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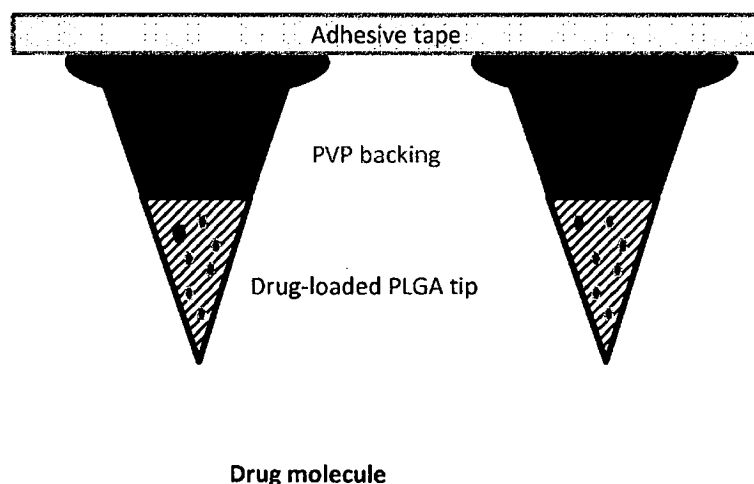
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(54) Title: MICRONEEDLE PATCH FOR DELIVERING AN ACTIVE INGREDIENT TO SKIN

Fig. 1a



(57) Abstract: The present invention relates to a microneedle patch composition comprising one or more microneedles each comprising: (a) a tapered tip portion containing a therapeutically active ingredient dispersed in a matrix of a biodegradable polymer capable of providing sustained release of the therapeutically active ingredient over a period of at least two days after insertion of the microneedle or microneedles into the skin, and (b) a fast dissolving microneedle backing layer portion containing a water-soluble polymer overlayering the tip portion, said microneedle or microneedles being attached to and extending from an adhesive surface of a removable substrate.



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MICRONEEDLE PATCH FOR DELIVERING AN ACTIVE INGREDIENT TO SKIN

FIELD OF INVENTION

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The present invention relates to a microneedle patch composition capable of providing sustained release of a therapeutically active ingredient in skin. The composition is intended for use in the treatment of skin conditions.

10 BACKGROUND OF THE INVENTION

Human skin, in particular the outer layer, the stratum corneum, provides an effective barrier against penetration into the body of microbial pathogens and toxic chemicals.

While this property of the skin is generally beneficial, it complicates the dermal
15 administration of pharmaceuticals in that a significant quantity, if not most, of an active ingredient applied on the skin of a patient suffering from a dermal disease may not penetrate into the viable layers of the skin where it exerts its activity. One way to obtain increased penetration of the active ingredient into the skin is to provide occlusion by formulating the active ingredient in a hydrophobic vehicle such as petrolatum.

20 Penetration into the dermis and epidermis may be boosted by providing the active ingredient in a dissolved state together with a low molecular weight solvent such as ethanol or propylene glycol which may also act as a penetration enhancer and/or by also adding a penetration enhancer to the formulation. However, such measures may not result in adequate penetration, and in addition formulations that contain a high
25 concentration of a hydrophobic excipient, e.g. petrolatum, generally have a tacky or greasy feel that persists for some time after application, and they are consequently considered to be less cosmetically acceptable.

Conventional topical formulations also have to be applied one or more times a day. This
30 is considered an onerous task by many patients who would prefer less frequent dosing and who are therefore more likely to adhere to therapy that involves application every 2 or 3 days or even longer.

Compositions comprising microneedles have been developed as an alternative to
35 transdermal patch formulations to deliver a therapeutically active ingredient or vaccine through skin. Compositions containing microneedles in which an active ingredient is incorporated have also been developed as an alternative to conventional topical

formulations such as ointments and creams. Microneedles are micron-scale structures designed to pierce the stratum corneum and permit delivery of an active ingredient transdermally or to the epidermis and dermis. Microneedle arrays have been prepared from many diverse materials such as silicon, stainless steel and biodegradable polymers.

- 5 One example of a microneedle formulation is solid microneedles coated with a formulation of the active ingredient which is released into the epidermis and dermis when the microneedles have pierced the stratum corneum. Another example of a microneedle formulation is dissolving or biodegradable microneedles prepared from a polymer incorporating the active ingredient which is released gradually as the polymer
10 degrades in the viable layers of the skin.

- WO 02/064193 discloses arrays of microneedles composed of polymers and/or metal, for instance a biodegradable polymer such as polylactic acid or polyglycolic acid. The polymer may include a therapeutically active ingredient which is released when the
15 microneedles are inserted into the skin.

- WO 2008/130587 discloses arrays of microneedles containing two layers of different polymers, e.g. polyvinyl alcohol and polylactic co-glycolic acid, respectively. One of the layers may contain a therapeutically active ingredient. The other polymer layer is cast on
20 top of the first layer, the solvent is removed, and the microneedle array is removed from the mould. WO 2008/130587 specifically discloses microneedles that comprise a drug-loaded tip composed of a fast dissolving polymer (e.g. polyvinylalcohol) and a base layer of a biodegradable polymer (polylactic co-glycolic acid).

- 25 WO 2012/153266 discloses a method of making microneedle arrays by filling microneedle-shaped cavities in a mould with a solvent, applying a microneedle-forming polymer solution on the cavities to mix the solvent and polymer solution by diffusion, removing the solvent and removing the resulting microneedles from the mould.

- 30 WO 2012/066506 discloses a method of making microneedles by spraying a composition into a mould, drying the composition and removing the dried composition from the mould.

- US 2007/0134829 discloses a method of producing microneedle arrays by wet etching of
35 silicon with a potassium hydroxide solution using a masking material provided with a number of openings for a sufficient period of time to produce microneedles of a specific

shape and sharpness. The microneedle arrays may be used for medical applications or as masters to cast moulds for making microneedles of polymeric materials.

It is an object of the invention to provide a topical composition comprising microneedles of a biodegradable polymer with the aim of improving delivery of a therapeutically active ingredient into the viable layers of the skin, in particular the dermis and/or epidermis. It is a further object of the invention to provide a microneedle composition which forms a drug reservoir in the skin from which the active ingredient is released over a prolonged period of time so that the composition may be administered less frequently than conventional topical formulations such as creams or ointments.

SUMMARY OF THE INVENTION

In the course of research leading to the present invention, it was found possible to provide a microneedle composition with a layered structure that permits insertion into the viable layers of the skin of a microneedle comprising a layer forming a tip and comprising a biodegradable sustained release polymer and one or more active ingredients. The microneedle further comprises a second layer on top of the first layer, the second layer comprising a polymer which dissolves shortly after insertion of the microneedle, thus permitting removal of a substrate on which the microneedle is attached. The microneedle composition exhibits desired physical and chemical stability and a desired rate of diffusion of the active ingredient from the polymer in which it is dispersed as well as a desired rate of degradation of the polymer to ensure release of the active ingredient over a prolonged period of time allowing less frequent dosing than the one or more times daily required when the composition is an ointment or cream.

Accordingly, in one aspect the present invention relates to a microneedle patch composition comprising one or more microneedles each comprising

- (a) a tapered tip portion containing a therapeutically active ingredient dispersed in a matrix of a biodegradable polymer capable of providing sustained release of the therapeutically active ingredient over a period of at least two days after insertion of the microneedle or microneedles into the skin, and
- (b) a fast dissolving microneedle backing layer portion containing a water-soluble polymer overlaying the tip portion,

said microneedle or microneedles being attached to and extending from an adhesive surface of a removable substrate.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1a is a graphic representation of a microneedle patch of the invention before insertion into the skin. The portion of the microneedle shown in dark grey represents the fast dissolving backing layer comprising for instance polyvinylpyrrolidone, and the portion of the microneedle shown as cross-hatched represents the tip comprising the biodegradable polymer mixed with active ingredient(s) (shown as pale grey ovals).

Fig. 1b is a graphic representation of the microneedle patch shown in Fig. 1a after insertion into the skin and after the fast dissolving backing layer has dissolved. The tip portion of the microneedles is present in the viable layer(s) of the skin.

Fig. 1c is a graphic representation of the microneedle patch shown in Fig. 1b showing release of active ingredient(s) into the skin.

Fig. 2a is a schematic representation of a method of preparing a microneedle patch composition of the invention ("DMN" is an abbreviation of dissolvable microneedle).

Fig. 2b is a schematic representation of an alternative method of preparing a microneedle patch composition of the invention ("DMN" is an abbreviation of dissolvable microneedle).

Fig. 3 is a graph showing the peak area ratio of the degradation product MC 1046 to total concentration of calcipotriol in microneedles comprising ester-terminated polylactide co-glycolide (PLGA-E) in the tip portion and polyvinylpyrrolidone (PVP) in the backing layer in the presence or absence of the antioxidant butylhydroxytoluene (BHT) in samples taken after drying the microneedles for 5 hours at $65^{\circ}\text{C} \pm 2^{\circ}\text{C}$ in a drying oven.

Fig. 4 is a graph showing the skin concentration (μM), 24 and 48 hours post application, of betamethasone-17,21-dipropionate (BDP) and betamethasone-17-propionate (B-17-P) in human skin explants treated with a microneedle patch composition of the invention compared to human skin explants treated with Daivobet[®] gel. B-17-P is predominantly formed in biological matrices and is thus considered a surrogate marker of BDP in skin.

Fig. 5a is a graph showing the mRNA levels, 24 and 48 hours post application, of CYP24A1 (a biomarker of calcipotriol exposure) in human skin explants treated with a

microneedle patch composition of the invention compared to human skin explants treated with Daivobet® gel.

Fig. 5b is a graph showing the mRNA levels, 24 and 48 hours post application, of CD14 (a biomarker of calcipotriol exposure) in human skin explants treated with a microneedle patch composition of the invention compared to human skin explants treated with Daivobet® gel.

Fig. 6a is a graph showing the mRNA levels, 24 hours and 4 days post application, of CYP24A1 in human skin explants treated with a microneedle patch composition of the invention compared to human skin explants treated with Daivobet® gel.

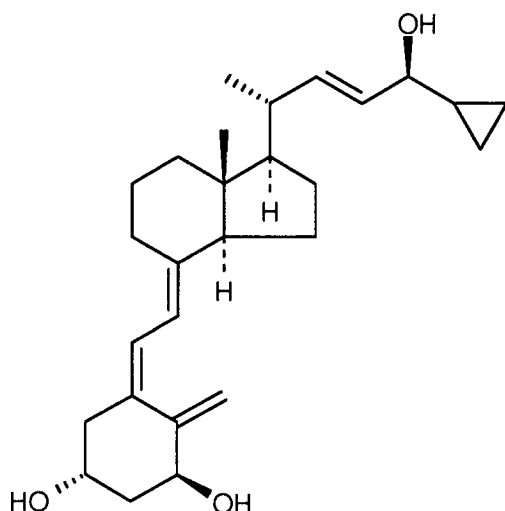
Fig. 6b is a graph showing the skin concentration (μM), 24 hours and 4 days post application, of BDP and B-17-P in human skin explants treated with a microneedle patch composition of the invention compared to human skin explants treated with Daivobet® gel.

Figs. 7a-7e show a series of reflectance confocal microscopy images of one microneedle after application of a 5x5 microneedle patch to human ex vivo skin and removal of the substrate (medical tape) after 45 minutes, taken by means of a Vivascope 1500 multilaser system at a wavelength of 785 nm.

DETAILED DESCRIPTION OF THE INVENTION

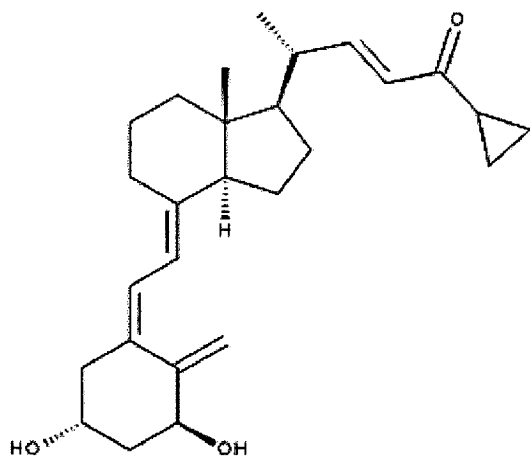
Definitions

In the present context, the term "calcipotriol" is intended to indicate a vitamin D analogue of the formula



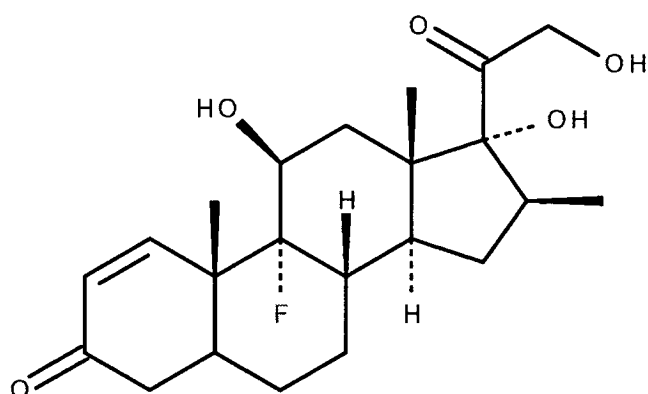
Calcipotriol has been found to exist in two crystalline forms, an anhydrate and a monohydrate. Calcipotriol monohydrate and its preparation are disclosed in WO 94/15912. The term "calcipotriol" is intended to cover any form of the compound, including crystalline, amorphous and dissolved forms.

The term "MC1046" is intended to indicate a compound of the formula



MC1046 is formed as a degradation product of calcipotriol under oxidative conditions.

The term "betamethasone ester" is intended to indicate a carboxylic acid ester of a compound of the formula



Examples of betamethasone esters that may be included in the present composition are betamethasone-17-valerate or betamethasone-17,21-dipropionate. A preferred betamethasone ester for the present purpose is betamethasone-17,21-dipropionate (referred to in the following as betamethasone dipropionate).

The term "dispersed" is intended to indicate that the active ingredient is either molecularly dispersed or present as a solid dispersion in the polymer matrix. Results from Raman spectroscopy of microneedle compositions of the invention suggest that both betamethasone dipropionate and calcipotriol are present as glass solutions molecularly dispersed in the polymer matrix.

The term "biodegradable" is intended to indicate that the polymer swells after insertion into the skin and subsequently degrades due to the hydrolysis of ester linkages in the presence of water.

The term "sustained release" is intended to indicate that the diffusion of active ingredient from the biodegradable polymer and/or the release of the active ingredient as a result of swelling, dissolution and/or degradation of the biodegradable polymer takes place over a prolonged period of time, such as at least two days, to enable delivery of a therapeutically effective dose of an active ingredient over the entire period, thus permitting less frequent dosing.

The term "fast dissolving" is intended to indicate that the backing layer portion of the microneedle dissolves within a period not exceeding 120 minutes, preferably not exceeding 60 minutes and which may be as short as about 15 minutes after insertion into the skin.

The term "chemical stability" or "chemically stable" is intended to indicate that no more than 10%, preferably no more than 5%, of either active ingredient degrades over the shelf-life of the product, which may be at least 1 year, but preferably at least 1.5 year or more preferably at least 2 years. An approximation of chemical stability at 5°C is obtained by subjecting the composition to accelerated stability studies at 25°C. If less than about 6% of the substance has degraded after 3 months at 25°C, this is usually taken to correspond to a shelf-life of 2 years at 5°C. More specifically, "chemical stability" of calcipotriol is intended to mean that the calcipotriol does not degrade significantly over time to 24-epi calcipotriol, MC1046 or other degradation products of calcipotriol in the finished pharmaceutical product.

The term "physical stability" or "physically stable" is intended to mean that the composition retains its macroscopic and microscopic appearance and physical properties over the shelf-life of the product. For instance, the composition is considered to be physically stable when the microneedles retain their shape and sharpness over time along with their mechanical strength as determined by the force required to provide sudden discontinuities (such as fractures) in the microneedle characteristic of sudden structural failure.

The term "ester-terminated" is intended to mean an alkyl ester of polylactic, polyglycolic or polylactic co-glycolic acid. The alkyl is preferably a C₁₋₂₀ alkyl, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, etc.

A method of preparing the microneedle patch composition of the invention

A method of preparing a microneedle patch composition of the present invention is shown schematically in Fig. 2. To make a mould for casting the microneedles, a template is initially prepared from a suitable material such as silicon or a metal such as steel or titanium or a polymer such as polycarbonate or polymethacrylic acid. The template comprise a plurality of microneedles which have a size and shape corresponding to the desired shape of the microneedles in the patch composition, i.e. typically either conical or pyramidal with a tapering tip. The mould may then be made by casting a liquid polymer material such as polydimethylsiloxane over the microneedle template. When the material is dried and cured the mould comprises microdepressions that retain the negative shape of the microneedles on which it is cast.

The length and number of microdepressions in the mould determine the length and number of the microneedles in the final patch. The number of microneedles per unit area may vary widely, typically between 2 and 100 microneedles per cm², but is more often in the range of 5-75 microneedles, more usually 10-50 microneedles, preferably 15-30 microneedles such as 20-25 microneedles per cm². Similarly, the length of the microneedles may vary, but they should be of sufficient length to penetrate the stratum corneum and not so long as to penetrate into the innervated part of the skin below the dermis as penetration to this depth may cause a painful sensation when the microneedle patch is applied on the skin. The microneedles may therefore have a length of 50-1000 µm, e.g. 100-800 µm, 300-700 µm, 400-600 µm or about 500 µm. Such a length of the microneedles generally ensures that the drug-loaded tip portion will lodge in the viable layers of the skin, i.e. the dermis and epidermis where the active ingredients exert their effect. As indicated above, the shape of the microneedles is also determined by the shape of the microdepressions in the mould and may be conical or pyramidal in shape and with a sharp tip. Furthermore, when the shape of the microneedle is pyramidal, it comprises a number, typically 4-8, of longitudinally extending ridges to facilitate the insertion of the microneedles into the skin. The aspect ratio of the microneedle (the length to width at the base of the microneedle) may vary according to the method used to produce the mould. When the mould template is prepared by wet etching (e.g. as described in US 2007/0134829), the aspect ratio is typically 3:2, i.e. the length is 1.5 times greater than the width at the base.

Microneedle patches according to the invention may then be made by filling the microdepressions in the mould with an appropriate solvent, e.g. dimethylformamide, and applying a solution of the active ingredients and the biodegradable polymer in the same solvent on top of the microdepressions to allow mixing of the two liquids. The solvent is then removed, e.g. by drying in a desiccator under vacuum and/or in a drying oven at an appropriate temperature. A second solution of the water-soluble polymer in an appropriate solvent is then applied on top of the partially filled microdepressions followed by drying, e.g. in a desiccator under vacuum or in a drying oven at an appropriate temperature. In a currently preferred embodiment, the solution of the water-soluble polymer is applied in such a manner that the backing layer portion when dried overlays the base of the tip portion in such a way that each microneedle is separated from the other microneedles on the patch and forms a discrete entity when the substrate is removed upon application of the patch on the skin.

Depending on the dose of the active ingredients to be delivered from each patch, the drug-loaded tip portion may constitute 5-95% of the total volume of the microneedle.

The dried microneedles may then be removed from the mould by applying adhesive tape on top of the mould and applying pressure to ensure good contact between the tape and the base of the microneedles followed by pulling the microneedles out of the mould. The tape should preferably be adhesive medical tape as this has been found to provide good adhesion to the base of the microneedles so that substantially all microneedles are removed from the mould when the tape is pulled. The composition of the resulting microneedles is shown graphically in Fig. 1a. The mould may either be cast to match the desired size of each patch or may be made in a larger size, and individual patches of an appropriate size may be prepared by cutting the tape into pieces of a desired shape and size. The latter option may be as advantage when treating psoriasis as psoriasis plaques are often of different sizes and shapes.

The dried microneedle patches may be stored in a sealed airtight vial or blister pack, optionally together with an appropriate dessicant, to prevent absorption of water vapour during storage.

Further details of microneedle preparation and alternative embodiments are disclosed in WO 2012/153266 which is hereby incorporated by reference.

Embodiments

In the course of research leading to the present invention, a large number of different biodegradable polymers were tested for their suitability to form a matrix from which the microneedles could be made. The majority of the tested polymers were found to be unsuitable for the preparation of microneedles of the present invention either because the microneedles prepared from them did not retain their shape, in particular their sharp tip, i.e. they were not physically stable, or because the therapeutically active ingredient(s) were released unacceptably quickly from the polymer due to fast dissolution thereof, or because the therapeutically active ingredient(s) were found to be chemically unstable therein. Thus, microneedles made from polyvinylpyrrolidone and poly(meth)acrylates or mixtures of these polymers resulted in an unacceptably fast release of the active ingredient(s). Microneedles made from polyvinylpyrrolidone alone tended to soften or melt when removed from the primary packaging.

In the end, these various problems were solved by developing a microneedle composition comprising a drug-loaded tip portion containing a polylactic acid or a derivative thereof such as an ester-terminated polylactide, polyglycolic acid or a derivative thereof such as an ester-terminated polyglycolide or polylactic co-glycolic acid (PLGA) or a derivative thereof such as an ester-terminated polylactide co-glycolide polymer. Satisfactory results were also obtained when a water-soluble polymer such as polyvinylpyrrolidone was used as the backing layer. It has been found that when a polylactic acid, polyglycolic acid or polylactic co-glycolic acid polymer (or an ester-terminated derivative of these polymers) was employed it was possible to obtain a composition from the active ingredient(s) are released over a prolonged period of time such as at least two days. When polyvinylpyrrolidone was used as the backing layer, the resulting microneedles were found to be physically stable, with a hard, sharp tip.

In a particularly favoured embodiment, the biodegradable polymer is PLGA which may optionally be ester-terminated. The PLGA may favourably have a molecular weight of >5000, such as a molecular weight of 7000-17000, 24000-38000, 38000-54000, 54000-69000 or 76000-116000, resulting in a viscosity that permits the formulation to be dispensed into the mould and on drying provides a satisfactory physical stability, in particular a sharp tip. The ratio of lactic acid to glycolic acid may preferably vary between 85:15 and 50:50, such as 85:15, 82:18, 75:25, 65:35 or 50:50. A currently preferred ratio of lactide to glycolide is 50:50.

In some cases it may be preferred to add an antioxidant to the biodegradable polymer matrix, e.g. butylhydroxytoluene, butylhydroxyanisole or α -tocopherol, or a mixture thereof, so as to reduce the formation of degradation products of the active ingredient under oxidative conditions. The antioxidant may suitably be present in a concentration in the range of 0.01-3% w/w, preferably 0.03-2% w/w such as 0.05-1% w/w of the dry tip portion. A currently preferred antioxidant is butylhydroxytoluene, which may be added in a concentration in the range of 0.03-2% by weight, e.g. 0.05% by weight, of the dry tip portion.

The water-soluble polymer included in the backing layer may be any polymer that dissolves quickly in the skin after the composition has been applied and which is compatible with the other components. The water-soluble polymer may for instance be selected from the group consisting of polyvinylpyrrolidone, a sugar such as sucrose or trehalose, dextran, carboxymethylcellulose or sodium alginate. A currently preferred water-soluble polymer is polyvinylpyrrolidone. While generally the use of

polyvinylpyrrolidone confers favourable properties to the backing layer portion in terms of physical stability of the microneedles, it may be somewhat brittle and its properties may be improved by including a plasticizer, e.g. glycerol, polyethylene glycol, dibutyl sebacate, diethyl phthalate, triethyl glycerin or triethyl citrate, to reduce the brittleness.

- 5 The concentration of the plasticizer in the backing layer portion may suitably be in the range of 0.5-6% by weight of the dry backing layer. A currently favoured plasticizer to include in the backing layer portion of the microneedles is glycerol, which may suitably be present in a concentration of about 2% by weight of the dry backing layer. It should be noted that the residual solvent remaining in the backing layer after the composition
10 has been dried may also act as a plasticizer. An example of such a solvent is ethanol which may be present as a residue in the composition after drying.

- In a specific embodiment, the present composition may comprise an active ingredient in the backing layer of the water-soluble polymer. This will provide immediate (i.e. within 2
15 hours or preferably 1 hour) release of a portion of the active ingredient(s) administered to the patient. The active ingredient included in the backing layer may be the same or different from the active ingredient included in the tip portion of the microneedle.

- The active ingredient(s) included in the present composition may be active ingredient(s)
20 that are suitable for the treatment of skin conditions and where less frequent dosing (less than once a day) is perceived as advantageous by patients. The active ingredient may suitably be selected from the group consisting of a vitamin D analogue, a glucocorticoid receptor modulator, ingenol or an ingenol derivative, a calcineurin inhibitor, a JAK inhibitor, a PDE4 inhibitor, a non-steroidal anti-inflammatory agent, an
25 antibiotic, an antifungal agent or a local anesthetic, or mixtures thereof.

Examples of vitamin D analogues are calcipotriol, calcitriol, maxacalcitol or tacalcitol.

