple growth factors derived from a three-dimensional tissue culture of human fibroblasts (NouriCel-MD, Smith & Nephew, La Jolla, CA, USA or SkinMedica Carlsbad CA USA), lysozyme [Park et al., J Invest Dermatol. 1996 May;106(5):1075-80], collagen, elastin, dexamethasone [stimulates fibroblast proliferation and epithelialization; Crutchley et al., Pharmacol Exp Ther 1982; 222:544-9], tranexamic acid [Verstraete et al., Acta Clin Belg 1977; 32(2):136-141], formoterol and/or budesonide [Heuckel et al., Arch Dis Child 2000; 83:334-339], Docetaxel [Cleveland et al., Cancer 2000; 88(5):1078-1079], carbamazepine [Verotti et al., Ann Neurol 2000; 47:385-388], Glutamine, prostaglandins [Crutchley et al., J Pharmacol Exp Ther 1982; 222:544-9], Cellx-C™ (www.cellx-c.com), retinoids of all sorts, for example tretinoin (which promotes detachment of cornified cells and enhances shedding of corneocytes), statins for treatment of acne and other skin disorders [Smythe et al. J Invest Dermatol. 1998 Jul;111(1):139-48], corticosteroids (e.g. triamcinolone, prednisone, prednisolone, cortisone/hydrocortisone, dexamethasone/betamethasone) for inhibiting elastase activity or expression and Stauvidine for inducing adipocyte proliferation, 1,4-

It will be appreciated that the microneedle arrays of the present invention can be used to deliver more than one type of an agent, either simultaneously or sequentially. Multilayered coatings of the micro arrays can be configured to release certain vitamins or growth factors in a preset sequence in the order they dissolve off. For example, an acid, (e.g. glycolic acid), can be coated as an outer layer and a neutralizing alkaline agent can be coated as an inner layer on top of the needles, such that it is released after the acid. Alternatively, a liquid formulation of these factors can be sequentially released from a device reservoir through hollow microneedles.

The arrays of the present invention can also be used to deliver an agent such as aluminum chloride or botulinum toxin or other compounds which inhibit or block sweat gland activity (cholinergic receptor antagonists) in order to treat excessive sweating (hyperhidrosis). It will be appreciated that use of a microneedle array is advantageous in that large area coverage can be easily obtained via a single application.

Likewise, many of the anti-acne medicines that are currently taken orally with dosages limited due to side effects (Isotretinoin, antibiotics) can be better applied locally with a personal an applicator “pen” that inserts a dissolvable microneedle “patch” to the area of the acne lesion, thereby depositing the drug of interest at a higher local concentration in the skin than if it were taken systemically, and at a much lower total dose. Likewise, those acne medicines that are applied topically, such as Benzoyl peroxide, or Tretinoin can be effectively delivered into the skin using the techniques of the present invention. A flexible backing or cup shaped application head would allow for the microneedles to fit around convex acne lesions.

The arrays of the present invention can also be used to treat gum disease as well as gum regression. Disorders of the gingiva affect nearly 80% of people at one point in their life. Some gingiva disorders as well as age dependent gingival degeneration can be attributed to a reduction of the collagen matrix in gingival tissue
[Mussig et al., J Orofac Orthop. 2005 Nov;66(6):422-33]. Thus, preferred agents administered by the arrays of the present invention include those that promote neocollagenesis and fibroblast recruitment.

The arrays of the present invention can also be used to deliver a local anesthetic in order to reduce pain associated with dermal procedures.

Thus, the present invention provides a device, systems and method for treating skin contour irregularities and dermal disorders.

As used herein the term “about” refers to ± 10%.

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLE

Reference is now made to the following example, which together with the above descriptions, illustrates the invention in a non limiting fashion.

Treatment of periorbital wrinkles

Figures 5a-b illustrates periorbital skin region treatment using applicator device 40 described in Figure 4 and a microneedle array 10 having an array support shape and microneedle distribution which is optimized for treatment of such a skin region.

Microneedle array 10 includes 1500 microneedles each having a height of 750μm, a diameter (at the base) of 100 μm mounted on a support which is fabricated as a 1.5 cm (h) by 2 cm (base) triangle via molding.

Microneedle array 10 is designed having a PLLA tip region 250 μm in length. The tip is attached to a 500 μm stem region composed of PEG (30,000 Dalton MW). The tip region of each microneedle has a mass of approximately 2×10⁻³ milligrams and therefore 1500 microneedles distributed over a patch area of 3 cm² implies an effective
intradermal PLLA dose of 1 mg/cm², which is sufficient to have a significant effect in reducing wrinkles.

Application of the microneedle array to periorbital regions is as follows, a user attaches microneedle array 10 to applicator head 42 of device 40 or loads a cartridge including several arrays 10 into applicator device 40.

As shown in Figure 5a, the user then applies applicator head 42 onto a skin surface region 78 to be treated (i.e. the periorbital skin region which includes "crows feet" wrinkles) and activates mechanism 48 of device 40, to deliver a single array 10 to the periorbital region (Figure 5b). Following a predetermined time period during which the linker dissolves and tip region detaches from stem region, array 10 is removed from the skin and a second array is applied if necessary.