- Examples of glucocorticoid receptor modulators are corticosteroids such as amcinonide,
30 betamethasone, budenoside, clobetasol, clobetasone, cortisone, desonide, desoxycortisone, desoximethasone, dexamethasone, diflucortolon, diflorasone, flucortisone, flumethasone, flunisolide, fluocinonide, fluocinolone, fluorometholone, fluprednisolone, flurandrenolide, fluticasone, halcinonide, halobetasol, hydrocortisone, meprednisone, methylprednisone, mometasone, paramethasone, prednicarbate,
35 prednisone, prednisolone and triamcinolone or a pharmaceutically acceptable ester or acetone thereof. The corticosteroid may preferably be selected from betamethasone, budenoside, clobetasol, clobetasone, desoximethasone, diflucortolon, diflorasone,

fluocinonide, fluocinolone, halcinonide, halobetasol, hydrocortisone, mometasone prednicarbate, or triamcinolone or a pharmaceutically acceptable ester thereof. The corticosteroid ester may for instance be betamethasone acetate, betamethasone dipropionate, betamethasone valerate, clobetasol propionate, dexamethasone acetate, 5 flumethasone pivalate, fluticasone propionate, hydrocortisone acetate, hydrocortisone butyrate or mometasone furoate. The acetonide may be selected from fluocinolone acetonide or triamcinolone acetonide.

An example of an ingenol derivative is ingenol mebutate.

10 Examples of calcineurin inhibitors are tacrolimus or pimecrolimus.

An example of a JAK inhibitor is tofacitinib.

15 Examples of PDE4 inhibitors are apremilast, roflumilast or cilomilast.

Examples of non-steroidal anti-inflammatory agents are ibuprofen, diclofenac, naproxen, indomethacin, dexibuprofen, ketoprofen, flurbiprofen, piroxicam, tenoxicam, lornoxicam or nabumeton.

20 Examples of antibiotics are fusidic acid or mupirocin.

Examples of local anesthetics are lidocain, bupivacain, mepivacain or ropivacain.

25 Examples of antifungal agents are ketoconazole, terbinafine, miconazole, clotrimazole, ciclopirox, bifonazole, nystatin, econazole or amorolfine.

The therapeutically active ingredient may also be selected from antiproliferative agents such as methotrexate or immunosuppressants such as cyclosporin.

30 In another aspect, the present invention relates to a method for treating a skin condition comprising

(a) applying a patch composition comprising one or more microneedles as described herein on a surface area of the skin of a patient in need of treatment,

35 (b) exerting sufficient force on the patch composition to permit the microneedles to penetrate through the stratum corneum and into the viable layers of the skin, and

(c) removing the adhesive substrate from the patch composition.

To prevent the microneedles from breaking on insertion into the skin, the mechanical strength of the microneedles should be such that the force required to fracture the microneedle is significantly greater than the force required to insert the microneedle into the skin. Generally, the force required to insert a microneedle patch into the skin and have it penetrate past the stratum corneum is in the range of 0.4-8N, for instance 2-7N, such as 5N, per patch containing 25 microneedles per cm². The failure force of the microneedle can be assessed as either a fracture force or the force required to compress the microneedle by a defined length. These forces can be determined using a texture analyser (e.g. a TA.XT Plus Texture Analyzer, Stable Micro Systems, Surrey, UK) or using a computer-controlled force-displacement station (Model 5565, Instron, Buckinghamshire, UK).

As indicated above, the backing layer comprising the water-soluble polymer starts dissolving upon insertion of the microneedles into the skin. This allows removal of the substrate within about 120 minutes, preferably within 60 minutes or 45 minutes or even as little as about 15 minutes, of application of the patch on skin. In general, it is preferred that at least 90% of the microneedles detach from the adhesive surface upon removal of the substrate within this timeframe to avoid that a substantial number of the microneedles are pulled out again when the substrate is peeled off.

The invention has been found able to provide delivery of the therapeutically active ingredients over a prolonged period of time. Thus, the therapeutically active ingredients may be released from the microneedles over a period of 2-21 days, preferably 2-14 days such as 2-7 days or 4-7 days. As shown in Example 2 below, increased mRNA levels of the biomarker CYP24A1 are observed 4 days after application of a microneedle patch containing calcipotriol indicating that calcipotriol is released from the microneedles for at least 4 days.

In the present method, step (b) may be carried out by applying pressure with a finger or by impact insertion, e.g. by using an applicator device, the latter being preferred as it increases insertion reproducibility (cf. van der Maaden et al., AAPS Journal 16(4), July 2014, pp. 681-684. Examples of applicator devices are disclosed in US 2002/0123675 or WO 2008/091602.

Skin conditions to be treated using the microneedle patch composition of the invention may be selected from psoriasis, e.g. plaque psoriasis, inverse psoriasis, nail psoriasis or

spot psoriasis, pustulosis palmoplantaris, actinic keratosis, squamous cell carcinoma, basal cell carcinoma, contact dermatitis, atopic dermatitis, eczema, hand eczema, warts, genital warts, alopecia, acne, rosacea or skin infections.

- 5 Psoriasis is a chronic inflammatory skin disease that manifests as erythematous, dry, scaling plaques resulting from hyperkeratosis. The plaques are most often found on the elbows, knees and scalp, though more extensive lesions may appear on other parts of the body, notably the lumbosacral region. A common treatment of mild to moderate psoriasis involves topical application of a composition containing a corticosteroid as the
- 10 active ingredient. While efficacious, application of corticosteroids has the disadvantage of a number of adverse effects such as skin atrophy, striae, acneiform eruptions, perioral dermatitis, overgrowth of skin fungus and bacteria, hypopigmentation of pigmented skin and rosacea.
- 15 Combination products for the treatment of psoriasis have been marketed by LEO Pharma for a number of years under the trade names Daivobet® ointment and Daivobet® gel. The product comprises calcipotriol and betamethasone dipropionate as the active ingredients formulated in an ointment or gel vehicle comprising polyoxypropylene stearyl ether as a solvent. While the efficacy of the combination products is significantly superior
- 20 to that of either active ingredient on its own, the products need to be applied once daily, and many patients, in particular those with extensive psoriatic lesions, would favour a greater ease of application such as less frequent application. It is considered desirable to further improve the biological efficacy of the combination of the two active ingredients by providing a formulation vehicle from which delivery of the active ingredients into the
- 25 skin is prolonged compared to the commercial product.

- Thus, in a currently favoured embodiment, the present invention relates to a microneedle patch composition comprising one or more microneedles each comprising
- 30 (a) a tapered tip portion containing one or more therapeutically active ingredients selected from the group consisting of calcipotriol and betamethasone esters dispersed in a matrix of a biodegradable polymer selected from the group consisting of ester-terminated polylactide, ester-terminated polyglycolide and ester-terminated polylactide co-glycolide, and
- (b) a fast dissolving microneedle backing layer portion containing a water-soluble
- 35 polymer overlaying the tip portion, said microneedle or microneedles being attached to and extending from an adhesive surface of a removable substrate.

In this embodiment, the betamethasone ester may be betamethasone dipropionate or betamethasone valerate. The prolonged delivery is expected to be sustained with a dose of calcipotriol of 0.08-30 μg of calcipotriol per cm^2 of patch and a dose of betamethasone ester of 1-60 μg of betamethasone ester per cm^2 of patch. The betamethasone ester is preferably betamethasone dipropionate.

During development of this embodiment it was found that calcipotriol was not chemically stable in a matrix of polylactic acid, polyglycolic acid or polylactic co-glycolic acid, probably due to the presence of acidic residues or impurities therein, while calcipotriol was chemically stable when ester-terminated polylactide, polyglycolide or polylactide co-glycolide were used as the biodegradable polymer.

In this embodiment, the biodegradable polymer is preferably an ester-terminated polylactide co-glycolide. The ester-terminated polylactide co-glycolide may favourably have a molecular weight of >5000 , such as a molecular weight of 7000-17000, 24000-38000, 38000-54000, 54000-69000 or 76000-116000, resulting in a viscosity that permits the formulation to be dispensed into the mould and on drying provides a satisfactory physical stability, in particular a sharp tip. The ratio of lactide to glycolide may preferably vary between 85:15 and 50:50, such as 85:15, 82:18, 75:25, 65:35 or 50:50. A currently preferred ratio of lactide to glycolide is 50:50.

In this embodiment, it may be preferred to add an antioxidant to the biodegradable polymer matrix, e.g. butylhydroxytoluene, butylhydroxyanisole or α -tocopherol, or a mixture thereof, so as to reduce the formation of MC 1046. The antioxidant may suitably be present in the concentration of the antioxidant is in the range of 0.03-3% w/w, preferably 0.05-2% w/w such as 0.05-1% w/w of the dry tip portion. A currently preferred antioxidant is butylhydroxytoluene, which may be added in a concentration in the range of 0.05-2% by weight of the dry tip portion.

In this embodiment, the water-soluble polymer may for instance be selected from the group consisting of polyvinylpyrrolidone, a sugar such as sucrose or trehalose, dextran, carboxymethylcellulose and sodium alginate. A currently preferred water-soluble polymer is polyvinylpyrrolidone. The backing layer portion may additionally comprise a plasticizer, e.g. glycerol, polyethylene glycol, dibutyl sebacate, diethyl phthalate, triethyl glycerin or triethyl citrate, which may be included in a concentration in the range of 0.5-6% by weight of the dry backing layer. A currently favoured plasticizer to include in the

backing layer portion of the microneedles is glycerol, which may suitably be present in a concentration of about 2% by weight of the dry backing layer.

In a specific embodiment, the present composition may comprise calcipotriol and/or a
5 betamethasone ester dispersed in the backing layer of the water-soluble polymer.

In this embodiment, the removable substrate may suitably be composed of adhesive medical tape.

10 The invention is further described in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXAMPLES

15 **Example 1**

Compositions of the invention

A microneedle mould was prepared by mixing about 45 g of polydimethylsiloxane (PDMS) elastomer base (Sylgard 184 silicone elastomer kit, part A) and about 4.5 g of
20 curing agent (Sylgard 184 silicone elastomer kit, part B) by hand using a spatula and beaker until thoroughly mixed. The resulting mixture was placed in a desiccator under vacuum for about 20 minutes. The PDMS was poured over a microneedle template (patterned silicon wafer obtained from the Tyndall National Institute, Ireland, and prepared essentially as disclosed in US 2007/0134829) and cured in a drying oven at
25 100°C for about 60 minutes. After cooling, the mould was peeled off the microneedle template and cut into individual moulds of 1x1 cm (containing 5x5 microdepressions).

The PDMS moulds were placed in a glass beaker and cleaned with dimethylformamide (DMF) under vacuum for 30 minutes and an ultrasonic bath for further 30 minutes at
30 room temperature. The cleaned moulds were placed in a glass beaker and the microdepressions were prefilled with DMF under vacuum.

A solution was prepared by dissolving 300 mg ester-terminated polylactide co-glycolide (lactide:glycolide 50:50, Mw 7000-17000, PLGA-E) in 1 ml DMF using a vortex mixer for
35 about 10 minutes until the PLGA-E was completely dissolved. In some embodiments, 0.5 mg/ml butylhydroxytoluene (BHT) was added to the PLGA-E solution. 20 mg calcipotriol and 40 mg betamethasone dipropionate (BDP) were dissolved in 1 ml of the resulting

solution using a vortex mixer for about 10 minutes until the active ingredients were completely dissolved. The drug-loaded PLGA-E solution was dispensed into the microdepressions of the PDMS moulds prefilled with DMF using a syringe pump and capillary tube dispenser and a flow rate of 0.5 µl/min. to a total volume of 0.15±0.03 µl per mould.

The moulds were dried for about 18 hours in a desiccator under vacuum and subsequently in a vacuum oven under 500 mbars for about 5 hours at 60±2°C.

A second solution was prepared by dissolving 400 mg of polyvinylpyrrolidone (PVP, Kollidon® 17 PF) in 1 ml of ethanol 96% using a vortex mixer for about 5 minutes. 10 mg of glycerol was added and the mixture was stirred for 2-3 minutes using the vortex mixer. The PVP solution was dispensed into the microdepressions of the PDMS moulds containing the dried drug-loaded PLGA-E solution using a syringe pump and capillary tube dispenser at a flow rate of 1.5 µl/min. so that the dispensed volume was 0.75±0.15 µl per mould.

The filled moulds were dried in a desiccator under vacuum for about 2 hours.

Medical adhesive tape (3M) was applied on the surface of the moulds using finger pressure and the microneedles were pulled out of the mould.

The patches were stored in hermetically sealed vials purged with nitrogen and closed with a rubber stopper, aluminium cap and crimper.

The dried microneedle patch has the following composition.

Ingredient	µg/patch	% w/w	mg/g
Betamethasone dipropionate	6	1.66	16.60
Calcipotriol monohydrate	3	0.83	8.30
PLGA-E	45	12.45	124.48
PVP	300	82.99	829.88
Glycerol 99.5%	7.5	2.07	20.75
Total	378.82	100	1000

Physical and chemical stability of the composition appears from the following table. It should be noted that storage of the microneedle patches at 40°C, which is the usual

temperature for accelerated stability studies, was not feasible since PLGA-E is not physically stable at 40°C.

Storage temperature/ time	Appearance	Calcipotriol % of start	24-epi- calcipotriol % area	MC1046 % area	BDP % of start
Start	OK	100.0 %	0.8 %	1.2 %	100.0 %
25°C/ 1 month	OK	95.5 %	1.0 %	1.5 %	98.3 %
25°C/ 3 months	Not evaluated	116.4 %	0.7 %	2.1 %	118.6 %
40°C/ 2 weeks	Not acceptable	95.5 %	0.9 %	Not evaluated	101.7 %

- 5 Microneedle patch compositions were prepared as described above with the exception that they contained 0%, 0.5% or 1% BHT by weight of the dry tip.

The results are shown in Fig. 3 which illustrates the percentage ratio of peak area of the degradation product MC 1046 to the total calcipotriol peak area for samples without BHT and samples with 0.5% w/w and 1% w/w BHT. The percentage peak area of MC 1046 relative to the total amount of calcipotriol was significantly reduced, indicating that the addition of BHT to the composition significantly reduced degradation of calcipotriol.

Example 2

15 Human explant skin exposure

Two experiments were performed to investigate exposure over time in human skin explants.

20 Experiment 1:

Full-thickness human skin obtained from female donors undergoing abdominoplasty maximally 24 hours prior to the start of the experiment was used. 22 mm punch biopsies were placed in 24 mm Transwell® inserts and placed in 6 well plates with 1 ml EpiLife® tissue culture medium supplemented with 0.2 ng/mL human EGF, 0.2 % bovine pituitary extract (BPE), 5 µg/mL bovine insulin, 5 µg/mL bovine transferrin, 0.18 µg/mL hydrocortisone and gentamycin.

Compositions prepared as described in Example 1 containing 2 µg calcipotriol and 6 µg BDP per cm² microneedle patch and 10 µl Daivobet[®] gel per cm² and Daivobet[®] gel vehicle were applied topically in triplicate. The following treatment schedules were tested: One dose of Daivobet[®] gel at t=0h with skin sampling at 24h and 48h. Two doses of Daivobet[®] gel at t=0 and 24h respectively with skin sampling at 48h, one patch applied at t=0h with skin sampling at 24h and 48h leaving the backing tape on the skin for the full duration of the experiment, and one patch applied at t=0h with skin sampling at t=48h but removing the backing tape at 24h. The skin biopsies were maintained in *ex vivo* culture at 37°C with 5% CO₂ for 48 hours with a change of medium at 24 h. At the end of the experiment, a 14 mm biopsy encompassing the dosed area of each explant was punched out and subsequently divided in two for compound analysis (tapestripped 10 times) and biomarker analysis, respectively.

Compound analysis was performed by extracting the active compounds from the skin biopsy using an organic solvent and subsequently analysing the extract using LC/MS-MS.

Total RNA was extracted from cells using the mirVana (Life Technologies, Grand Island, NY, USA) according to the instructions provided. cDNA synthesis was performed with the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA). 2.5 µL of cDNA (equivalent to 5 ng RNA) from each sample was amplified in a total volume of 10 µL by quantitative realtime PCR using Taqman Gene Expression Assays (CYP24A1 (Hs00167999_m1), CD14 (Hs02621496_s1), PPIA (Hs99999904_m1) GAPDH (Hs99999905_m1), TBP (Hs99999910_m1) and HMBS (Hs00609297_m1)) and PRISM7900HT sequence detection system (SDS 2.3) from Applied Biosystems. PPIA, GAPDH, TBP and HMBS were used for normalization.

It appears from Fig. 4 that after application BDP could reside either inside microneedle patch compositions or in the stratum corneum of the skin after Daivobet[®] gel applications and thus be unavailable for pharmacological action. B-17-P is predominantly formed in biological matrices and is thus considered a surrogate marker of BDP available for pharmacological action in skin. It appears that the amount of B-17-P formed in the skin increases over time for both explants treated with Daivobet[®] gel and with microneedle patch compositions of the invention. The skin concentrations of B-17-P observed after application of Daivobet[®] gel are higher than what was observed after application of microneedle patch compositions of the invention, however the increase over time may indicate a prolonged release from the patches.

It appears from Figs. 5(a) and 5(b) that the PD biomarkers for calcipotriol, CYP24A1 and CD14, are induced over time by Daivobet® gel. The level of biomarker induction elicited by microneedle patches is lower, but increasing over time, indicating a slower onset but potentially a prolonged effect of calcipotriol than what is observed from Daivobet® gel.

5

Experiment 2:

NativeSkin®Plus skin models with an available surface area of 2.5 cm² were acquired from Genoskin, France and cultured according to the manufacturer's specification. Compositions prepared as disclosed in Example 1 containing 0.5 µg calcipotriol and 6 µg BDP per cm² microneedle patch and 4.3 µl Daivobet® gel per cm² and Daivobet® gel vehicle were applied topically in triplicate. The following treatment schedules were tested: One daily dose of Daivobet® gel or placebo gel with skin sampling at 24h and 96h. One patch applied at t=0h with skin sampling at 24h and 96h leaving the backing tape on the skin for 24h, and two patches applied at t=0h and t=48h with skin sampling at t=96h. At the end of the experiment, two 4 mm biopsies were punched out and subsequently either analysed for compound (after being tapestripped 10 times) or the presence of biomarker.

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It appears from Fig. 6(a) that the biomarker for calcipotriol, CYP24A1, is induced over time by Daivobet® gel applied at time 0, day 1 and day 2 of the experiment and sampled on day 4. The level of biomarker induction elicited by the microneedle patch applied once is initially lower (at day 1), but increases over time, indicating a slower onset but potentially a protracted effect of calcipotriol over 4 days compared to what is observed from Daivobet® gel.

30

It appears from Fig. 6b that the amount of B-17-P formed in the skin increases over time for both explants treated with Daivobet® gel and with a microneedle patch composition of the invention. The skin concentrations of B-17-P observed after application of Daivobet® gel applied at time 0, day 1 and day 2 of the experiment are higher on day 4 than concentrations observed after application once of a microneedle patch composition of the invention, however the increase over time may indicate a prolonged release from the patches.

Example 3

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Reflectance confocal microscopy of a microneedle composition in human explant skin

A microneedle patch as described in Example 1 was applied to fresh human ex vivo skin prepared as described in Example 2. 45 minutes after application the medical adhesive tape was removed and it was conformed that none of the microneedles was left on the tape before reflectance confocal microscopy (RCM) imaging was conducted using a

5 Vivascope 1500 multilaser system in accordance with the procedure described in H. Skvara et al. *Dermatol Pract Concept* 2(1), 2012, pp.3-12, and Calzavara-Pinton et al., *Photochemistry and Photobiology*, 84, 2008, pp.1421-30. In this technique laser light with a wavelength of 785 nm is passed through a beam splitter and an optical lens in contact with skin. In the skin, light is focused on a small tissue spot a few microns of

10 diameter. Reflection (back scattering) occurs at the boundary between two structures having different indexes of refraction. Light reflected from the focal point propagates back toward the lens through a pinhole. Light reflected from above and below the point in focus is masked out by the pinhole so that the detector receives light only from the thin plane of the specimen that is in focus. By changing the depth at which the objective

15 lens focuses in the vertical plane horizontal images can be generated at particular depths within the skin.

The scanned field of view was 500 x 500 μm . Depth measurements were done in steps of 3 μm with an axial resolution of < 5 μm . The limit of detection of the RCM is a depth

20 of about 150 μm .

The results appear from Fig. 7, in which

Fig. 7a shows a microneedle penetrating the stratum corneum at a depth of 12 μm . The PVP backing layer has dissolved before the removal of the substrate and only a thin

25 octagonal shell of the PLGA-E polymer reflects the light on this plane.

Fig. 7b shows a microneedle penetrating the stratum corneum at a depth of 27 μm . The PVP backing layer has dissolved before the removal of the substrate and only appears as a circle in the middle of a thin octagonal shell of the PLGA-E biodegradable polymer.

Fig. 7c shows a microneedle penetrating the stratum corneum at a depth of 45 μm . The

30 PLGA-E polymer microneedle tip reflects the light on this plane as does a thin octagonal shell of the PLGA-E polymer.

Fig. 7d shows a microneedle penetrating the epidermis at a depth of 96 μm . Only the tip of the needle composed of the PLGA-E biodegradable polymer is visible.

Fig. 7e shows a microneedle penetrating the epidermis at a depth of 150 μm . Only the

35 tip of the needle composed of the PLGA-E biodegradable polymer is visible at this depth.

CLAIMS

1. A microneedle patch composition comprising one or more microneedles each comprising
 - 5 (a) a tapered tip portion containing a therapeutically active ingredient dispersed in a matrix of a biodegradable polymer capable of providing sustained release of the therapeutically active ingredient over a period of at least two days after insertion of the microneedle or microneedles into the skin, and
 - (b) a fast dissolving microneedle backing layer portion containing a water-soluble
- 10 polymer overlayering the tip portion,
said microneedle or microneedles being attached to and extending from an adhesive surface of a removable substrate.
2. A patch composition according to claim 1 comprising 2-100 microneedles per cm²,
15 e.g. 5-75 microneedles, 10-50 microneedles, 15-30 microneedles or 20-25 microneedles per cm².
3. A patch composition according to claim 1 or 2, wherein the biodegradable polymer is polylactic acid or a derivative thereof such as an ester-terminated polylactide,
20 polyglycolic acid or a derivative thereof such as an ester-terminated polyglycolide, or polylactic co-glycolic acid or a derivative thereof such as an ester-terminated polylactide co-glycolide.
4. A patch composition according to any one of claims 1-3, wherein the biodegradable
25 polymer has a molecular weight of >5000, such as a molecular weight of 7000-17000, 24000-38000, 38000-54000, 54000-69000 or 76000-116000.
5. A patch composition according to claim 3 or 4, wherein the ratio of lactide to glycolide
30 is between 85:15 and 50:50, such as 85:15, 82:18, 75:25, 65:35 or 50:50.
6. A patch composition according to any one of claims 1-5, wherein the biodegradable polymer matrix further comprises an antioxidant, e.g. butylhydroxytoluene, butylhydroxyanisole or α -tocopherol, or a mixture thereof.
- 35 7. A patch composition according to claim 6, wherein the concentration of the antioxidant is in the range of 0.01-3% w/w, preferably 0.03-2% w/w such as 0.05-1% w/w of the dry tip portion.

8. A patch composition according to any one of claims 1-7, wherein the water-soluble polymer is selected from the group consisting of polyvinylpyrrolidone, a sugar such as sucrose or trehalose, dextran, carboxymethylcellulose and sodium alginate.

5

9. A patch composition according to claim 8, wherein the water-soluble polymer is polyvinylpyrrolidone.

10

10. A patch composition according to any one of claims 1-9, wherein the backing layer portion comprises a plasticizer, e.g. glycerol, polyethylene glycol, dibutyl sebacate, diethyl phthalate, triethyl glycerin or triethyl citrate.

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11. A patch composition according to claim 10, wherein the concentration of the plasticizer is in the range of 0.5-6% by weight of the dry backing layer.

12. A patch composition according to any one of claims 1-11, wherein the backing layer comprises a therapeutically active ingredient dispersed in the matrix of the water-soluble polymer.

20

13. A patch composition according to any one of claims 1-12, wherein the microneedles have a length of 50-1000 μm , e.g. 100-800 μm , 300-700 μm , 400-600 μm or about 500 μm .

25

14. A patch composition according to any one of claims 1-13, wherein the tip portion constitutes 5-95% of the total volume of the microneedle.

15. A patch composition according to any one of claims 1-14, wherein the substrate is composed of adhesive medical tape.

30

16. A patch composition according to any one of claims 1-15, wherein the backing layer portion overlayers the base of the tip portion in such a manner that each microneedle is separated from the other microneedles on the patch and forms a discrete entity when the substrate is removed upon application of the patch on the skin.

35

17. A patch composition according to any one of claims 1-16, wherein the microneedles are either conical or pyramidal thus comprising a number of longitudinally extending ridges to facilitate the insertion of the microneedles into the skin.

18. A patch composition according to claim 17, wherein the microneedles comprise 4-8 longitudinally extending edges.

19. A patch composition according to any one of claims 1-18, wherein the therapeutically active ingredient is selected from the group consisting of a vitamin D analogue, a glucocorticoid receptor modulator, ingenol or an ingenol derivative, a calcineurin inhibitor, a JAK inhibitor, a PDE4 inhibitor, a non-steroidal anti-inflammatory agent, an antibiotic, an antifungal agent or a local anesthetic, or mixtures thereof.

20. A patch composition according to any one of claims 1-19 comprising one or more microneedles each comprising

(a) a tapered tip portion containing one or more therapeutically active ingredients selected from the group consisting of calcipotriol and a betamethasone ester dispersed in a matrix of a biodegradable polymer selected from the group consisting of an ester-terminated polylactide, an ester-terminated polyglycolide and an ester-terminated polylactide co-glycolide, and

(b) a fast dissolving microneedle backing layer portion containing a water-soluble polymer overlaying the tip portion,

said microneedle or microneedles being attached to and extending from an adhesive surface of a removable substrate.

21. A patch composition according to claim 20, wherein the betamethasone ester is betamethasone dipropionate or betamethasone valerate, in particular betamethasone dipropionate.

22. A patch composition according to claim 20 or 21 comprising 0.08-30 μg of calcipotriol per cm^2 .

23. A patch composition according to any one of claims 20-22 comprising 1-60 μg of betamethasone dipropionate per cm^2 .

24. A patch composition according to any one of claims 20-23, wherein the biodegradable polymer is an ester-terminated polylactide co-glycolide.

25. A patch composition according to any one of claims 20-24, wherein the biodegradable polymer has a molecular weight of >5000 , such as a molecular weight of 7000-17000, 24000-38000, 38000-54000, 54000-69000 or 76000-116000.

5 26. A patch composition according to claim 24 or 25, wherein the ratio of lactide to glycolide is between 85:15 and 50:50, such as 85:15, 82:18, 75:25, 65:35 or 50:50.

27. A patch composition according to any one of claims 20-27, wherein the backing layer comprises calcipotriol and/or a betamethasone ester dispersed in the matrix of the
10 water-soluble polymer.

28. A patch composition according to any one of claims 20-27, wherein the water-soluble polymer is polyvinylpyrrolidone.

15 29. A method for treating a skin condition comprising
(a) applying a patch composition comprising one or more microneedles according to any one of claims 1-28 on a surface area of the skin of a patient in need of treatment,
(b) exerting sufficient force on the patch composition to permit the microneedles to penetrate through the stratum corneum and into the viable layers of the skin, and
20 (c) removing the adhesive substrate from the patch composition.

30. The method of claim 29, wherein the force required to insert the patch composition into the skin is in the range of 2-8N, for instance 5N, per patch containing 25 microneedles per cm^2 .

25 31. The method according to claim 29 or 30, wherein at least 90% of the microneedles detach from the adhesive surface of the substrate upon removal of the substrate within a period of 120 minutes, preferably within a period of 60 minutes.

30 32. The method according to any one of claims 29-31, wherein the therapeutically active ingredient is released from the microneedles over a period of 2-21 days, preferably 2-14 days such as 2-7 days.

33. The method according to any one of claims 29-32, wherein step (b) of the method of
35 claim 29 is carried out by applying pressure with a finger or by impact insertion, optionally using an applicator device.

34. The method according to any one of claims 29-33, wherein the skin condition is psoriasis, actinic keratosis, squamous cell carcinoma, basal cell carcinoma, contact dermatitis, atopic dermatitis, eczema, hand eczema, warts, genital warts, alopecia, acne, rosacea or skin infections.

Fig. 1a

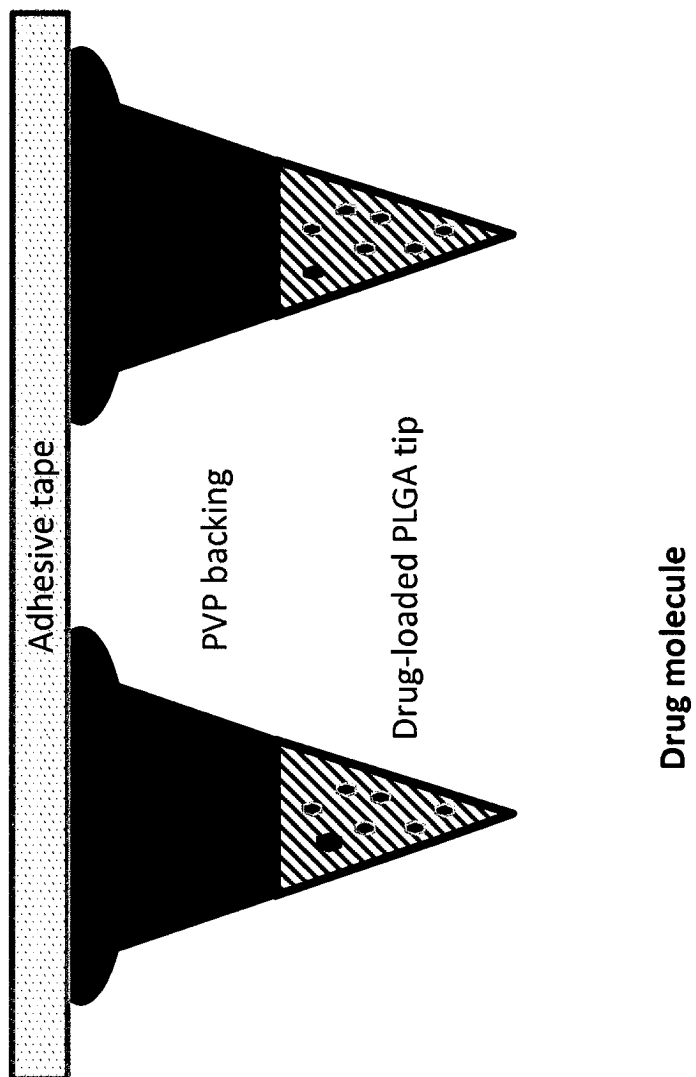


Fig. 1b

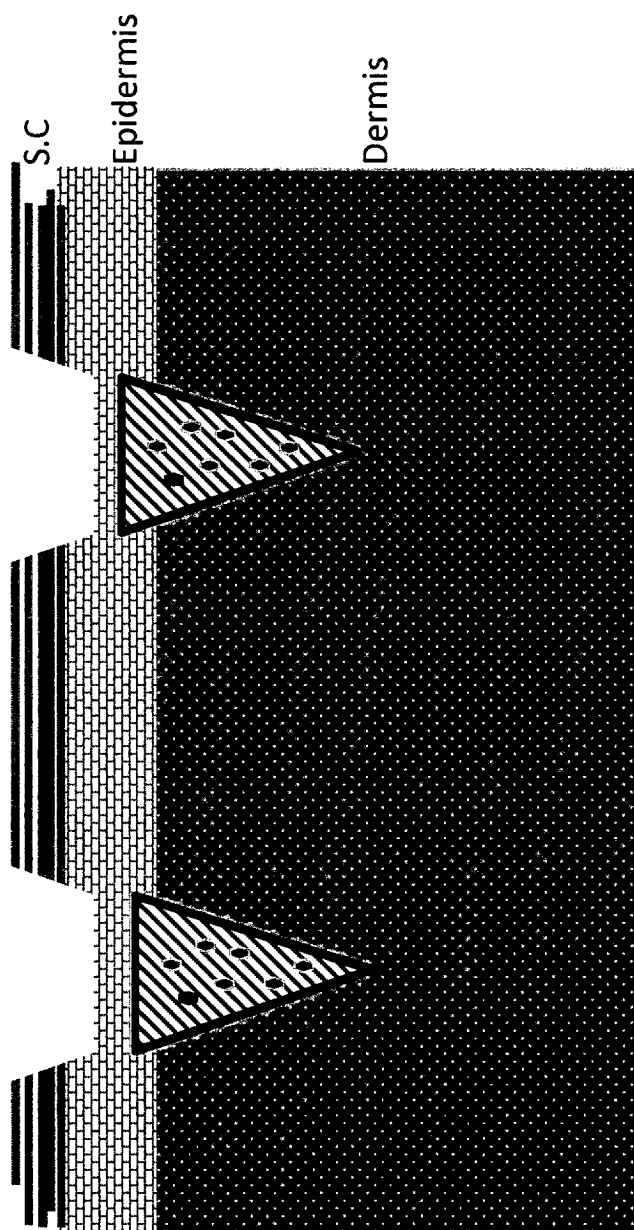
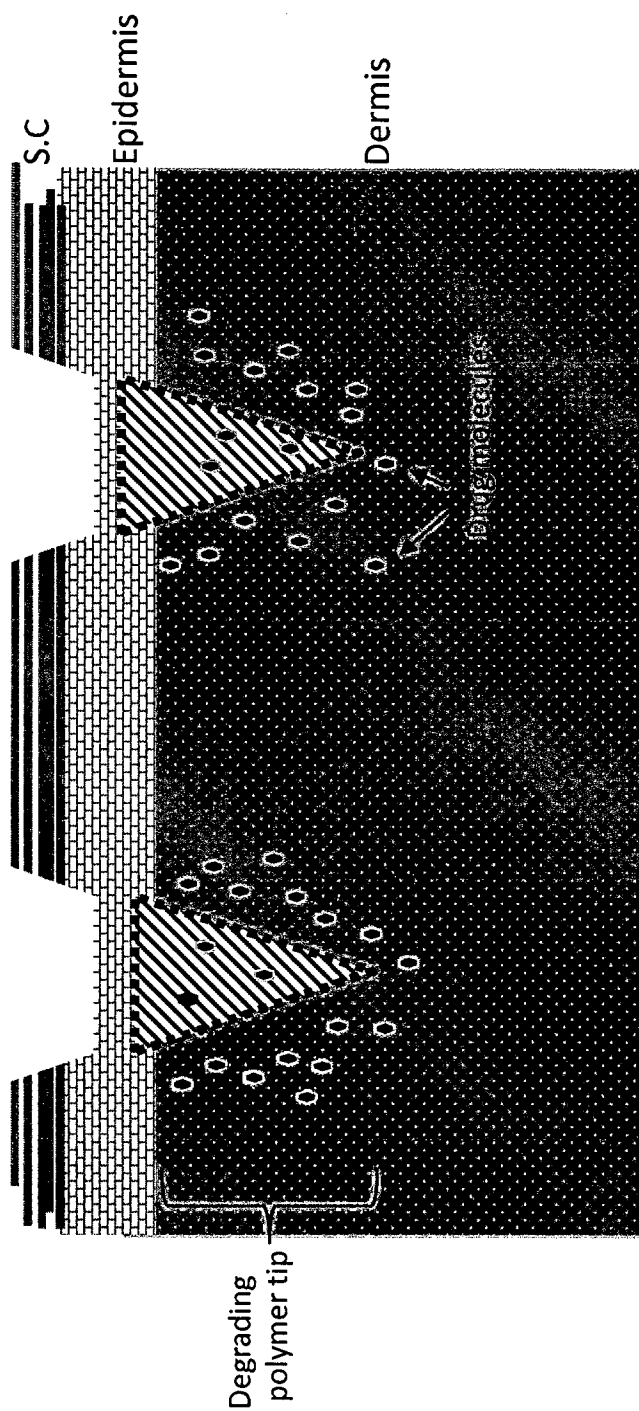