It will be appreciated that in cases where larger coverage is effected using several arrays, the skin region to be treated can be marked with a grid and the device can be repeatedly used within the grid to cover the area to be treated. Alternatively, the wrinkle of interest can be marked with a marker and an applicator device incorporating a sensor can be used to identify the location of these markings on the skin and deliver microneedles to the areas that are marked.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application
shall not be construed as an admission that such reference is available as prior art to the present invention.
WHAT IS CLAIMED IS:

1. A microneedle array comprising a plurality of microneedles each having a stem region and a tip region, wherein said tip region comprises a substance being capable of promoting remodeling of skin tissue or for treating a dermal disorder.

2. The microneedle array of claim 1, wherein said stem region is devoid of said substance.

3. The microneedle array of claim 1, wherein said substance is formulated as slow release particles.

4. The microneedle array of claim 1, wherein said substance is selected from the group consisting of glycolic acid, lactic acid, combinations thereof and ascorbic acid.

5. The microneedle array of claim 1, wherein said tip region is composed of said substance.

6. The microneedle array of claim 1, wherein each of said microneedles further comprises a linker region between said tip region and said stem region, said linker region being designed for facilitating release of said tip region from said stem region following introduction of said microneedles into skin tissue.

7. The microneedle array of claim 6, wherein said linker region is composed of a biodegradable substance.

8. The microneedle array of claim 6, wherein said linker region is designed for mechanically detaching from said tip region and/or said stem region following introduction of said microneedles into skin tissue.
9. The microneedle array of claim 1, wherein a length of each of said microneedles is selected such that following introduction of said microneedles into skin tissue said tip region resides within a dermal skin layer or subcutaneous fat.

10. The microneedle array of claim 1, wherein said microneedles are attached to a support designed for application onto a surface of a skin region predisposed to, or being characterized by wrinkling.

11. The microneedle array of claim 10, wherein said support is fabricated from a material being compressible under load, wherein application of the microneedle array onto a skin region and loading of said material drives said microneedles into said skin region.

12. A microneedle array comprising a plurality of microneedles each comprising a substance within a solid matrix forming said microneedles, said substance being capable of promoting remodeling of skin tissue or for treating a dermal disorder.

13. The microneedle array of claim 12, wherein said substance is formulated for slow release.

14. The microneedle array of claim 12, wherein said solid matrix is biodegradable.

15. The microneedle array of claim 12, wherein said substance is provided as a particles.

16. The microneedle array of claim 15, wherein said particles are composed of a substance selected from the group consisting of poly-glycolic acid, poly-lactic acid, combinations thereof and ascorbic acid.

17. The microneedle array of claim 12, wherein said substance is only within a tip region of said microneedles.
18. The microneedle array of claim 12, wherein said solid matrix is PEG.

19. A method of preventing or diminishing skin contour irregularities or treating dermal disorders comprising delivering an agent suitable for treatment of skin contour irregularities or dermal disorders under the stratum corneum using a microneedle array thereby preventing or diminishing skin contour irregularities or treating the dermal disorders.

20. The method of claim 19, wherein said microneedle array is capable of releasing glycolic acid, lactic acid or ascorbic acid.

21. The method of claim 19, wherein said delivering is effected using an applicator capable of accelerating said microneedle array into skin.

22. A device for treating dermal disorders comprising:
   (a) an applicator head having a surface designed suitable for contacting skin, said surface including microneedles having a length selected capable of penetrating the stratum corneum when said surface contacts said skin; and
   (b) a mechanism for accelerating said microneedles through said stratum corneum.

23. The device of claim 22, further comprising:
   (c) a reservoir containing at least one agent useful for treating a dermal disorder, said reservoir being in fluid communication with said microneedles.

24. The device of claim 22, wherein said microneedles are hollow microneedles.

25. The device of claim 22, wherein said microneedles are solid microneedles.
### INTERNATIONAL SEARCH REPORT

**International application No**

PCT/IL2007/001324

#### A. CLASSIFICATION OF SUBJECT MATTER

**INV. A61M37/00**

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

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61M A61K

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

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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<td>figure 3, paragraphs [0016], [0041], [0043], [0045] - [0048], [0092], [0115], [0123], [0126], [0143]</td>
<td>4,16,18</td>
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* Further documents are listed in the continuation of Box C.

See patent family annex.

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* Special categories of cited documents:

- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the International filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the International filing date but later than the priority date claimed

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

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

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

**&** document member of the same patent family

**Date of the actual completion of the international search**

29 January 2008

**Date of mailing of the international search report**

13/02/2008

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV RIJSWIL

Tel.: +41 (31) 340-2040, Tx. 31 651 epo nl

Fax: +41 (31) 340-3016

**Authorized officer**

Türkayci, Levent
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<td>WO 2006/101459 A (AGENCY SCIENCE TECH &amp; RES [SG]; ILLIESCU CIPRIAN [SG]; TAY FRANCIS ENG) 28 September 2006 (2006-09-28) abstract; figure 8</td>
<td>1-18, 22-25</td>
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INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.: 19–21
   because they relate to subject matter not required to be searched by this Authority, namely:
   see FURTHER INFORMATION sheet PCT/ISA/210

2.   Claims Nos.:  
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.   Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

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

1.   As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

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

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

4.   No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
Continuation of Box II.1

Claims Nos.: 19-21

Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy
The Method according to independent claim 19 defines a method for treatment of the human body by therapy because it claims "delivering an agent under the stratum corneum using a microneedle array". So the method according to claim 19 and related dependent claims 20,21 are not acceptable. (Rules 35 and 39.1 (iv) PCT).
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