Fig. 1c



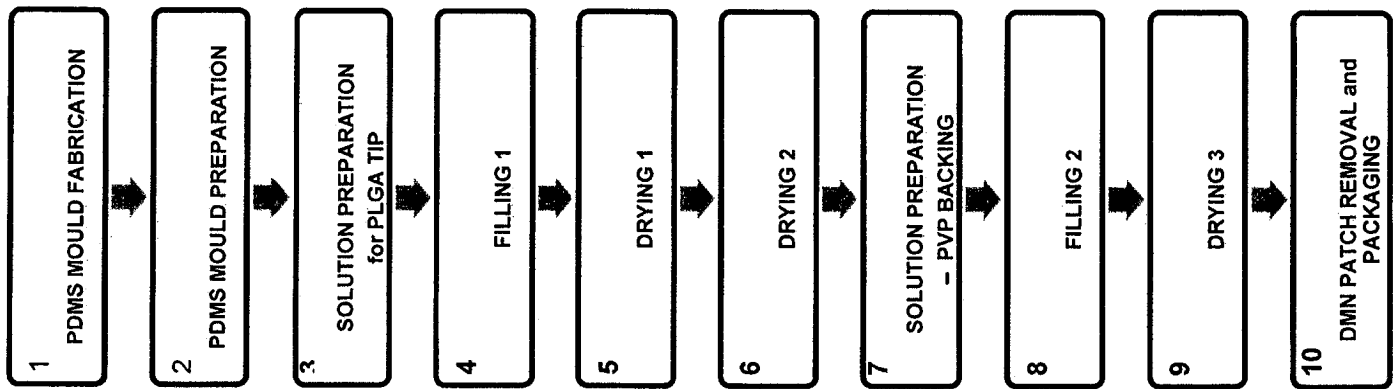


Fig. 2a

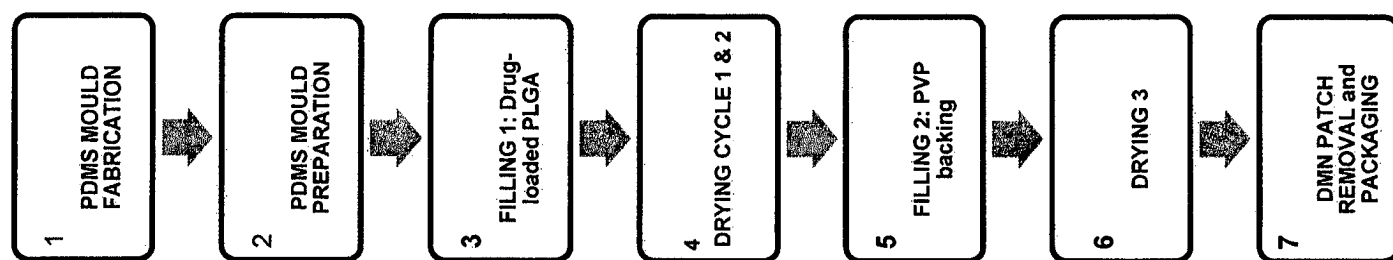


Fig. 2b

Fig. 3

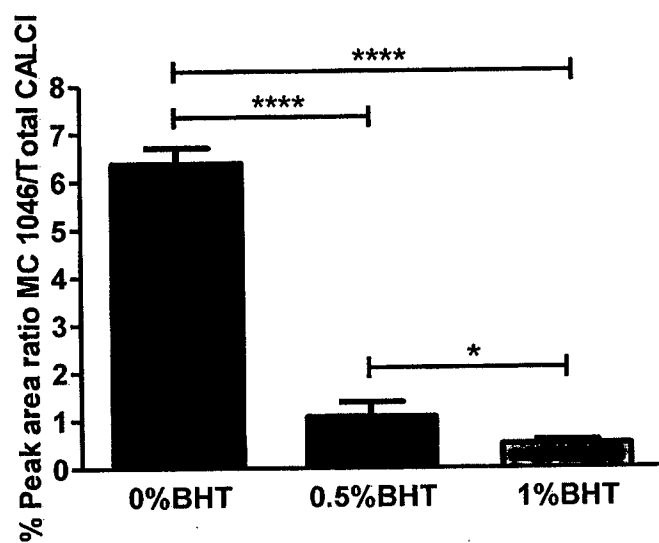


Fig. 4

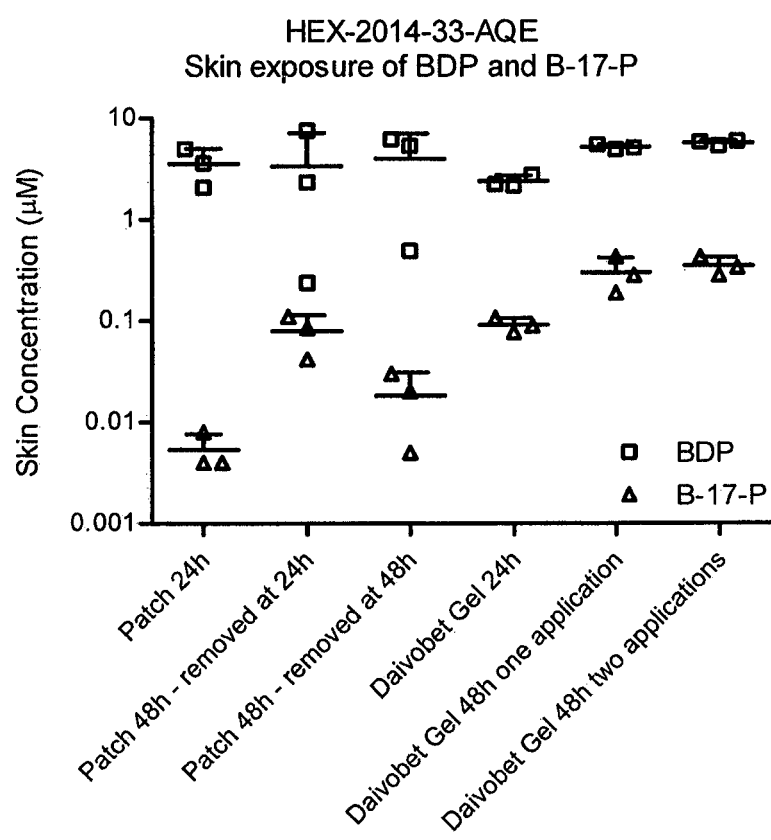


Fig. 5a

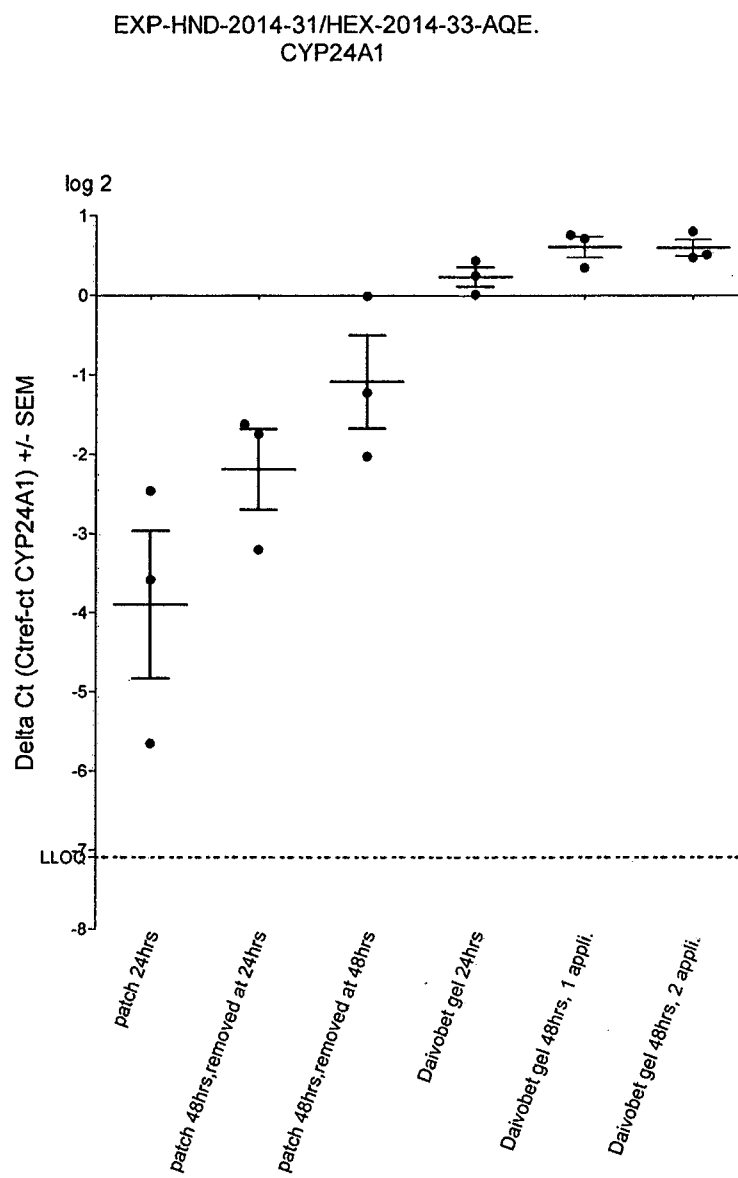


Fig. 5b

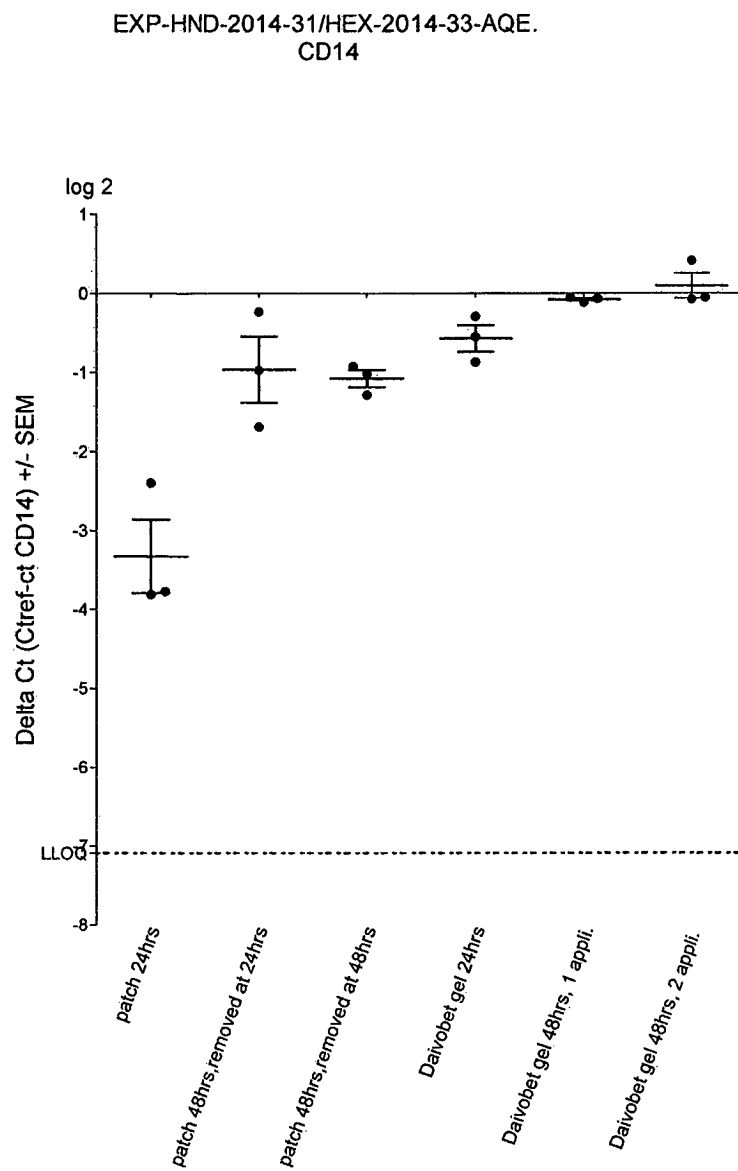


Fig. 6a

EXP-AQE-2015-17-HEX
qPCR - CYP24A1

Delta Ct (Ctref-ct CYP24A1) +/- SEM

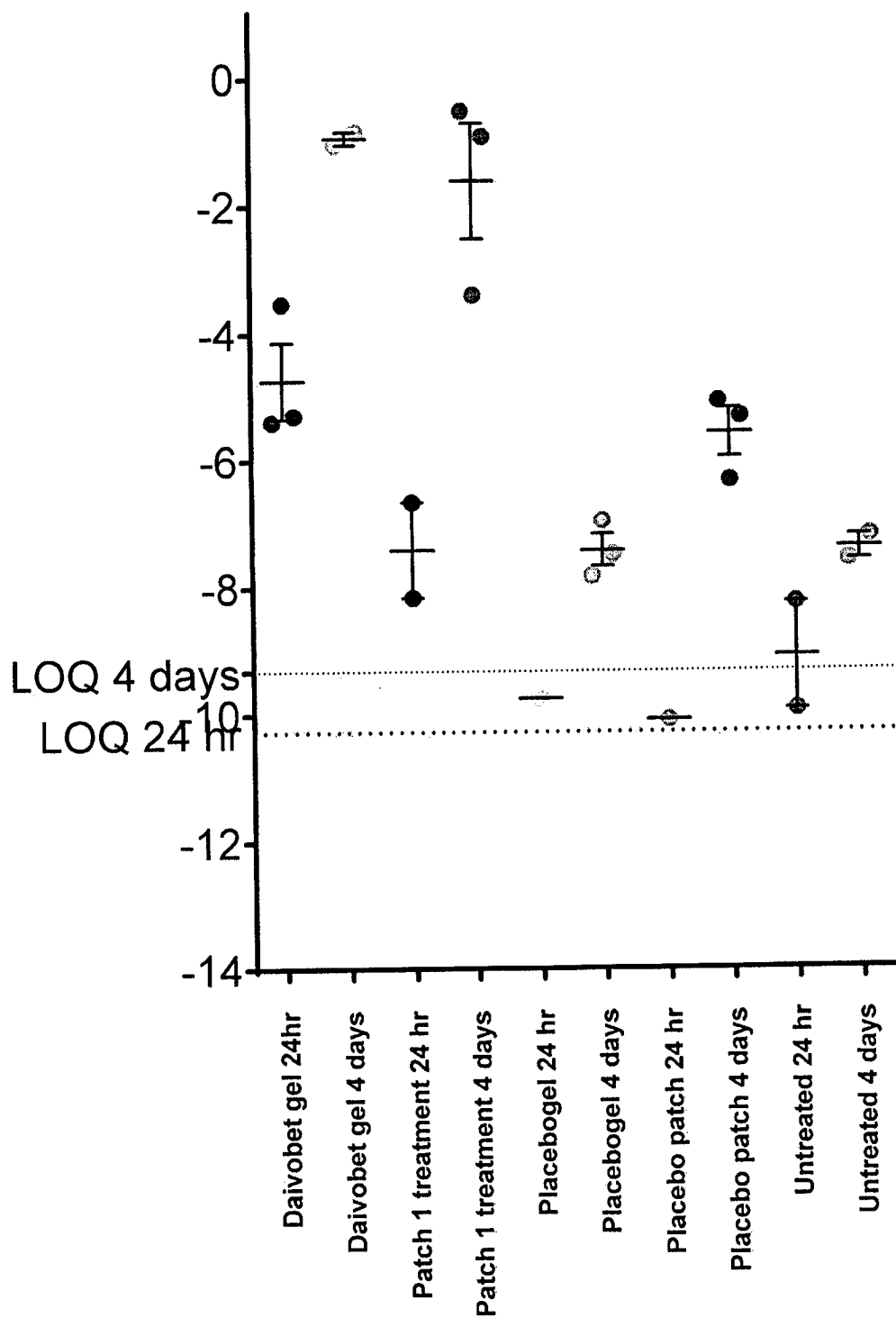


Fig. 6b

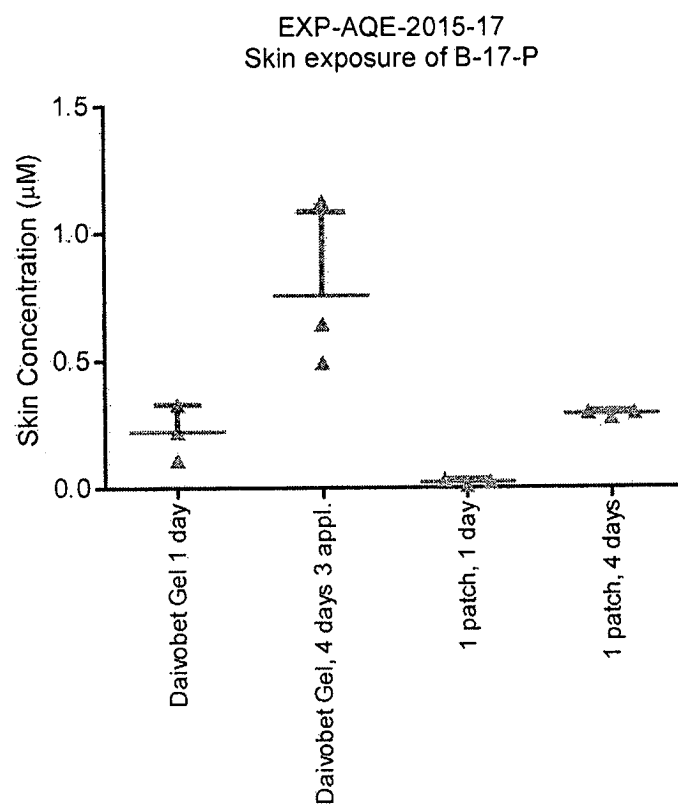


Fig. 7a

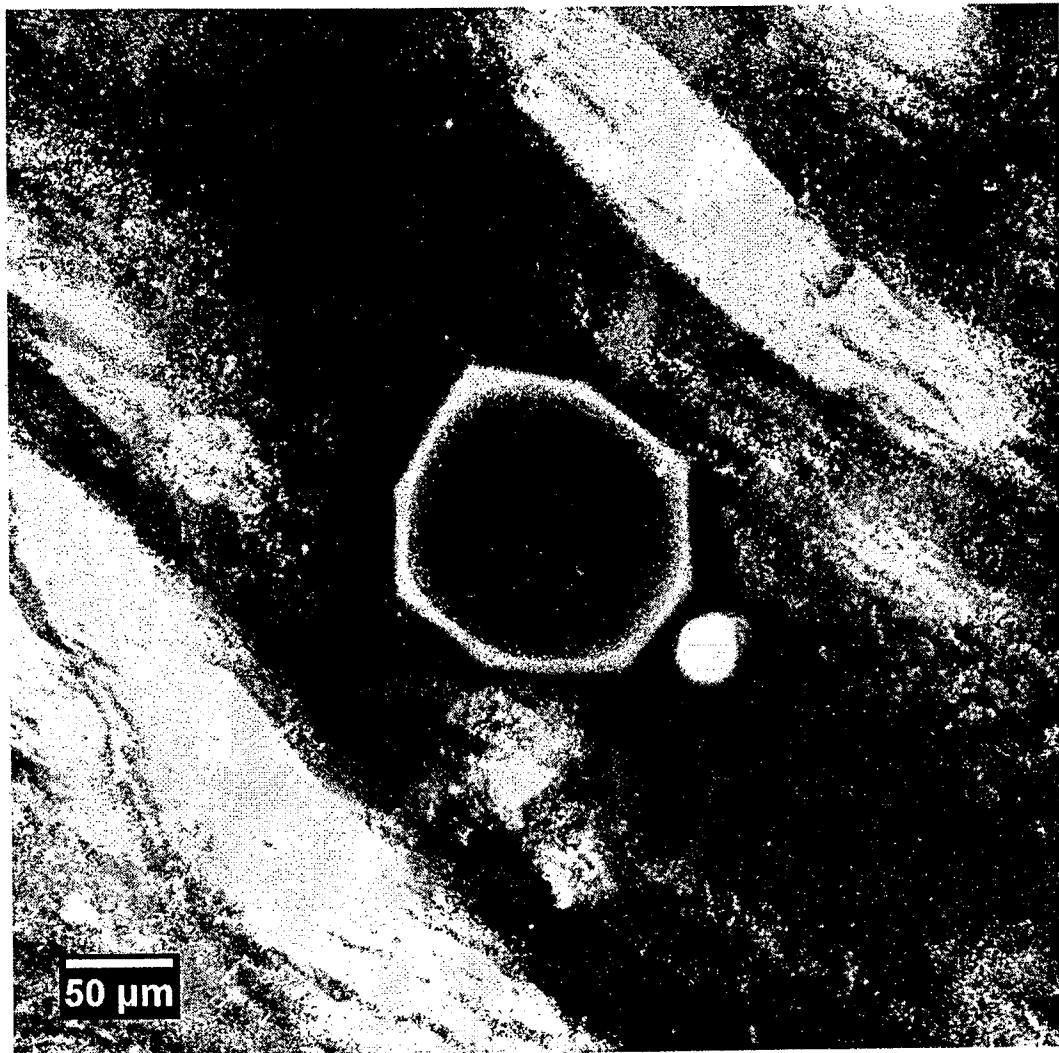


Fig. 7b

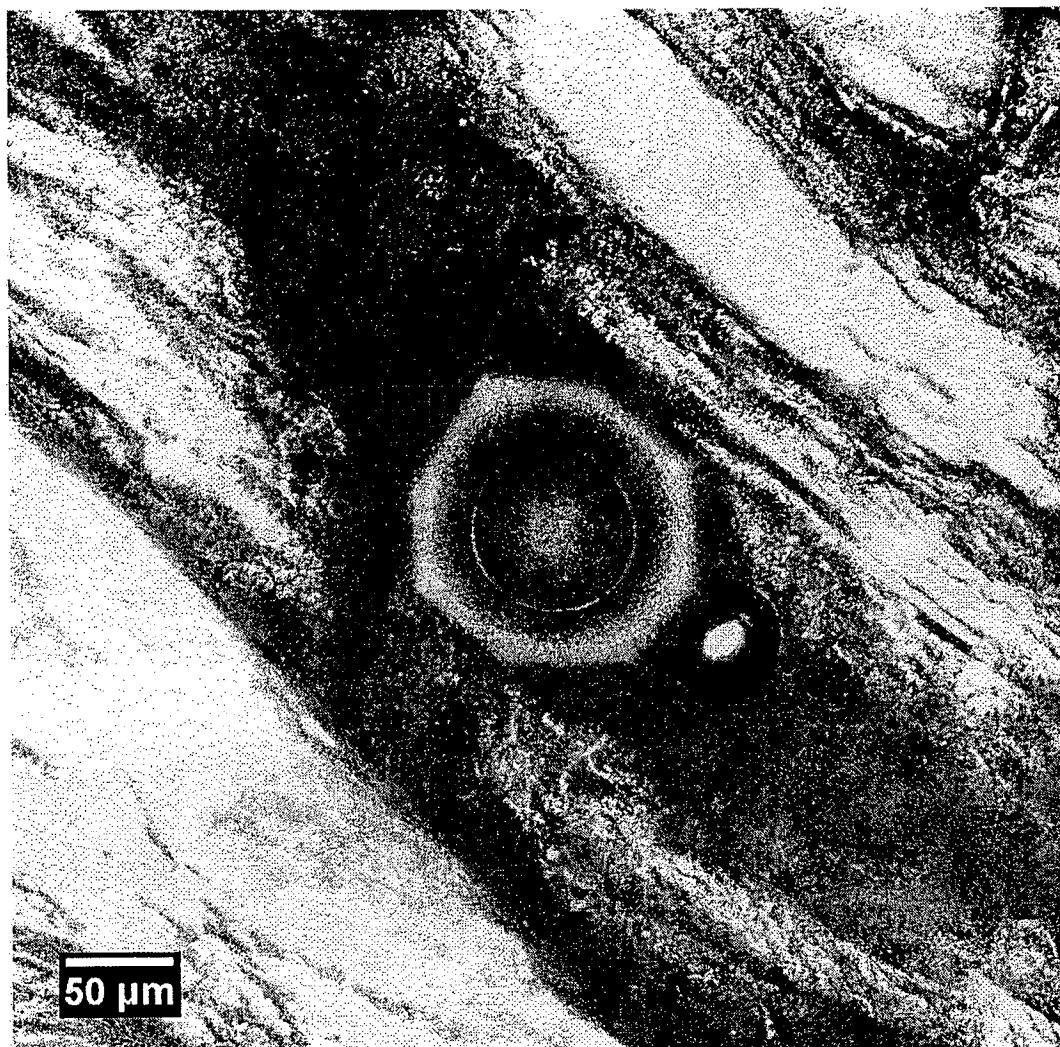


Fig. 7c

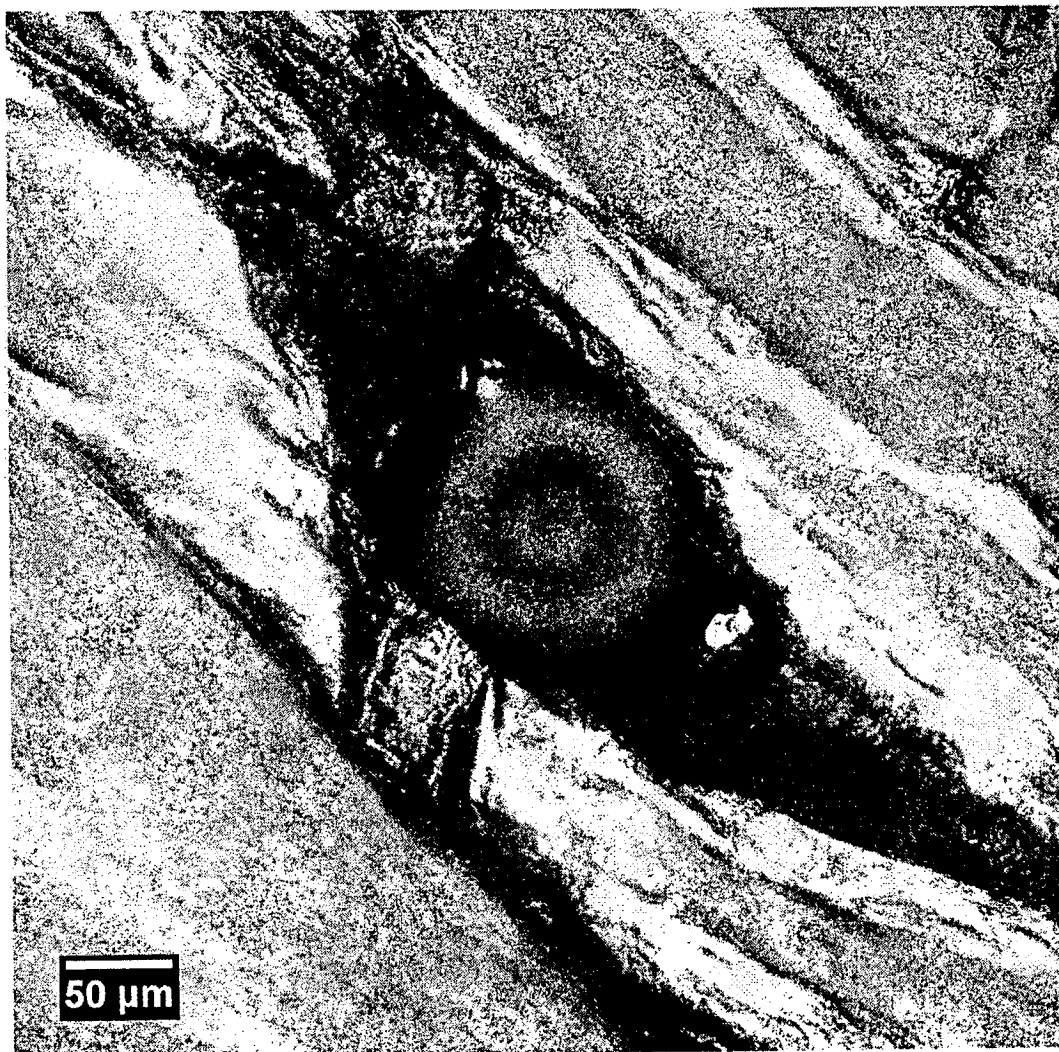


Fig. 7d

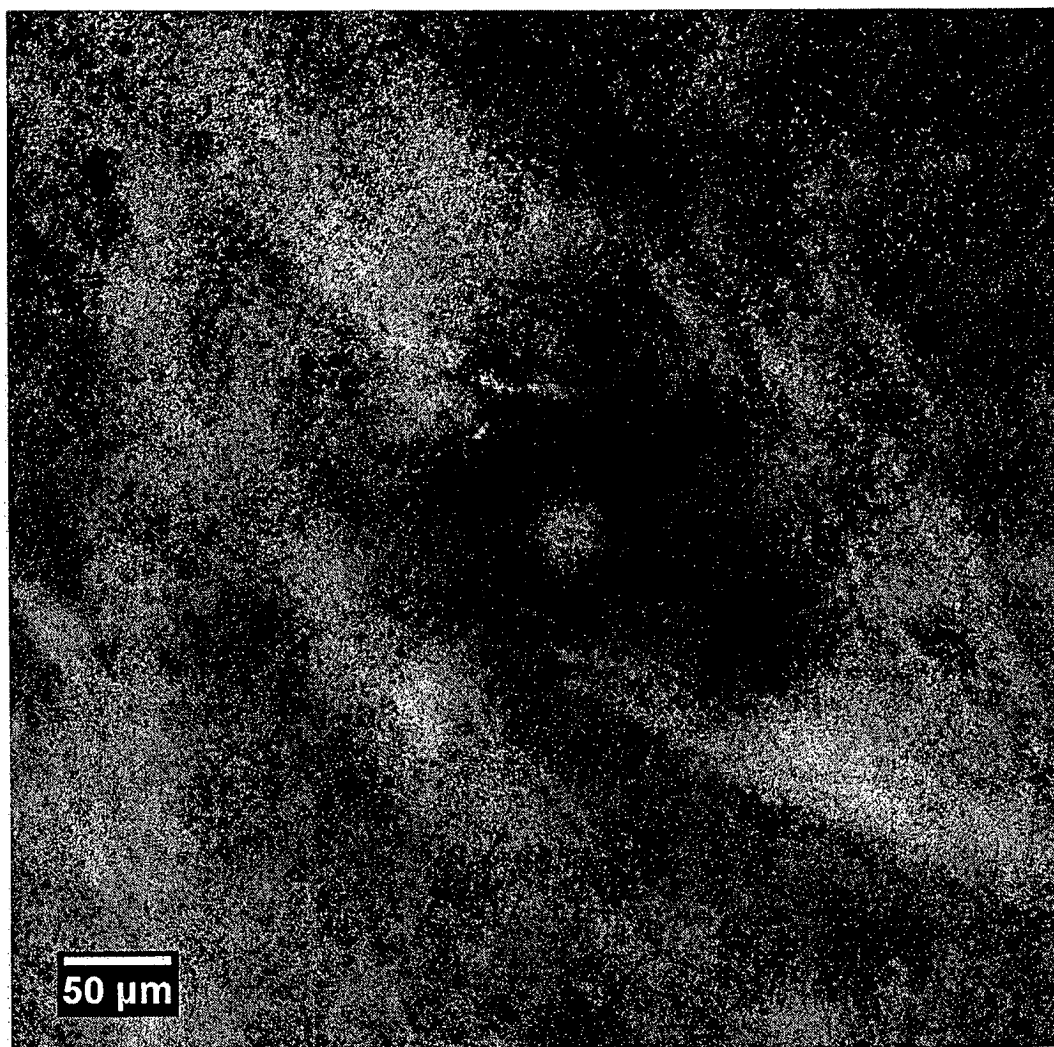
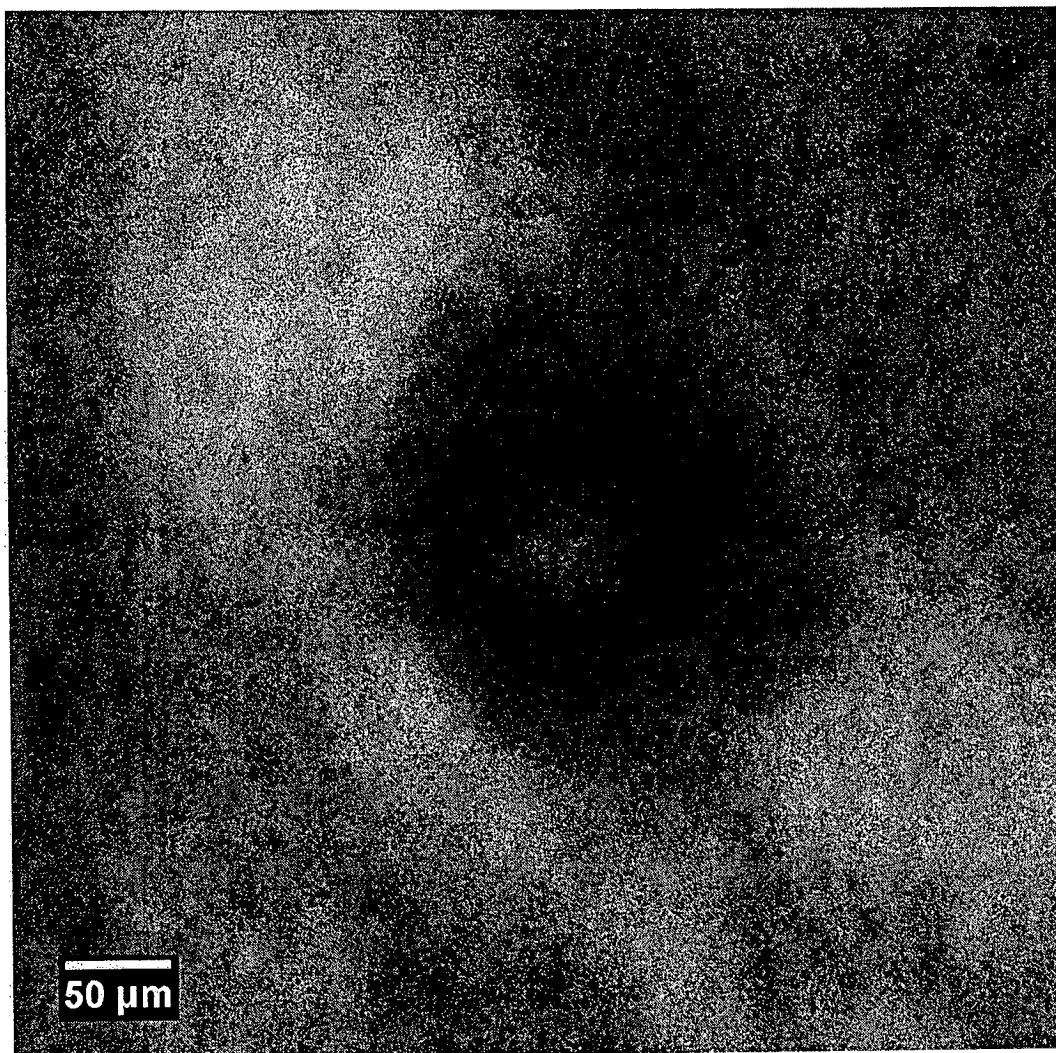


Fig. 7e



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/025026

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K31/593 A61K31/661
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 2014 200 648 A1 (CORIUM INT INC) 27 February 2014 (2014-02-27)	1-5,8, 13,14,16
Y	paragraph [0020] - paragraph [0022] paragraph [0089] examples 7-9 claims 1-11 figure 5b	1-34
Y	----- US 2011/276028 A1 (SINGH PARMINDER [US] ET AL) 10 November 2011 (2011-11-10) figure 9b paragraph [0012] - paragraph [0021] paragraph [0080] - paragraph [0084] examples 1-11 claims 1-18 ----- -/--	1-34

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

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 "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

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Date of the actual completion of the international search

6 June 2016

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Sindel, Ulrike

INTERNATIONAL SEARCH REPORT

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PCT/EP2016/025026

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/182306 A1 (LEE JEONG WOO [US] ET AL) 16 July 2009 (2009-07-16) paragraph [0060] paragraph [0072] examples 1-7 claims 1-29 -----	1-34
Y	WO 2012/066506 A2 (UNIV CORK [IE]; CREAN ABINA M [IE]; MCGRATH MARIE G [IE]; O'MAHONY CON) 24 May 2012 (2012-05-24) cited in the application page 5, line 16 - line 25 page 7, line 19 - line 20 page 17, line 31 - page 18, line 2 examples 2,3 claims 1-20 figures 4a,4b -----	1-34
Y	WO 00/64450 A1 (LEO PHARM PROD LTD [DK]; DIDRIKSEN ERIK [DK]; HOEY GERT [DK]) 2 November 2000 (2000-11-02) examples 1-3 claims 1-30 -----	1-34
A	US 2015/057505 A1 (BANGERA MAHALAXMI GITA [US] ET AL) 26 February 2015 (2015-02-26) example 2 -----	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/025026

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US 2015057505	A1	26-02-2015	NONE



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A·克莱恩

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11247

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A61K 47/32(2006.01)

A61K 47/36(2006.01)

A61K 47/38(2006.01)

A61P 17/06(2006.01)

A61P 17/00(2006.01)

A61P 35/00(2006.01)

A61P 31/20(2006.01)

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A·H·埃里克松 A·摩尔

S·乌森 C·欧苏利文

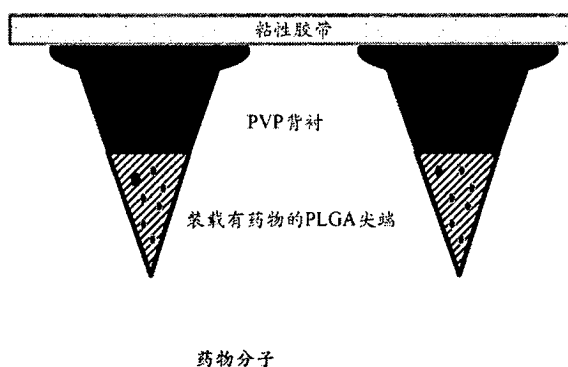
权利要求书3页 说明书13页 附图14页

(54)发明名称

用于向皮肤递送活性成分的微针贴片

(57)摘要

本发明涉及一种包括一个或多个微针的微针贴片组合物,所述微针各自包括:(a)含有分散在可生物降解聚合物的基质中的治疗活性成分的锥形尖端部分,其能够在将所述一个或多个微针插入皮肤中之后历经至少两天的时期提供所述治疗活性成分的持续释放,和(b)覆盖于所述尖端部分上的含有水溶性聚合物的快速溶解性微针背衬层部分,所述一个或多个微针被附着于可移除基底的粘性表面并从所述粘性表面延伸。



1. 一种包括一个或多个微针的微针贴片组合物,所述微针各自包括

(a) 含有分散在可生物降解聚合物的基质中的治疗活性成分的锥形尖端部分,其能够在将所述一个或多个微针插入皮肤中之后历经至少两天的时期提供所述治疗活性成分的持续释放,和

(b) 覆盖于所述尖端部分上的含有水溶性聚合物的快速溶解性微针背衬层部分,所述一个或多个微针被附着于可移除基底的粘性表面并从所述粘性表面延伸。

2. 根据权利要求1所述的贴片组合物,其包括2-100个微针/cm²,例如5-75个微针/cm²、10-50个微针/cm²、15-30个微针/cm²或20-25个微针/cm²。

3. 根据权利要求1或2所述的贴片组合物,其中所述可生物降解聚合物是聚乳酸或其衍生物诸如酯封端的聚丙交酯、聚乙醇酸或其衍生物诸如酯封端的聚乙交酯、或聚乳酸共乙醇酸或其衍生物诸如酯封端的聚丙交酯共乙交酯。

4. 根据权利要求1-3中任一项所述的贴片组合物,其中所述可生物降解聚合物具有>5000的分子量,诸如7000-17000、24000-38000、38000-54000、54000-69000或76000-116000的分子量。

5. 根据权利要求3或4所述的贴片组合物,其中丙交酯与乙交酯的比率在85:15与50:50之间,诸如是85:15、82:18、75:25、65:35或50:50。

6. 根据权利要求1-5中任一项所述的贴片组合物,其中所述可生物降解聚合物基质进一步包含抗氧化剂,例如丁基羟基甲苯、丁基羟基苯甲醚或 α -生育酚或其混合物。

7. 根据权利要求6所述的贴片组合物,其中所述抗氧化剂的浓度在干燥尖端部分的0.01-3%w/w,优选0.03-2%w/w,诸如0.05-1%w/w的范围内。

8. 根据权利要求1-7中任一项所述的贴片组合物,其中所述水溶性聚合物选自自由聚乙烯吡咯烷酮、糖诸如蔗糖或海藻糖、葡聚糖、羧甲基纤维素和海藻酸钠组成的组。

9. 根据权利要求8所述的贴片组合物,其中所述水溶性聚合物是聚乙烯吡咯烷酮。

10. 根据权利要求1-9中任一项所述的贴片组合物,其中所述背衬层部分包含增塑剂,例如甘油、聚乙二醇、癸二酸二丁酯、邻苯二甲酸二乙酯、甘油三乙酯或柠檬酸三乙酯。

11. 根据权利要求10所述的贴片组合物,其中所述增塑剂的浓度在干燥背衬层的0.5-6重量%的范围内。

12. 根据权利要求1-11中任一项所述的贴片组合物,其中所述背衬层包含分散在所述水溶性聚合物的基质中的治疗活性成分。

13. 根据权利要求1-12中任一项所述的贴片组合物,其中所述微针具有50-1000 μ m,例如100-800 μ m、300-700 μ m、400-600 μ m或约500 μ m的长度。

14. 根据权利要求1-13中任一项所述的贴片组合物,其中所述尖端部分占所述微针的总体积的5-95%。

15. 根据权利要求1-14中任一项所述的贴片组合物,其中所述基底由粘性医学胶带组成。

16. 根据权利要求1-15中任一项所述的贴片组合物,其中所述背衬层部分以下述方式覆盖于所述尖端部分的基部上:每个微针与所述贴片上的其它微针分隔,并且当在皮肤上施加所述贴片后移除所述基底时形成离散实体。

17. 根据权利要求1-16中任一项所述的贴片组合物,其中所述微针是圆锥形或金字塔

形,由此包括若干纵向延伸隆脊以有助于将所述微针插入皮肤中。

18. 根据权利要求17所述的贴片组合物,其中所述微针包括4-8个纵向延伸边缘。

19. 根据权利要求1-18中任一项所述的贴片组合物,其中所述治疗活性成分选自由以下组成的组:维生素D类似物、糖皮质激素受体调节剂、巨大戟二萜醇或巨大戟二萜醇衍生物、钙调神经磷酸酶抑制剂、JAK抑制剂、PDE4抑制剂、非甾体抗炎剂、抗生素、抗真菌剂或局部麻醉剂或其混合物。

20. 根据权利要求1-19中任一项所述的贴片组合物,其包括一个或多个微针,所述微针各自包括

(a) 含有一种或多种分散在选自由酯封端的聚丙交酯、酯封端的聚乙交酯和酯封端的聚丙交酯共乙交酯组成的组的可生物降解聚合物的基质中的选自由钙泊三醇和倍他米松酯组成的组的治疗活性成分的锥形尖端部分,和

(b) 覆盖于所述尖端部分上的含有水溶性聚合物的快速溶解性微针背衬层部分,所述一个或多个微针被附着于可移除基底的粘性表面并从所述粘性表面延伸。

21. 根据权利要求20所述的贴片组合物,其中所述倍他米松酯是二丙酸倍他米松或戊酸倍他米松,特别是二丙酸倍他米松。

22. 根据权利要求20或21所述的贴片组合物,其包含0.08-30 μg 钙泊三醇/ cm^2 。

23. 根据权利要求20-22中任一项所述的贴片组合物,其包含1-60 μg 二丙酸倍他米松/ cm^2 。

24. 根据权利要求20-23中任一项所述的贴片组合物,其中所述可生物降解聚合物是酯封端的聚丙交酯共乙交酯。

25. 根据权利要求20-24中任一项所述的贴片组合物,其中所述可生物降解聚合物具有>5000的分子量,诸如7000-17000、24000-38000、38000-54000、54000-69000或76000-116000的分子量。

26. 根据权利要求24或25所述的贴片组合物,其中丙交酯与乙交酯的比率在85:15与50:50之间,诸如是85:15、82:18、75:25、65:35或50:50。

27. 根据权利要求20-27中任一项所述的贴片组合物,其中所述背衬层包含分散在所述水溶性聚合物的基质中的钙泊三醇和/或倍他米松酯。

28. 根据权利要求20-27中任一项所述的贴片组合物,其中所述水溶性聚合物是聚乙烯吡咯烷酮。

29. 一种用于治疗皮肤病状的方法,其包括

(a) 在需要治疗的患者的皮肤的表面区域上施加根据权利要求1-28中任一项所述的包括一个或多个微针的贴片组合物,

(b) 在所述贴片组合物上施加足够的力以容许所述微针穿透角质层并进入活的皮肤层中,以及

(c) 从所述贴片组合物移除所述粘性基底。

30. 如权利要求29所述的方法,其中将所述贴片组合物插入皮肤中所需的所述力在每个每 cm^2 含有25个微针的贴片2-8N的范围内,例如是5N。

31. 根据权利要求29或30所述的方法,其中在120分钟的时期内,优选在60分钟的时期内移除所述基底后,所述微针中有至少90%从所述基底的粘性表面脱离。

32. 根据权利要求29-31中任一项所述的方法, 其中所述治疗活性成分历经2-21天, 优选2-14天, 诸如2-7天的时期从所述微针释放。

33. 根据权利要求29-32中任一项所述的方法, 其中通过用手指施加压力或通过任选使用施加器装置冲击插入来进行如权利要求29所述的方法的步骤(b)。

34. 根据权利要求29-33中任一项所述的方法, 其中所述皮肤病状是牛皮癣、光化性角化病、鳞状细胞癌、基底细胞癌、接触性皮炎、异位性皮炎、湿疹、手部湿疹、疣、生殖器疣、秃发症、痤疮、酒糟鼻或皮肤感染。

用于向皮肤递送活性成分的微针贴片

发明领域

[0001] 本发明涉及一种能够提供治疗活性成分在皮肤中持续释放的微针贴片组合物。所述组合物旨在用于治疗皮肤病状。

[0002] 发明背景

[0003] 人皮肤,特别是外层,即角质层,提供抵抗微生物病原体和毒性化学物质穿透至身体中的有效屏障。尽管皮肤的这个性质通常是有益的,但这使经皮进行药物施用复杂化,因为施加在罹患皮肤疾病的患者的皮肤上的大量(即使不是大多数)活性成分可能不穿透进入其施加它的活性所处的活的皮肤层中。一种用以获得活性成分向皮肤中的穿透增强的方式在于通过在疏水性媒介物诸如矿脂中配制活性成分来提供阻塞。可通过以下方式加强向真皮和表皮中的穿透:提供处于溶解状态的活性成分以及也可充当穿透增强剂的低分子量溶剂诸如乙醇或丙二醇,和/或也将穿透增强剂添加至制剂中。然而,这些措施可能不导致充分穿透,并且此外,含有高浓度的疏水性赋形剂例如矿脂的制剂通常在施加之后具有持续一定时间的粘性或油性感觉,因此它们被视为在美容学上具有较小可接受度。

[0004] 常规表面制剂也必须一天施加一次或多次。这被将更喜欢以较小频率给药以及因此更可能遵循涉及每2或3天或甚至更久进行施加的疗法的许多患者视为繁重任务。

[0005] 包括微针的组合物已作为经皮贴片制剂的替代物被开发来穿过皮肤递送治疗活性成分或疫苗。含有其中并有活性成分的微针的组合物也已作为常规局部制剂诸如软膏剂和乳膏剂的替代物被开发。微针是被设计以刺穿角质层,并且容许经皮或向表皮和真皮中递送活性成分的微米级结构。已由许多不同材料诸如硅、不锈钢和可生物降解聚合物制备微针阵列。微针制剂的一个实例是用活性成分的制剂涂布的固体微针,所述活性成分在所述微针已刺穿角质层时被释放至表皮和真皮中。微针制剂的另一实例是由并有活性成分的聚合物制备的溶解性微针或可生物降解微针,当所述聚合物在活的皮肤层中降解时,所述活性成分被逐渐释放。

[0006] WO 02/064193公开由聚合物和/或金属(例如可生物降解聚合物诸如聚乳酸或聚乙醇酸)组成的微针的阵列。聚合物可包括在微针插入皮肤中时被释放的治疗活性成分。

[0007] WO 2008/130587公开含有两层不同聚合物(例如分别是聚乙烯醇和聚乳酸共乙醇酸)的微针的阵列。一层可含有治疗活性成分。将另一聚合物层浇铸在第一层之上,移除溶剂,并且从模具移除微针阵列。WO 2008/130587明确公开包括装载有药物的尖端的微针,其由快速溶解性聚合物(例如聚乙烯醇)和基层可生物降解聚合物(聚乳酸共乙醇酸)组成。

[0008] WO 2012/153266公开一种通过以下方式制备微针阵列的方法:用溶剂填充模具中的微针形空腔,在所述空腔上施加形成微针的聚合物溶液以通过扩散来混合所述溶剂和所述聚合物溶液,移除所述溶剂以及从所述模具移除所得微针。

[0009] WO 2012/066506公开一种通过以下方式制备微针的方法:将组合物喷雾至模具中,使所述组合物干燥,以及从所述模具移除经干燥的组合物。

[0010] US 2007/0134829公开一种通过以下方式产生微针阵列的方法:使用具有许多开口的掩蔽材料,用氢氧化钾溶液对硅进行湿性蚀刻一段足够的时间段以产生具有特定形

状和锐度的微针。所述微针阵列可用于医学应用或作为母版用于铸造模具以制备聚合材料的微针。

[0011] 本发明的一目标在于提供一种包括可生物降解聚合物的微针的局部组合物,其目的在于改进治疗活性成分向活的皮肤层特别是真皮和/或表皮中的递送。本发明的另一目标在于提供一种在皮肤中形成药物贮器的微针组合物,活性成分历经延长的时期从所述药物贮器释放以使所述组合物相比于常规局部制剂诸如乳膏剂或软膏剂,可以较小频率施用。

[0012] 发明概述

[0013] 在达成本发明的研究的过程中,发现有可能提供一种具有层状结构的微针组合物,所述层状结构容许包括形成尖端以及包含可生物降解持续释放聚合物和一种或多种活性成分的层的微针插入活的皮肤层中。微针进一步包括在第一层之上的第二层,所述第二层包含在插入微针之后即刻溶解,由此容许移除微针附着于其上的基底的聚合物。微针组合物展现所需物理和化学稳定性及活性成分从它分散于其中的聚合物扩散所需的速率,以及为确保历经延长的时期释放活性成分所需的聚合物降解速率,从而相比于当组合物是软膏剂或乳膏剂时所需的每日一次或多次,允许进行较小频率给药。

[0014] 因此,在一个方面,本发明涉及一种包括一个或多个微针的微针贴片组合物,所述微针各自包括

[0015] (a) 含有分散在可生物降解聚合物的基质中的治疗活性成分的锥形尖端部分,其能够在将所述一个或多个微针插入皮肤中之后历经至少两天的时期提供所述治疗活性成分的持续释放,和

[0016] (b) 覆盖于所述尖端部分上的含有水溶性聚合物的快速溶解性微针背衬层部分,

[0017] 所述一个或多个微针被附着于可移除基底的粘性表面并从所述粘性表面延伸。

[0018] 附图简述

[0019] 图1a是本发明的微针贴片在插入皮肤中之前的图示。微针的以暗灰色显示的部分代表包含例如聚乙烯吡咯烷酮的快速溶解性背衬层,并且微针的显示为交叉影线的部分代表包含可生物降解聚合物与活性成分(显示为淡灰色椭圆形)混合的尖端。

[0020] 图1b是图1a中所示的微针贴片在插入皮肤中之后以及在快速溶解性背衬层已溶解之后的图示。微针的尖端部分存在于活的皮肤层中。

[0021] 图1c是图1b中所示的微针贴片的显示活性成分向皮肤中释放的图示。

[0022] 图2a是制备本发明的微针贴片组合物的方法的示意性图示(“DMN”是可溶解微针的缩写)。

[0023] 图2b是制备本发明的微针贴片组合物的替代性方法的示意性图示(“DMN”是可溶解微针的缩写)。

[0024] 图3是显示在于干燥烘箱中在 $65^{\circ}\text{C} \pm 2^{\circ}\text{C}$ 下使微针干燥5小时之后获取的样品中存在或不存在抗氧化剂丁基羟基甲苯(BHT)的情况下,微针中降解产物MC 1046相对于钙泊三醇(calcipotriol)的总浓度的峰面积比率的图,所述微针在尖端部分中包含酯封端的聚丙交酯共乙交酯(PLGA-E),并且在背衬层中包含聚乙烯吡咯烷酮(PVP)。

[0025] 图4是显示相较于用Daivobet®凝胶治疗的人皮肤外植体,用本发明的微针贴片组合物治疗的人皮肤外植体中倍他米松-17,21-二丙酸酯(BDP)和倍他米松-17-丙酸酯(B-

17-P) 在施加后24和48小时的皮肤浓度(μM)的图。B-17-P主要在生物基质中形成,因此被视为皮肤中BDP的替代标志物。

[0026] 图5a是显示相较于用Daivobet[®]凝胶治疗的人皮肤外植体,用本发明的微针贴片组合物治疗的人皮肤外植体中CYP24A1(钙泊三醇暴露的生物标志物)在施加后24和48小时的mRNA水平的图。

[0027] 图5b是显示相较于用Daivobet[®]凝胶治疗的人皮肤外植体,用本发明的微针贴片组合物治疗的人皮肤外植体中CD14(钙泊三醇暴露的生物标志物)在施加后24和48小时的mRNA水平的图。

[0028] 图6a是显示相较于用Daivobet[®]凝胶治疗的人皮肤外植体,用本发明的微针贴片组合物治疗的人皮肤外植体中CYP24A1在施加后24小时和4天的mRNA水平的图。

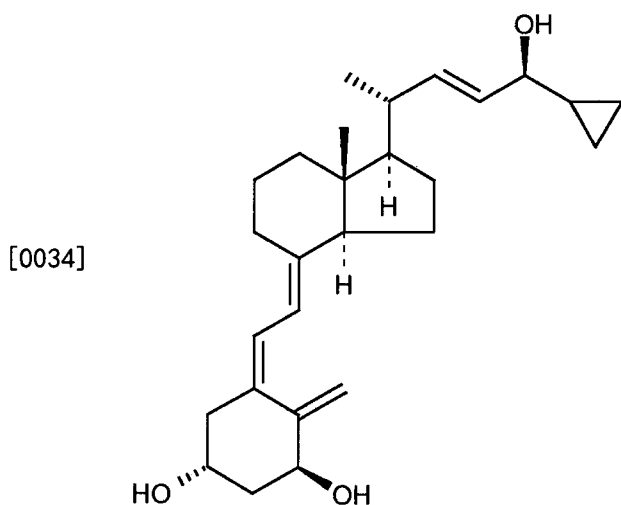
[0029] 图6b是显示相较于用Daivobet[®]凝胶治疗的人皮肤外植体,用本发明的微针贴片组合物治疗的人皮肤外植体中BDP和B-17-P在施加后24小时和4天的皮肤浓度(μM)的图。

[0030] 图7a-7e显示在将5x5微针贴片施加于人离体皮肤以及在45分钟之后移除基底(医学胶带)之后,借助于Vivascope 1500多激光系统在785nm的波长下所获取的一个微针的一系列反射共焦显微图像。

[0031] 发明详述

[0032] 定义

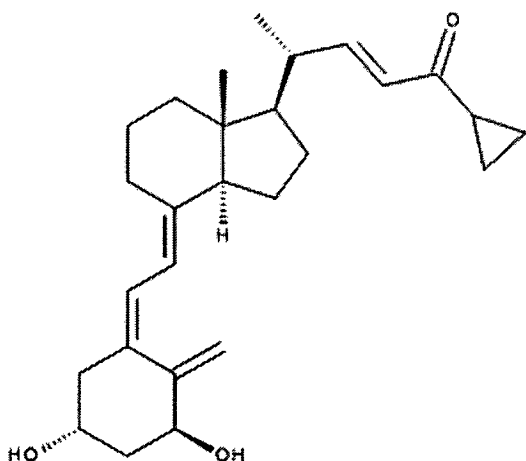
[0033] 在本发明情形下,术语“钙泊三醇”旨在指示下式维生素D类似物



[0035] 已发现钙泊三醇以两种结晶形式即无水物和单水合物存在。钙泊三醇单水合物和它的制剂公开于W0 94/15912中。术语“钙泊三醇”旨在涵盖所述化合物的任何形式,包括结晶、非晶和溶解形式。

[0036] 术语“MC1046”旨在指示下式化合物

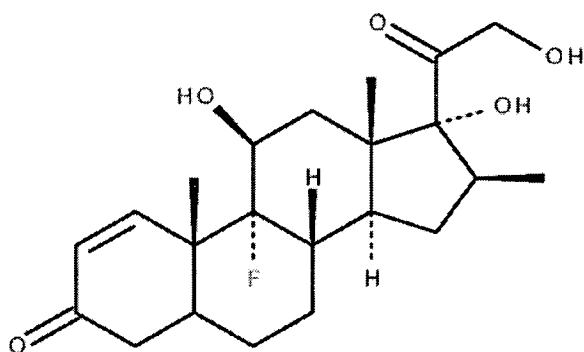
[0037]



[0038] MC1046作为钙泊三醇在氧化条件下的降解产物而形成。

[0039] 术语“倍他米松 (betamethasone) 酯”旨在指示下式化合物的羧酸酯

[0040]



[0041] 可包含在本发明组合物中的倍他米松酯的实例是倍他米松-17-戊酸酯或倍他米松-17,21-二丙酸酯。优选用于本发明目的的倍他米松酯是倍他米松-17,21-二丙酸酯(在下文中称为二丙酸倍他米松)。

[0042] 术语“分散的”旨在指示活性成分以分子形式分散或以固体分散体形式存在于聚合物基质中。来自对本发明的微针组合物的拉曼(Raman)光谱测定的结果表明二丙酸倍他米松与钙泊三醇两者均以玻璃液形式存在,所述玻璃液以分子形式分散在聚合物基质中。

[0043] 术语“可生物降解的”旨在指示聚合物在插入皮肤中之后溶胀,随后由于在水存在下酯键水解而降解。

[0044] 术语“持续释放”旨在指示历经延长的时期诸如至少两天,活性成分从可生物降解聚合物扩散和/或活性成分由于可生物降解聚合物发生溶胀、溶解和/或降解而释放,以使得能够历经整个时期递送治疗有效剂量的活性成分,由此容许进行较小频率给药。

[0045] 术语“快速溶解性”旨在指示微针的背衬层部分在插入皮肤中之后不超过120分钟,优选不超过60分钟,以及可短至约15分钟的时期内溶解。

[0046] 术语“化学稳定性”或“化学稳定的”旨在指示历经产品的可为至少1年,但优选至少1.5年或更优选至少2年的储存期限,有至多10%,优选至多5%的任一活性成分降解。通过使组合物经受在25℃下的加速稳定性研究来获得在5℃下的化学稳定性的近似值。如果在25℃下3个月之后,小于约6%的物质已降解,那么这通常被视为对应于在5℃下2年储存期限。更具体来说,钙泊三醇的“化学稳定性”意指在成品药物产品中,钙泊三醇不随时间推移而显著降解成24-表钙泊三醇、MC1046或钙泊三醇的其它降解产物。

[0047] 术语“物理稳定性”或“物理稳定”意指历经产品的储存期限,组合物保持它的宏观

和微观形貌和物理性质。举例来说,当微针随时间推移而保持它们的形状和锐度以及它们的机械强度时,组合物被视为是物理稳定的,所述机械强度如由为在微针中提供表征突然结构破坏的突然不连续性(诸如断裂)所需的力所确定。

[0048] 术语“酯封端的”意指聚乳酸、聚乙醇酸或聚乳酸共乙醇酸的烷基酯。烷基优选是C₁₋₂₀烷基,诸如甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、壬基、癸基、十一基、十二基等。

[0049] 制备本发明的微针贴片组合物的方法

[0050] 制备本发明的微针贴片组合物的方法示意性显示于图2中。为制造用于铸造微针的模具,初始由适合材料诸如硅或金属(诸如钢或钛)或聚合物(诸如聚碳酸酯或聚甲基丙烯酸)制备模板。所述模板包括具有一定尺寸和形状的多个微针,所述形状对应于贴片组合物中的微针的所需形状,即通常是具有锥形尖端的圆锥形或金字塔形。模具可接着通过在微针模板上浇铸液体聚合物材料诸如聚二甲基硅氧烷来制造。当材料干燥和固化时,模具包括保持它被铸造所基于的微针的反向形状的微小凹陷。

[0051] 模具中微小凹陷的长度和数目决定最终贴片中微针的长度和数目。每单位面积微针的数目可广泛变化,通常在2-100个微针/cm²之间,但更常在5-75个微针/cm²,更通常10-50个微针/cm²,优选15-30个微针/cm²诸如20-25个微针/cm²的范围内。类似地,微针的长度可变化,但它们应具有足以穿透角质层的长度,并且不应长达穿透至皮肤的在真皮以下的神经支配部分,因为当在皮肤上施加微针贴片时,穿透至这个深度可导致疼痛感觉。因此,微针可具有50-1000μm,例如100-800μm、300-700μm、400-600μm或约500μm的长度。这种长度的微针通常确保装载有药物的尖端部分将安置在活性成分施加它们的作用所处的活的皮肤层即真皮和表皮中。如上所指示,微针的形状也由模具中微小凹陷的形状决定,并且在形状上可为圆锥形或金字塔形并具有尖锐尖端。此外,当微针的形状是金字塔形时,它包括一定数目(通常是4-8个)的纵向延伸隆脊以有助于将微针插入皮肤中。微针的纵横比(微针的长度相对于在基部的宽度)可根据用于产生模具的方法而变化。当模具模板通过湿性蚀刻制备时(例如如US2007/0134829中所述),纵横比通常是3:2,即长度比在基部的宽度大1.5倍。

[0052] 本发明的微针贴片可接着通过以下方式制备:用适当溶剂例如二甲基甲酰胺填充模具中的微小凹陷,以及在微小凹陷之上施加活性成分和可生物降解聚合物于相同溶剂中的溶液以允许混合两种液体。接着例如通过在真空下在干燥器中和/或在适当温度下在干燥烘箱中干燥来移除溶剂。接着在部分填充的微小凹陷之上施加水溶性聚合物于适当溶剂中的第二溶液,继之以例如在真空下在干燥器中或在适当温度下在干燥烘箱中进行干燥。在当前优选实施方案中,以背衬层部分在干燥时以下述方式覆盖于尖端部分的基部上的方式施加水溶性聚合物的溶液:每个微针与贴片上的其它微针分隔,并且当在皮肤上施加贴片后移除基底时形成离散实体。

[0053] 视待从各贴片递送的活性成分的剂量而定,装载有药物的尖端部分可占微针的总体积的5-95%。

[0054] 可接着通过在模具之上施加粘性胶带以及施加压力以确保胶带与微针的基部之间良好接触,继之以将微针牵拉出模具来从模具移除干燥微针。胶带应优选是粘性医学胶带,因为已发现这提供与微针的基部的良好粘着以致当牵拉胶带时,大致上所有微针都从

模具移除。所得微针的组合物图解显示于图1a中。模具可被铸造以匹配各贴片的所需尺寸，或可以较大尺寸制造，并且可通过将胶带切割成具有所需形状和尺寸的片块来制备具有适当尺寸的个别贴片。当治疗牛皮癣时，后述选项可作为优势，因为牛皮癣斑块常具有不同尺寸和形状。

[0055] 可将干燥微针贴片储存在密封不透汽小瓶或泡罩包装中，任选连同适当干燥剂一起，以防止在储存期间吸收水蒸汽。

[0056] 微针制备和替代性实施方案的其它细节公开于W0 2012/153266中，所述专利据此以引用的方式并入本文。

[0057] 实施方案

[0058] 在达成本发明的研究的过程中，测试许多不同可生物降解聚合物形成可由其制备微针的基质的适合性。发现大多数测试聚合物不适于制备本发明的微针，因为它们制备的微针不保持微针的形状，特别是微针的尖锐尖端，即它们不是物理稳定的，或因为治疗活性成分由于聚合物快速溶解而从其不可接受地快速释放，或因为发现治疗活性成分在其中是化学不稳定的。因此，由聚乙烯吡咯烷酮和聚(甲基)丙烯酸酯或这些聚合物的混合物制得的微针导致活性成分不可接受地快速释放。由单独聚乙烯吡咯烷酮制得的微针在从初级包装移除时倾向于软化或熔化。

[0059] 最后，这些各种问题通过开发微针组合物而解决，所述微针组合物包括装载有药物的尖端部分，其含有聚乳酸或其衍生物诸如酯封端的聚丙交酯、聚乙醇酸或其衍生物诸如酯封端的聚乙交酯、或聚乳酸共乙醇酸(PLGA)或其衍生物诸如酯封端的聚丙交酯共乙交酯聚合物。当水溶性聚合物诸如聚乙烯吡咯烷酮用作背衬层时，也获得令人满意的结果。已发现当采用聚乳酸、聚乙醇酸或聚乳酸共乙醇酸聚合物(或这些聚合物的酯封端的衍生物)时，有可能获得活性成分历经延长时期诸如至少两天从其释放的组合物。当聚乙烯吡咯烷酮用作背衬层时，发现所得微针是物理稳定的，具有硬质尖锐尖端。

[0060] 在特别有利实施方案中，可生物降解聚合物是可任选被酯封端的PLGA。PLGA可有利地具有>5000的分子量，诸如7000-17000、24000-38000、38000-54000、54000-69000或76000-116000的分子量，从而产生容许制剂被分配至模具中，并且在干燥时提供令人满意的物理稳定性特别是尖锐尖端的粘度。乳酸与乙醇酸的比率可优选在85:15与50:50之间变化，诸如是85:15、82:18、75:25、65:35或50:50。丙交酯与乙交酯的当前优选比率是50:50。

[0061] 在一些情况下，可优选的是向可生物降解聚合物基质中添加抗氧化剂例如丁基羟基甲苯、丁基羟基苯甲醚或 α -生育酚或其混合物，以便降低在氧化条件下形成活性成分的降解产物。抗氧化剂可适合地以在干燥尖端部分的0.01-3%w/w，优选0.03-2%w/w，诸如0.05-1%w/w的范围内的浓度存在。当前优选抗氧化剂是丁基羟基甲苯，其可以在干燥尖端部分的0.03-2重量%的范围内，例如是0.05重量%的浓度添加。

[0062] 包含在背衬层中的水溶性聚合物可为在已施加组合物之后在皮肤中快速溶解，并且可与其它组分相容的任何聚合物。水溶性聚合物可例如选自由聚乙烯吡咯烷酮、糖诸如蔗糖或海藻糖、葡聚糖、羧甲基纤维素或海藻酸钠组成的组。当前优选水溶性聚合物是聚乙烯吡咯烷酮。尽管通常使用聚乙烯吡咯烷酮会对背衬层部分赋予就微针的物理稳定性而言有利的性质，但它可为稍微脆弱的，并且它的性质可通过包括增塑剂例如甘油、聚乙二醇、癸二酸二丁酯、邻苯二甲酸二乙酯、甘油三乙酯或柠檬酸三乙酯以降低脆弱性来改进。背衬

层部分中增塑剂的浓度可适合地在干燥背衬层的0.5–6重量%的范围内。用以包含在微针的背衬层部分中的当前有利增塑剂是甘油,其可适合地以干燥背衬层的约2重量%的浓度存在。应注意在组合物已被干燥之后剩余在背衬层中的残余溶剂也可充当增塑剂。这种溶剂的一实例是乙醇,其可在干燥之后作为残余物存在于组合物中。

[0063] 在一特定实施方案中,本发明组合物可在水溶性聚合物的背衬层中包含活性成分。这将提供一部分向患者施用的活性成分的即刻(即在2小时或优选1小时内)释放。包含在背衬层中的活性成分可与包含在微针的尖端部分中的活性成分相同或不同。

[0064] 包含在本发明组合物中的活性成分可为适于治疗皮肤病状,并且其中较小频率给药(小于一天一次)被患者认为有利的活性成分。活性成分可适合地选自自由以下组成的组:维生素D类似物、糖皮质激素受体调节剂、巨大戟二萜醇(ingenol)或巨大戟二萜醇衍生物、钙调神经磷酸酶(calcineurin)抑制剂、JAK抑制剂、PDE4抑制剂、非甾体抗炎剂、抗生素、抗真菌剂或局部麻醉剂或其混合物。

[0065] 维生素D类似物的实例是钙泊三醇、钙三醇(calcitriol)、马沙骨化醇(maxacalcitol)或他卡西醇(tacalcitol)。

[0066] 糖皮质激素受体调节剂的实例是皮质甾体,诸如安西缩松(amcinonide)、倍他米松、布地奈德(budenoside)、氯倍他索(clobetasol)、氯氟美松酮(clobetasone)、可的松(cortisone)、地索奈德(desonide)、脱氧可的松(desoxycortisone)、去羟米松(desoximethasone)、地塞米松(dexamethasone)、二氟可龙(diflucortolon)、二氟拉松(diflorasone)、氟氢可的松(flucortisone)、氟米松(flumethasone)、氟尼缩松(flunisolide)、氟西奈德(fluciclonide)、氟新诺龙(fluciclonolone)、氟甲龙(fluorometholone)、氟泼尼松龙(fluprednisolone)、氟氢缩松(flurandrenolide)、氟替卡松(fluticasone)、哈西缩松(halcinonide)、卤倍他索(halobetasol)、氢化可的松(hydrocortisone)、甲泼尼松(meprednisone)、甲泼尼松(methylprednisone)、莫米松(mometasone)、对氟米松(paramethasone)、泼尼卡酯(prednicarbate)、泼尼松(prednisone)、泼尼松龙(prednisolone)和曲安西龙(triamcinolone)或其药学上可接受的酯或丙酮化物。皮质甾体可优选选自倍他米松、布地奈德、氯倍他索、氯氟美松酮、去羟米松、二氟可龙、二氟拉松、氟西奈德、氟新诺龙、哈西缩松、卤倍他索、氢化可的松、莫米松、泼尼卡酯或曲安西龙或其药学上可接受的酯。皮质甾体酯可例如是乙酸倍他米松、二丙酸倍他米松、戊酸倍他米松、丙酸氯倍他索、乙酸地塞米松、特戊酸氟米松、丙酸氟替卡松、乙酸氢化可的松、丁酸氢化可的松或糠酸莫米松。丙酮化物可选自丙酮化氟新诺龙或丙酮化曲安西龙。

[0067] 巨大戟二萜醇衍生物的一实例是巨大戟二萜醇甲基丁烯酸酯。

[0068] 钙调神经磷酸酶抑制剂的实例是他克莫司(tacrolimus)或吡美莫司(pimecrolimus)。

[0069] JAK抑制剂的一实例是托法替尼(tofacitinib)。

[0070] PDE4抑制剂的实例是阿普司特(apremilast)、罗氟司特(roflumilast)或西洛司特(cilomilast)。

[0071] 非甾体抗炎剂的实例是布洛芬(ibuprofen)、双氯芬酸(diclofenac)、萘普生(naproxen)、吲哚美辛(indomethacin)、右布洛芬(dexibuprofen)、酮洛芬(ketoprofen)、

氟比洛芬(flurbiprofen)、吡罗昔康(piroxicam)、替诺昔康(tenoxicam)、氯诺昔康(lornoxicam)或萘丁美酮(nabumeton)。

[0072] 抗生素的实例是梭链孢酸(fusidic acid)或莫匹罗星(mupirocin)。

[0073] 局部麻醉剂的实例是利多卡因(lidocain)、布比卡因(bupivacain)、甲吡卡因(mepivacain)或罗哌卡因(ropivacain)。

[0074] 抗真菌剂的实例是酮康唑(ketoconazole)、特比萘芬(terbinafine)、咪康唑(miconazole)、克霉唑(clotrimazole)、环匹罗司(ciclopirox)、联苯苄唑(bifonazole)、制霉菌素(nystatin)、益康唑(econazole)或阿莫罗芬(amorolfine)。

[0075] 治疗活性成分也可选自抗增生剂诸如甲氨蝶呤(methotrexate)或免疫抑制剂诸如环孢菌素(cyclosporin)。

[0076] 在另一方面,本发明涉及一种用于治疗皮肤病状的方法,其包括

[0077] (a) 在需要治疗的患者的皮肤的表面区域上施加如本文所述的包括一个或多个微针的贴片组合物,

[0078] (b) 在所述贴片组合物上施加足够的力以容许所述微针穿透角质层并进入活的皮肤层中,以及

[0079] (c) 从所述贴片组合物移除粘性基底。

[0080] 为防止微针在插入皮肤中时破裂,微针的机械强度应是如此以致为使微针断裂所需的力显著大于为将微针插入皮肤中所需的力。通常,为将微针贴片插入皮肤中,并且使它穿透角质层所需的力在每个每 cm^2 含有25个微针的贴片0.4-8N的范围内,例如是2-7N,诸如5N。微针的破损力可被评估为断裂力或为将微针挤压确定长度所需的力。这些力可使用质构仪(例如TA.XT Plus质构仪,Stable Micro Systems,Surrey,UK)或使用计算机控制的力-位移工作站(5565型,Instron,Buckinghamshire,UK)测定。

[0081] 如上所指示,包含水溶性聚合物的背衬层在微针插入皮肤中后开始溶解。这允许在皮肤上施加贴片的约120分钟内,优选在60分钟或45分钟或甚至至少至约15分钟内移除基底。一般来说,优选的是在这个时间段内移除基底后有至少90%的微针从粘性表面脱离以避免当剥离基底时有大量微针再次被牵拉出。

[0082] 已发现本发明能够历经延长时期提供治疗活性成分的递送。因此,治疗活性成分可历经2-21天,优选2-14天,诸如2-7天或4-7天的时期从微针释放。如以下实施例2中所示,在施加含有钙泊三醇的微针贴片之后4天观察到生物标志物CYP24A1的mRNA水平增加,从而指示钙泊三醇持续至少4天从微针释放。

[0083] 在本发明方法中,步骤(b)可通过用手指施加压力或通过冲击插入例如通过使用施加器装置来进行,后者是优选的,因为它使插入再现性增加(参见van der Maaden等,AAPS Journal 16(4),2014年7月,第681-684页)。施加器装置的实例公开于US 2002/0123675或WO 2008/091602中。

[0084] 待使用本发明的微针贴片组合物治疗的皮肤病状可选自牛皮癣例如斑块牛皮癣、皮褶性牛皮癣、甲牛皮癣(nail psoriasis)或斑点牛皮癣、掌跖脓疱病(pustulosis palmoplantaris)、光化性角化病、鳞状细胞癌、基底细胞癌、接触性皮炎、异位性皮炎、湿疹、手部湿疹、疣、生殖器疣、秃发症、痤疮、酒糟鼻或皮肤感染。

[0085] 牛皮癣是一种显现为由角化过度所致的红斑性干燥脱鳞屑斑块的慢性炎症性皮

肤疾病。斑块最常见于肘部、膝部和头皮上,但更广泛病变可出现在身体的其它部分,特别是腰骶区域上。对轻度至中度牛皮癣的常用治疗涉及表面施加含有皮质甾体作为活性成分的组合物。尽管有效,但施加皮质甾体具有许多不利作用的劣势,所述不利作用诸如皮肤萎缩、条纹、痤疮样疹、口周皮炎、皮肤真菌和细菌过度生长、色素沉着皮肤的色素沉着不足和酒糟鼻。

[0086] 用于治疗牛皮癣的组合产品已由LEO Pharma以商标名Daivobet[®]软膏和Daivobet[®]凝胶销售多年。所述产品包含在包含聚氧丙烯硬脂基醚作为溶剂的软膏或凝胶媒介物中配制的钙泊三醇和二丙酸倍他米松作为活性成分。尽管组合产品的功效显著优于任一活性成分独自的功效,但产品需要每日施加一次,并且许多患者,特别是具有广泛牛皮癣病变者,将青睐更简易施加,诸如较小频率施加。被视为合乎需要的是通过提供相较于商业产品,活性成分从其向皮肤中的递送得以延长的配制媒介物来进一步改进两种活性成分的组合的生物功效。

[0087] 因此,在当前有利实施方案中,本发明涉及一种包括一个或多个微针的微针贴片组合物,所述微针各自包括

[0088] (a) 含有一种或多种分散在选自酯封端的聚丙交酯、酯封端的聚乙交酯和酯封端的聚丙交酯共乙交酯组成的组的可生物降解聚合物的基质中的选自钙泊三醇和倍他米松酯组成的组的治疗活性成分的锥形尖端部分,和

[0089] (b) 覆盖于所述尖端部分上的含有水溶性聚合物的快速溶解性微针背衬层部分,

[0090] 所述一个或多个微针被附着于可移除基底的粘性表面并从所述粘性表面延伸。

[0091] 在这个实施方案中,倍他米松酯可为二丙酸倍他米松或戊酸倍他米松。预期在每cm²贴片0.08-30μg钙泊三醇的钙泊三醇剂量和每cm²贴片1-60μg倍他米松酯的倍他米松酯剂量的情况下会维持延长递送。倍他米松酯优选是二丙酸倍他米松。

[0092] 在开发这个实施方案期间,发现钙泊三醇在聚乳酸、聚乙醇酸或聚乳酸共乙醇酸的基质中不是化学稳定的,可能是由于其中存在酸性残余物或杂质,而当酯封端的聚丙交酯、聚乙交酯或聚丙交酯共乙交酯用作可生物降解聚合物时,钙泊三醇是化学稳定的。

[0093] 在这个实施方案中,可生物降解聚合物优选是酯封端的聚丙交酯共乙交酯。酯封端的聚丙交酯共乙交酯可有利地具有>5000的分子量,诸如7000-17000、24000-38000、38000-54000、54000-69000或76000-116000的分子量,从而产生容许制剂被分配至模具中,并且在干燥时提供令人满意的物理稳定性特别是尖锐尖端的粘度。丙交酯与乙交酯的比率可优选在85:15与50:50之间变化,诸如是85:15、82:18、75:25、65:35或50:50。丙交酯与乙交酯的当前优选比率是50:50。

[0094] 在这个实施方案中,可优选的是向可生物降解聚合物基质中添加抗氧化剂例如丁基羟基甲苯、丁基羟基苯甲醚或α-生育酚或其混合物,以便降低MC 1046的形成。抗氧化剂可适合地以在干燥尖端部分的0.03-3%w/w,优选0.05-2%w/w,诸如0.05-1%w/w的范围内的抗氧化剂浓度存在。当前优选抗氧化剂是丁基羟基甲苯,其可以在干燥尖端部分的0.05-2重量%的范围内的浓度添加。

[0095] 在这个实施方案中,水溶性聚合物可例如选自聚乙烯吡咯烷酮、糖诸如蔗糖或海藻糖、葡聚糖、羧甲基纤维素和海藻酸钠组成的组。当前优选水溶性聚合物是聚乙烯吡咯烷酮。背衬层部分可另外包含增塑剂例如甘油、聚乙二醇、癸二酸二丁酯、邻苯二甲酸二乙

酯、甘油三乙酯或柠檬酸三乙酯,其可以在干燥背衬层的0.5-6重量%的范围内的浓度被包含。用以包含在微针的背衬层部分中的当前有利增塑剂是甘油,其可适合地以干燥背衬层的约2重量%的浓度存在。

[0096] 在一特定实施方案中,本发明组合物可包含分散在水溶性聚合物的背衬层中的钙泊三醇和/或倍他米松酯。

[0097] 在这个实施方案中,可移除基底可适合地由粘性医学胶带组成。

[0098] 本发明进一步描述于以下实施例中,所述实施例无论如何都不旨在限制如所要求保护的本发明的范围。

实施例

[0099] 实施例1

[0100] 本发明的组合物

[0101] 通过使用刮勺和烧杯手动混合约45g聚二甲基硅氧烷(PDMS)弹性体基质(Sylgard 184硅酮弹性体试剂盒,A部分)和约4.5g固化剂(Sylgard 184硅酮弹性体试剂盒,B部分)直至彻底混合来制备微针模具。将所得混合物在真空下放置在干燥器中约20分钟。将PDMS倾注在微针模板(从Tyndall National Institute,Ireland获得,并且基本上如US 2007/0134829中所公开加以制备的图案化硅片)上,并且在干燥烘箱中在100℃下固化约60分钟。在冷却之后,将模具从微针模板剥离,并且切割成1x1cm的个别模具(含有5x5个微小凹陷)。

[0102] 将PDMS模具放置在玻璃烧杯中,并且在真空下用二甲基甲酰胺(DMF)清洁30分钟,以及在室温下在超声波浴中再清洁30分钟。将清洁模具放置在玻璃烧杯中,并且在真空下用DMF预填充微小凹陷。

[0103] 使用涡旋混合器,通过将300mg酯封端的聚丙交酯共乙交酯(丙交酯:乙交酯50:50,Mw 7000-17000,PLGA-E)溶解于1ml DMF中持续约10分钟直至PLGA-E完全溶解来制备溶液。在一些实施方案中,将0.5mg/ml丁基羟基甲苯(BHT)添加至PLGA-E溶液中。使用涡旋混合器,将20mg钙泊三醇和40mg二丙酸倍他米松(BDP)溶解于1ml所得溶液中持续约10分钟直至活性成分完全溶解。使用注射泵和毛细管分配器以及0.5 μ l/min的流速将装载有药物的PLGA-E溶液分配至PDMS模具的用DMF预填充的微小凹陷中以获得每个模具0.15 $\pm$ 0.03 μ l的总体积。

[0104] 在真空下在干燥器中使模具干燥约18小时,随后在真空烘箱中在60 $\pm$ 2℃下在500mbar下干燥约5小时。

[0105] 通过使用涡旋混合器,将400mg聚乙烯吡咯烷酮(PVP, Kollidon®17PF)溶解于1ml 96%乙醇中持续约5分钟来制备第二溶液。添加10mg甘油,并且使用涡旋混合器,将混合物搅拌2-3分钟。使用注射泵和毛细管分配器,在1.5 μ l/min的流速下,将PVP溶液分配至PDMS模具的含有经干燥的装载有药物的PLGA-E溶液的微小凹陷中,以使分配体积是每个模具0.75 $\pm$ 0.15 μ l。

[0106] 在真空下在干燥器中使填充模具干燥约2小时。

[0107] 使用手指压力将医学粘性胶带(3M)施加在模具的表面上,并且将微针牵拉出模具。

[0108] 将贴片储存在用氮气净化的气密小瓶中,并且用橡胶塞、铝盖和压紧钳密闭。

[0109] 干燥微针贴片具有以下组成。

[0110]

成分	μg/贴片	w/w%	mg/g
二丙酸倍他米松	6	1.66	16.60
钙泊三醇单水合物	3	0.83	8.30
PLGA-E	45	12.45	124.48
PVP	300	82.99	829.88
99.5%甘油	7.5	2.07	20.75
总计	378.82	100	1000

[0111] 组合物的物理和化学稳定性由下表可见。应注意在作为加速稳定性研究的常用温度的40℃下储存微针贴片不可行,因为PLGA-E在40℃下不是物理稳定的。

[0112]	储存温度/时间	外观	相对于起始的钙泊三醇%	24-表-钙泊三醇面积%	MC1046面积%	相对于起始的BDP%
	起始	良好	100.0%	0.8%	1.2%	100.0%
	25℃/1个月	良好	95.5%	1.0%	1.5%	98.3%
	25℃/3个月	未评估	116.4%	0.7%	2.1%	118.6%
	40℃/2周	不可接受	95.5%	0.9%	未评估	101.7%

[0113] 如上所述制备微针贴片组合物,例外之处是以干燥尖端的重量计,它们含有0%、0.5%或1%BHT。

[0114] 结果显示于图3中,其说明不具有BHT的样品和具有0.5%w/w和1%w/w BHT的样品的降解产物MC 1046的峰面积相对于总体钙泊三醇峰面积的百分比率。MC 1046相对于钙泊三醇的总量的峰面积百分比得以显著降低,从而指示向组合物中添加BHT使钙泊三醇的降解显著降低。

[0115] 实施例2

[0116] 人外植体皮肤暴露

[0117] 进行两个实验以探究在人皮肤外植体中随时间推移的暴露。

[0118] 实验1:

[0119] 使用在开始实验之前最多24小时从经受腹部整形术的女性供给者获得的全层人皮肤。将22mm穿孔活检体放置在24mm Transwell® 插件中,并且放置在具有1ml EpiLife® 组织培养基的6孔板中,所述组织培养基补充有0.2ng/mL人EGF、0.2%牛垂体提取物(BPE)、5μg/mL牛胰岛素、5μg/mL牛转铁蛋白(transferrin)、0.18μg/mL氢化可的松和庆大霉素(gentamycin)。

[0120] 一式三份经表面施加如实施例1中所述制备的每cm²微针贴片含有2μg钙泊三醇和

6 μ g BDP的组合物以及每cm² 10 μ l **Daivobet**[®]凝胶和**Daivobet**[®]凝胶媒介物。测试以下治疗时程:在t=0小时施加一剂**Daivobet**[®]凝胶,其中在24小时和48小时进行皮肤取样。在t=0和24小时施加分别两剂**Daivobet**[®]凝胶,其中在48小时进行皮肤取样,在t=0小时施加一个贴片,其中在24小时和48小时进行皮肤取样,在实验的完整持续时间使背衬胶带保留在皮肤上,以及在t=0小时施加一个贴片,其中在t=48小时进行皮肤取样,但在24小时移除背衬胶带。在37℃下在5%CO₂下以离体培养维持皮肤活检体48小时,其中在24小时更换培养基。在实验结束时,将每个外植体的涵盖给药区域的14mm活检体冲出,随后分成两份以分别进行化合物分析(胶带剥离10次)和生物标志物分析。

[0121] 通过使用有机溶剂从皮肤活检体提取活性化合物,随后使用LC/MS-MS分析提取物来进行化合物分析。

[0122] 使用mirVana (Life Technologies, Grand Island, NY, USA), 根据提供的说明书从细胞提取总RNA。用高容量cDNA逆转录试剂盒 (Applied Biosystems, Foster City, CA, USA) 进行cDNA合成。通过使用来自Applied Biosystems的Taqman基因表达测定 (CYP24A1 (Hs00167999_m1)、CD14 (Hs02621496_s1)、PPIA (Hs99999904_m1)、GAPDH (Hs99999905_m1)、TBP (Hs99999910_m1) 和HMBS (Hs00609297_m1)) 和PRISM7900HT序列检测系统 (SDS 2.3) 进行定量实时PCR来以10 μ L的总体积扩增来自每个样品的2.5 μ L cDNA (等效于5ng RNA)。PPIA、GAPDH、TBP和HMBS用于进行标准化。

[0123] 由图4可见在施加之后BDP可驻留在微针贴片组合物内部,或在施加**Daivobet**[®]凝胶之后驻留在皮肤的角质层中,因此不可用于达成药理学作用。B-17-P主要在生物基质中形成,因此被视为皮肤中可用于达成药理学作用的BDP的替代标志物。似乎对于用**Daivobet**[®]凝胶和用本发明的微针贴片组合物治疗的两个外植体,在皮肤中形成的B-17-P的量均随时间推移而增加。在施加**Daivobet**[®]凝胶之后观察到的皮肤B-17-P浓度高于在施加本发明的微针贴片组合物之后观察到的浓度,然而,随时间推移而增加可指示从贴片进行延长释放。

[0124] 由图5 (a) 和5 (b) 可见钙泊三醇的PD生物标志物CYP24A1和CD14随时间推移由**Daivobet**[®]凝胶所诱导。由微针贴片引发的生物标志物诱导的水平较低,但随时间推移而增加,从而指示相比于从**Daivobet**[®]凝胶所观察到的作用,钙泊三醇的作用的发生较慢,但潜在地得以延长。

[0125] 实验2:

[0126] 从Genoskin, France获得具有2.5cm²的可用表面积 of **NativeSkin**[®]Plus皮肤模型,并且根据制造商说明书加以培养。一式三份经表面施加如实施例1中所公开制备的每cm²微针贴片含有0.5 μ g钙泊三醇和6 μ g BDP的组合物以及每cm² 4.3 μ l **Daivobet**[®]凝胶和**Daivobet**[®]凝胶媒介物。测试以下治疗时程:每日一剂**Daivobet**[®]凝胶或安慰剂凝胶,其中在24小时和96小时进行皮肤取样。在t=0小时施加一个贴片,其中在24小时和96小时进行皮肤取样,使背衬胶带保留在皮肤上24小时,以及在t=0小时和t=48小时施加两个贴片,其中在t=96小时进行皮肤取样。在实验结束时,将两个4mm活检体冲出,随后分析化合物(在胶带剥离10次之后)或生物标志物的存在性。

[0127] 由图6(a)可见钙泊三醇的生物标志物CYP24A1随时间推移由在实验的时间0、第1天和第2天时施加,并且在第4天取样的Daivobet[®]凝胶所诱导。由施加一次的微针贴片引发的生物标志物诱导的水平初始较低(在第1天),但随时间推移而增加,从而指示相较于从Daivobet[®]凝胶所观察到的作用,钙泊三醇的作用的发生较慢,但潜在地历经4天得以延长。

[0128] 由图6b可见对于用Daivobet[®]凝胶和用本发明的微针贴片组合物治疗的两个外植体,在皮肤中形成的B-17-P的量均随时间推移而增加。在第4天,在施加在实验的时间0、第1天和第2天时施加的Daivobet[®]凝胶之后观察到的皮肤B-17-P浓度高于在施加一次本发明的微针贴片组合物之后观察到的浓度,然而,随时间推移而增加可指示从贴片进行延长释放。

[0129] 实施例3

[0130] 对人外植体皮肤中的微针组合物的反射共焦显微分析

[0131] 将如实施例1中所述的微针贴片施加于如实施例2中所述制备的新鲜人离体皮肤。在施加之后45分钟,移除医学粘性胶带,并且确认无微针遗留在胶带上,随后根据H.Skvara等Dermatol Pract Concept 2(1),2012,第3-12页以及Calzavara-Pinton等,Photochemistry and Photobiology,84,2008,第1421-30页中所述的程序,使用Vivascope1500多激光系统进行反射共焦显微术(RCM)成像。在这个技术中,使具有785nm的波长的激光穿过光束分离器和与皮肤接触的光学透镜。在皮肤中,光被聚焦在直径是数微米的小组织斑点上。反射(反向散射)发生在具有不同折射指数的两个结构之间的边界处。从焦点反射的光朝向透镜进行回传播穿过针孔。从所聚焦的点的上方和下方反射的光被针孔掩蔽以致检测器仅接收来自试样的所聚焦的薄平面的光。通过改变物镜在垂直平面中聚焦所处的深度,可产生在皮肤内特定深度处的水平图像。

[0132] 扫描视场是500x 500 μm 。以<5 μm 的轴向分辨率,以3 μm 的阶跃进行深度测量。RCM的检测限是约150 μm 的深度。

[0133] 结果由图7可见,其中

[0134] 图7a显示以12 μm 的深度穿透角质层的微针。在移除基底之前,PVP背衬层已溶解,并且仅有PLGA-E聚合物的薄八角形外壳反射这个平面上的光。

[0135] 图7b显示以27 μm 的深度穿透角质层的微针。在移除基底之前,PVP背衬层已溶解,并且仅显现为在PLGA-E可生物降解聚合物的薄八角形外壳中间的圆圈。

[0136] 图7c显示以45 μm 的深度穿透角质层的微针。PLGA-E聚合物微针尖端反射这个平面上的光,PLGA-E聚合物的薄八角形外壳也是如此。

[0137] 图7d显示以96 μm 的深度穿透表皮的微针。仅有针的由PLGA-E可生物降解聚合物组成的尖端可见。

[0138] 图7e显示以150 μm 的深度穿透表皮的微针。在这个深度,仅有针的由PLGA-E可生物降解聚合物组成的尖端可见。

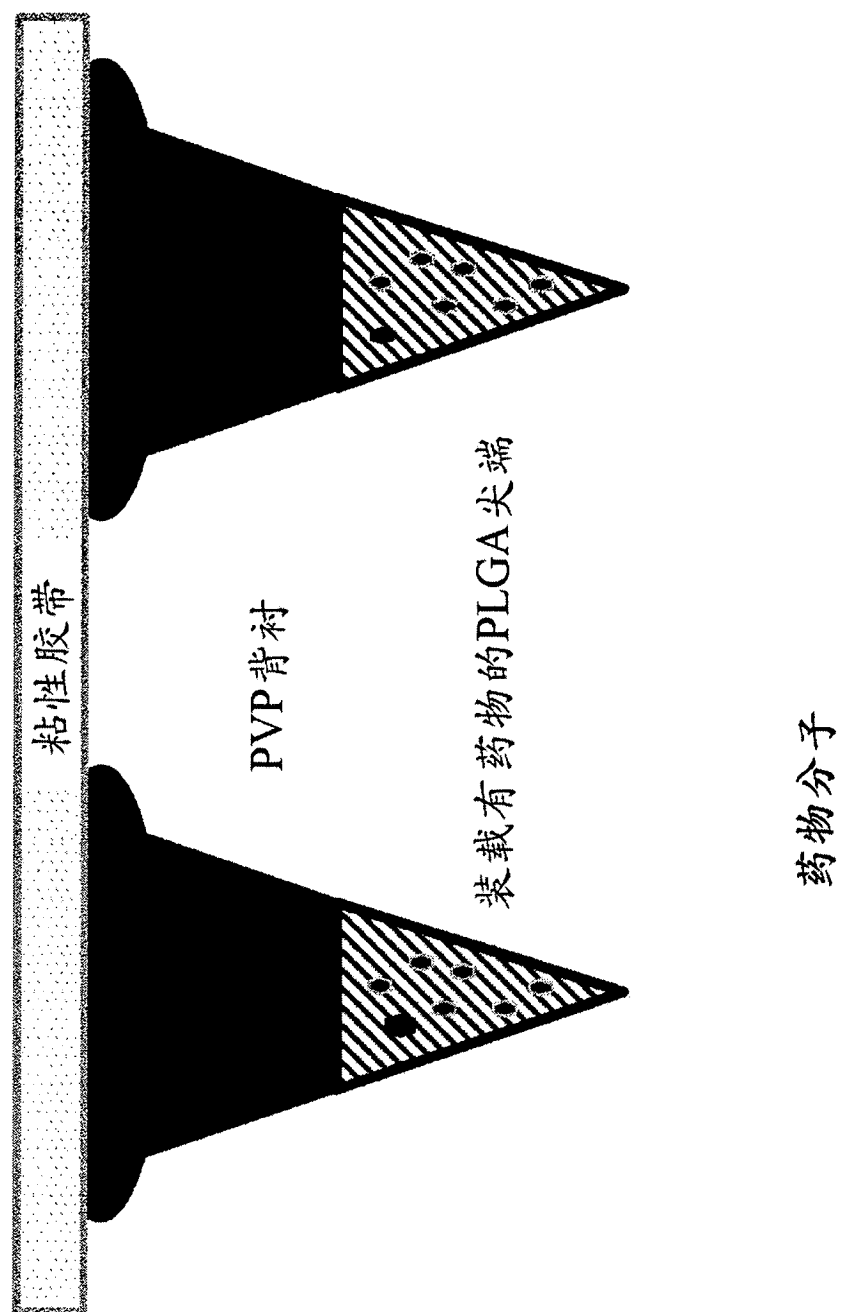


图1a

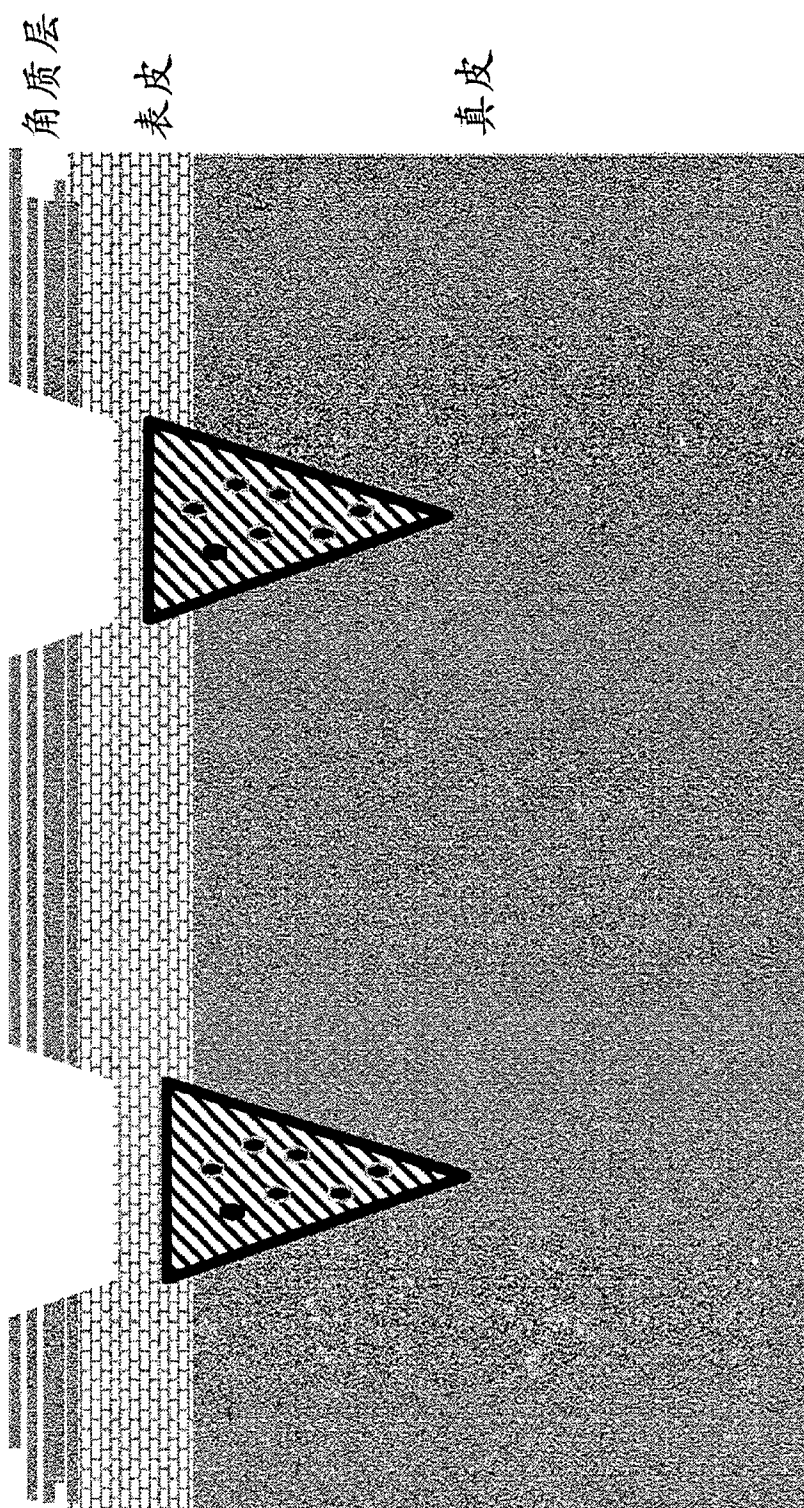


图1b

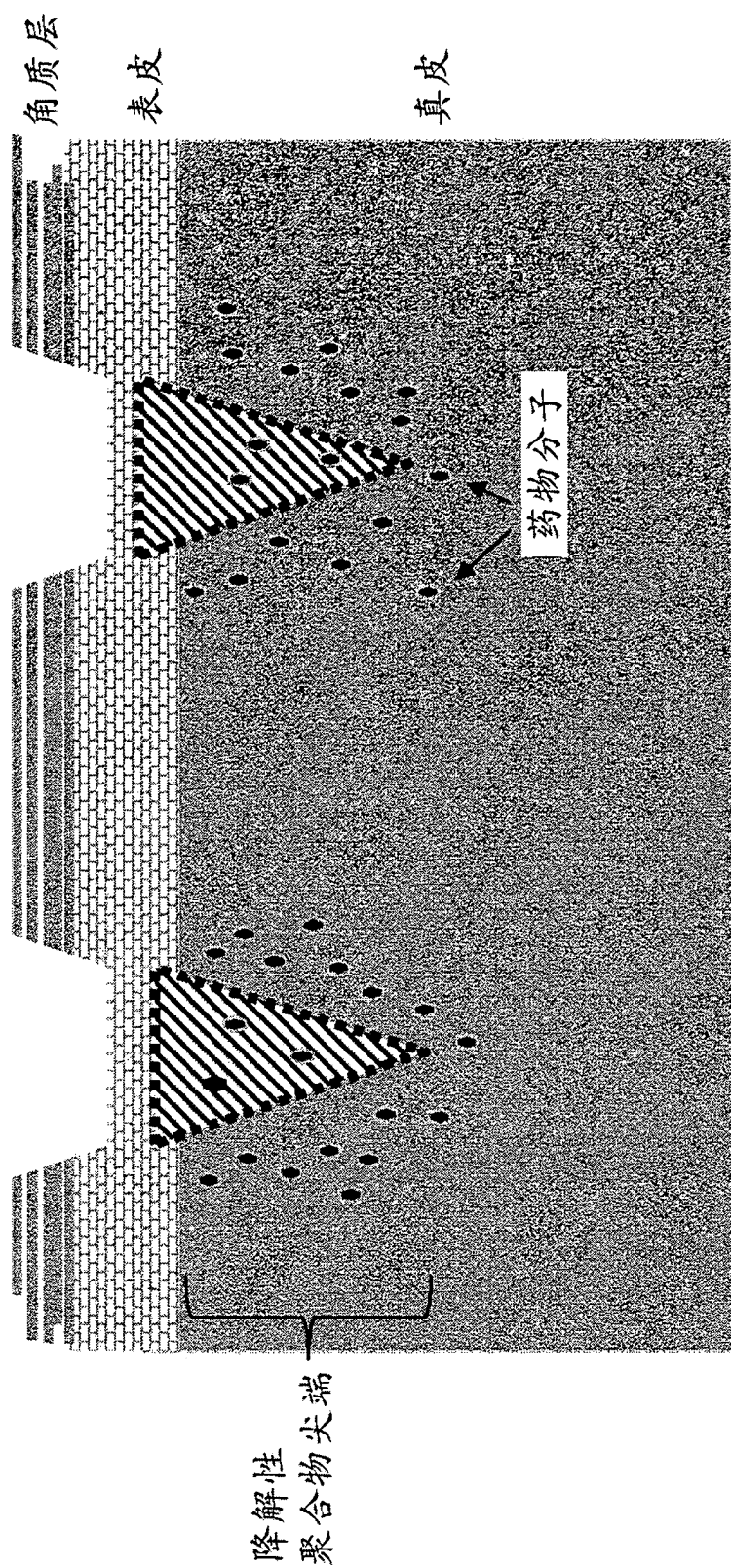


图1C

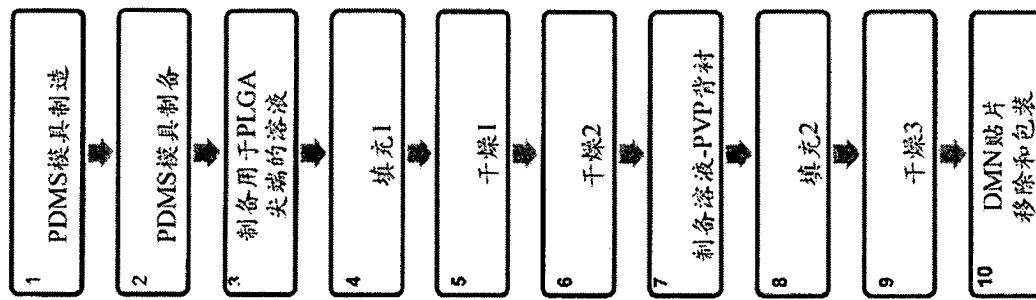


图2a

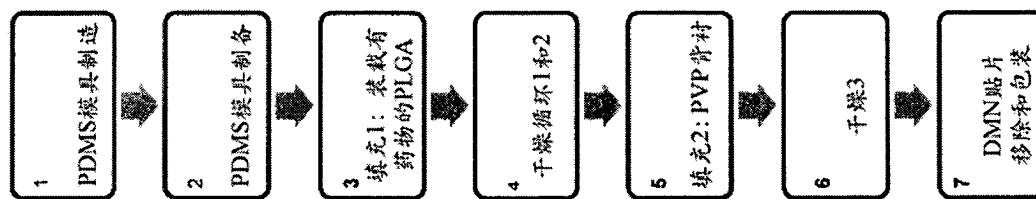


图2b

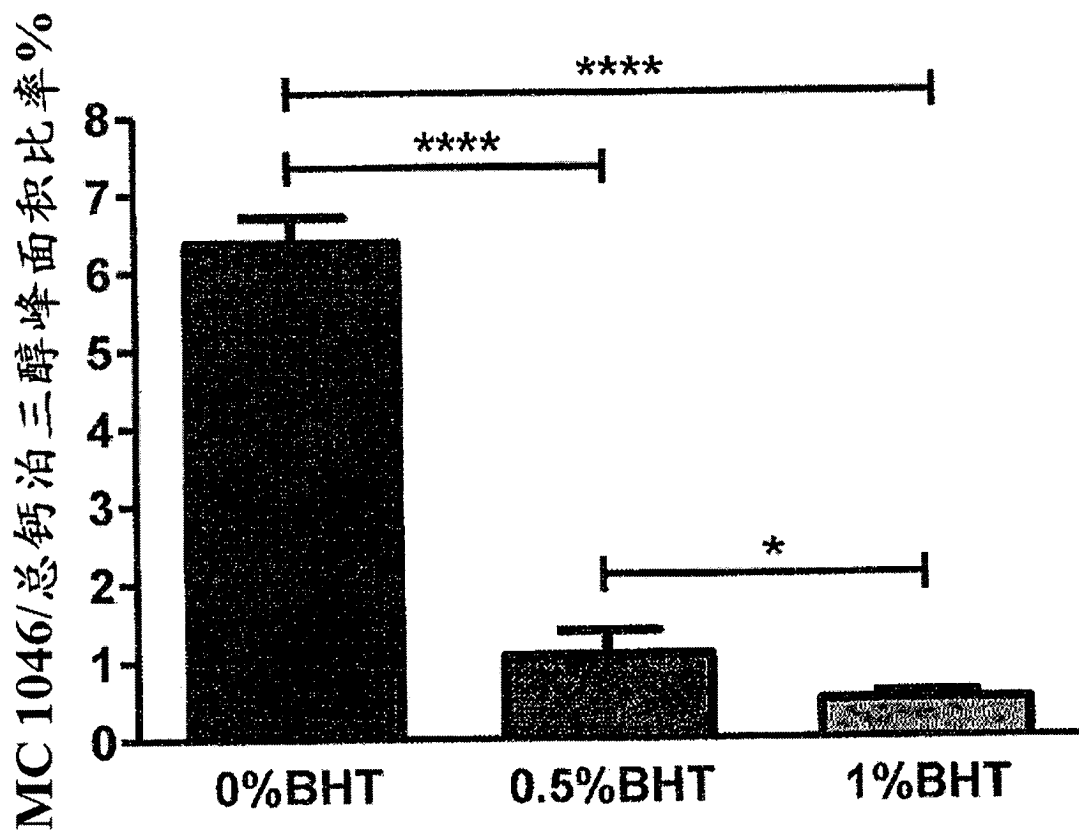


图3

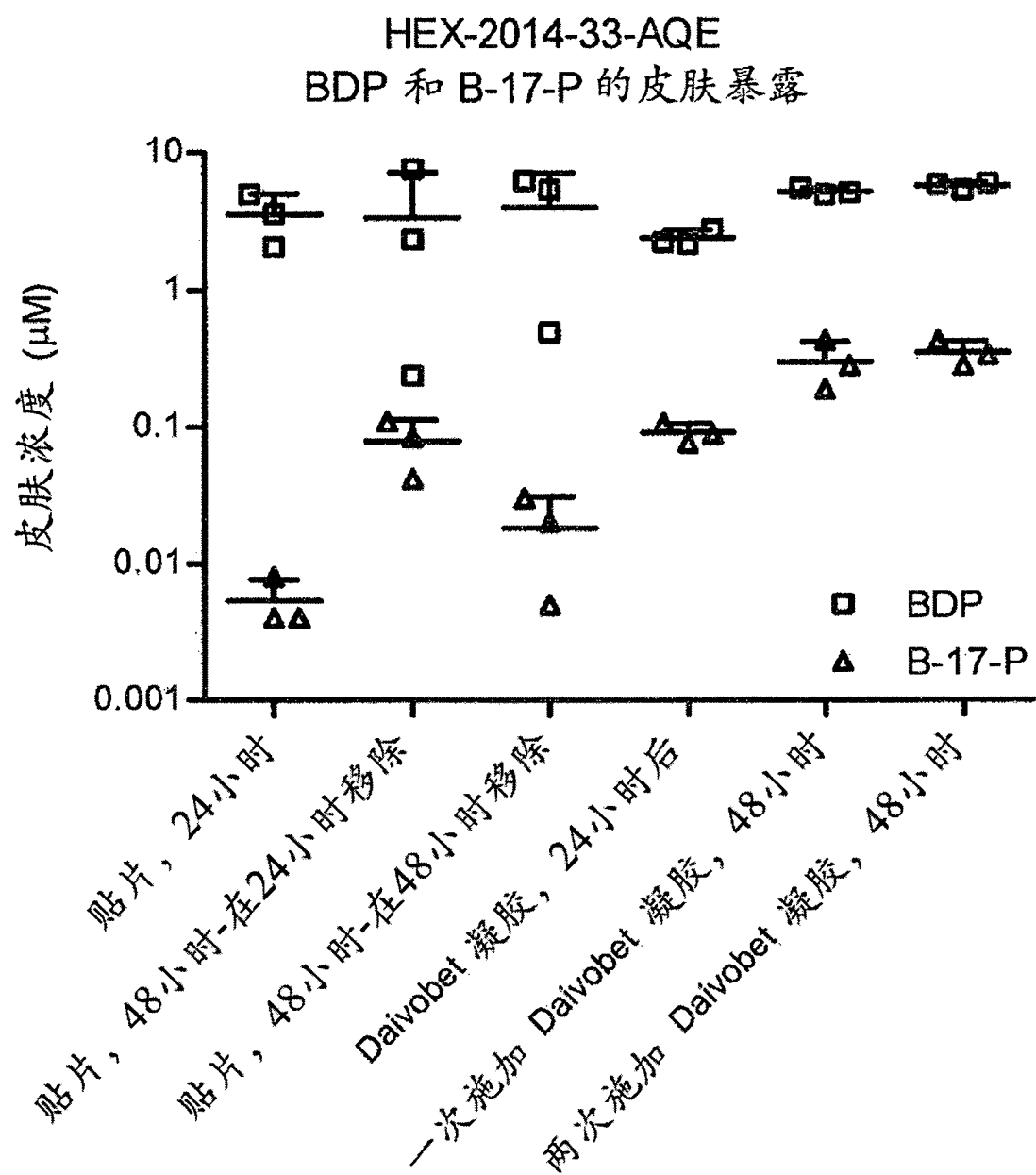


图4

EXP-HND-2014-31/HEX-2014-33-AQE.
CYP24A1

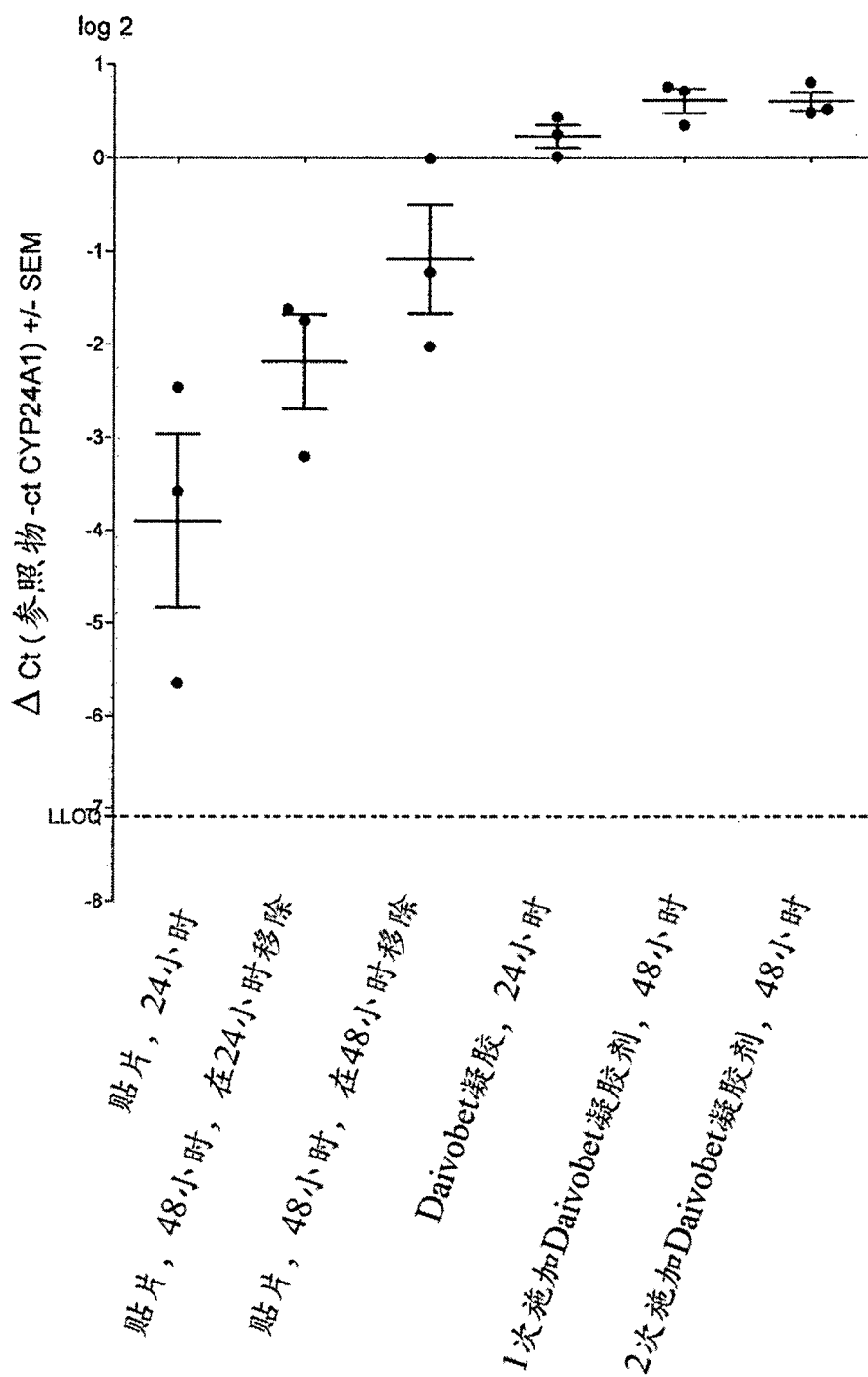


图5a

EXP-HND-2014-31/HEX-2014-33-AQE.
CD14

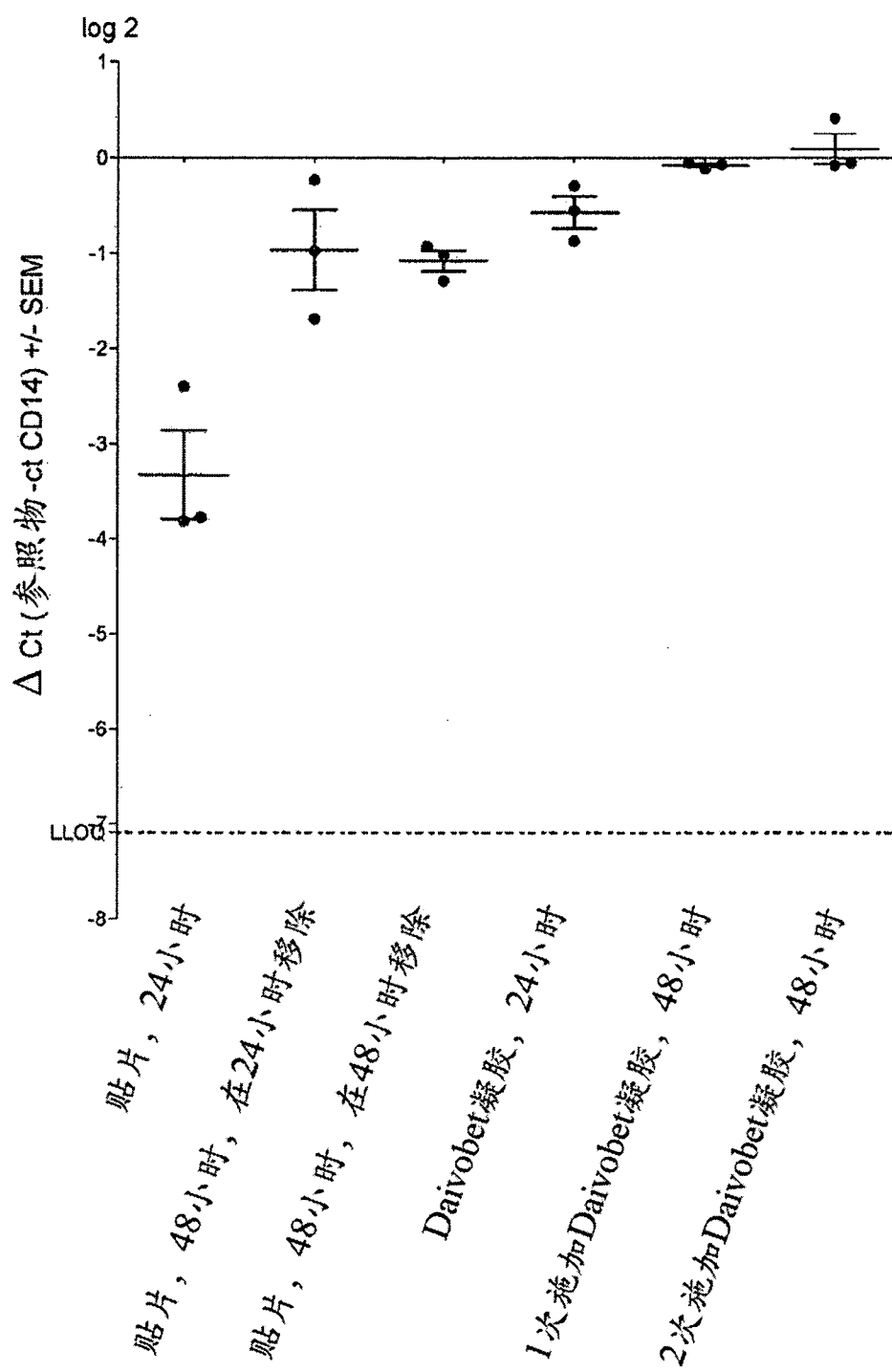


图5b

EXP-AQE-2015-17-HEX qPCR - CYP24A1

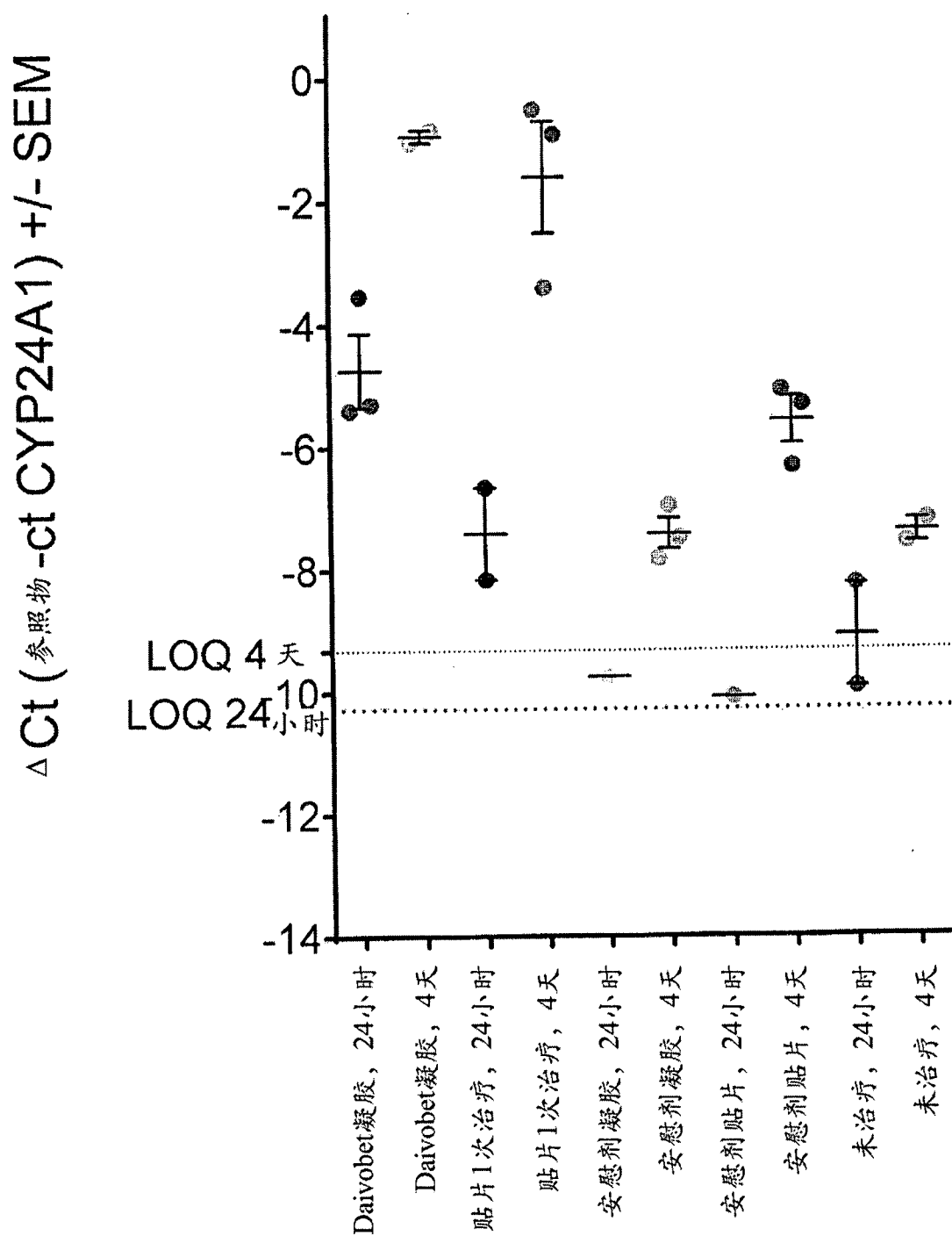


图6a

EXP-AQE-2015-17
B-17-P 的皮肤暴露

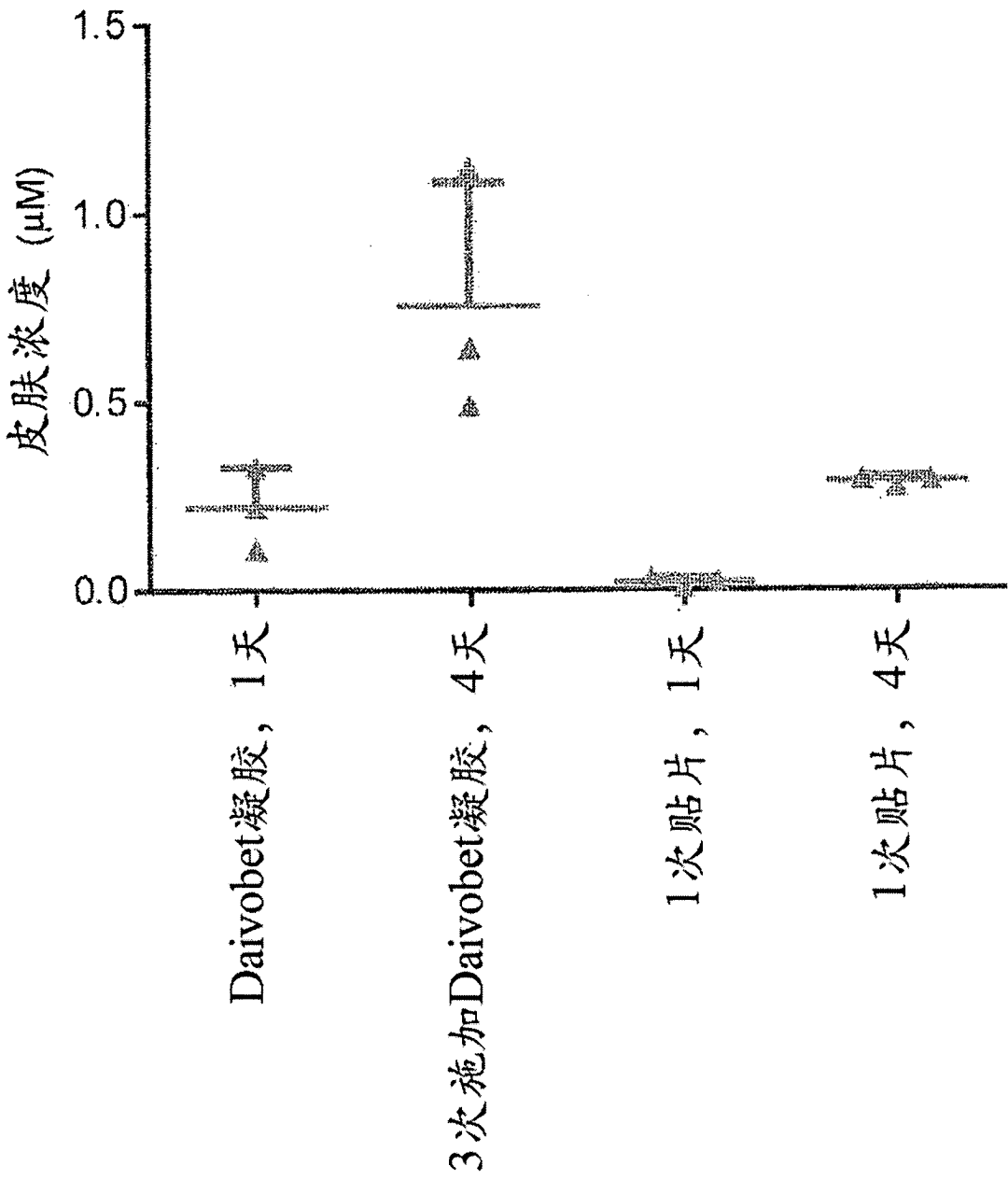


图6b

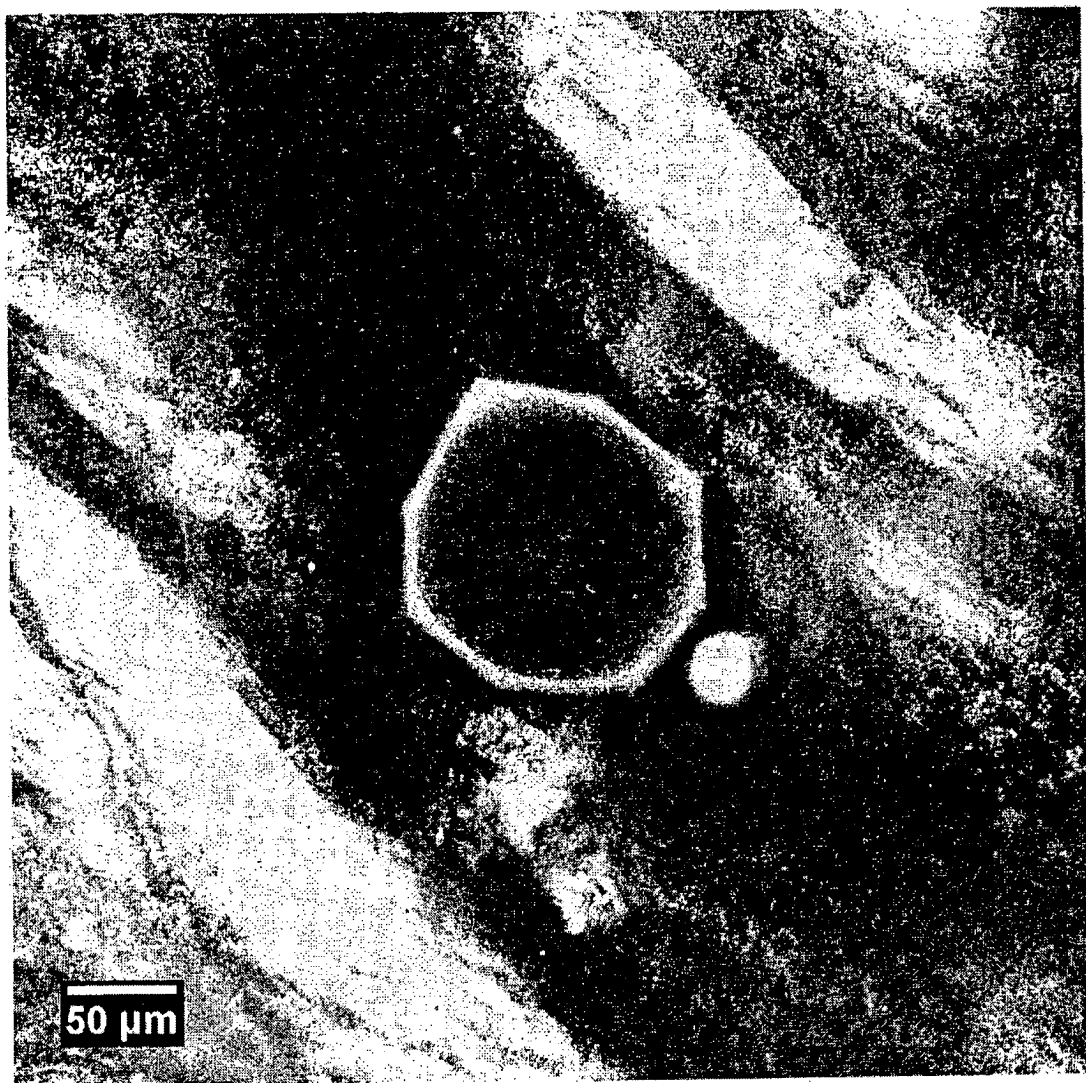


图7a

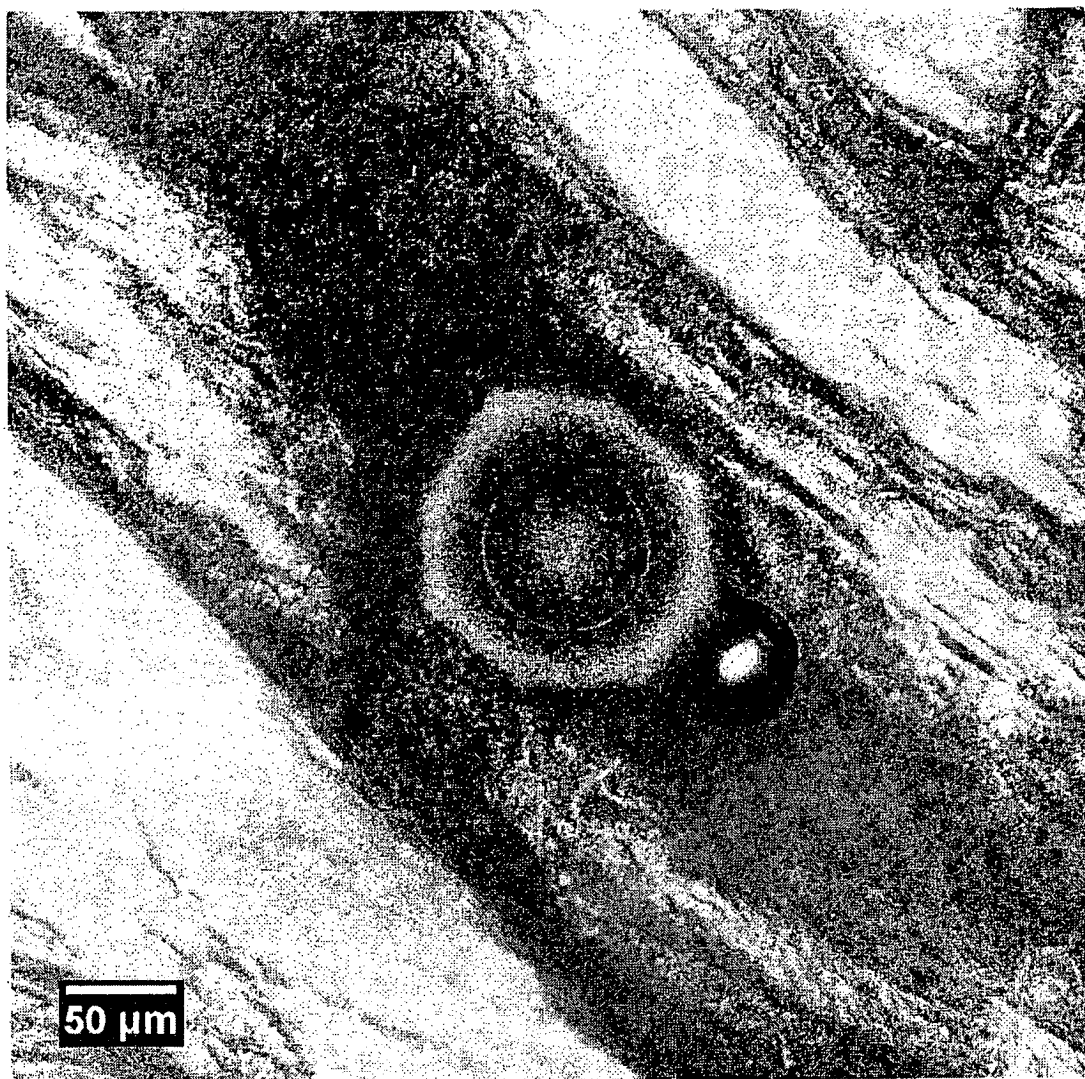


图7b

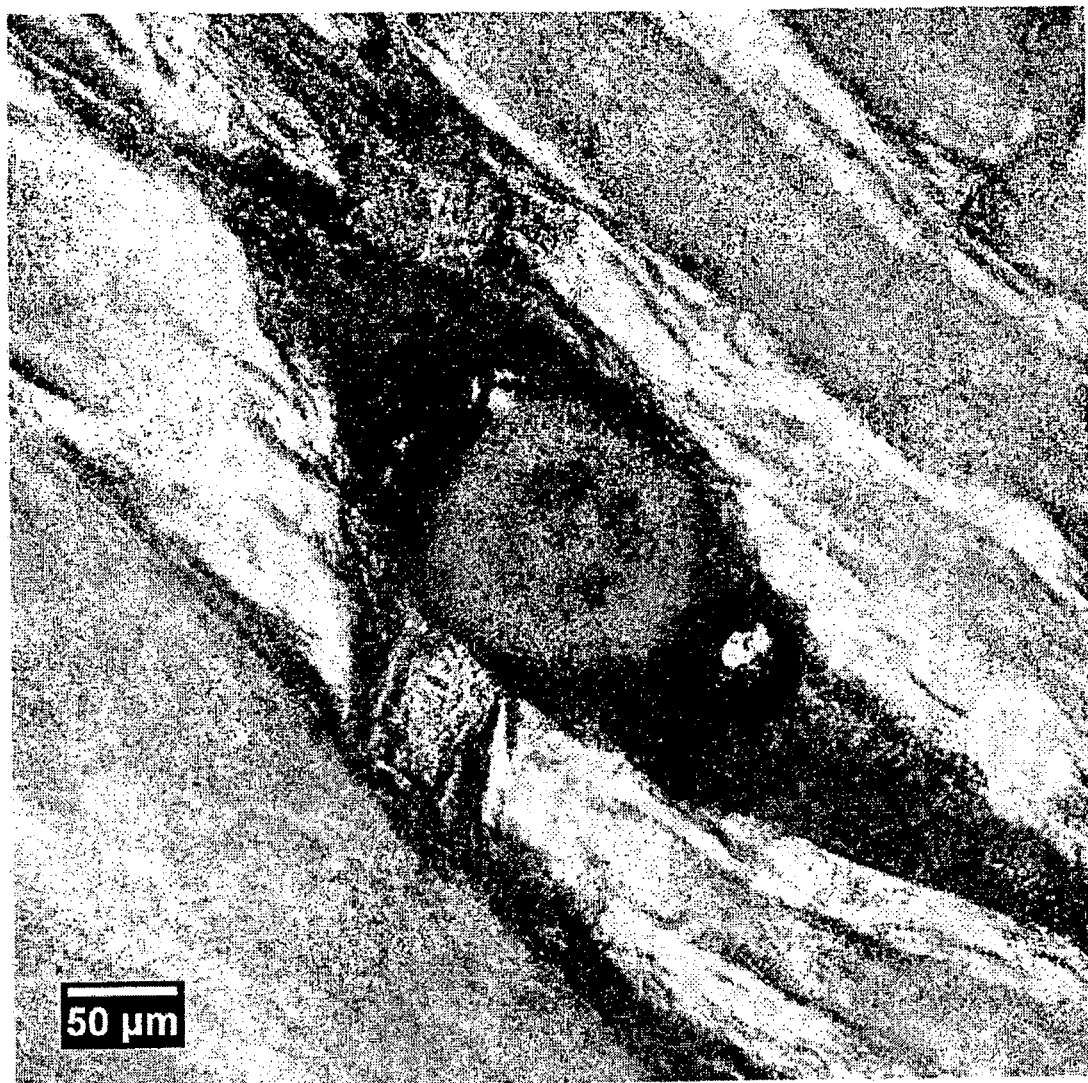


图7c

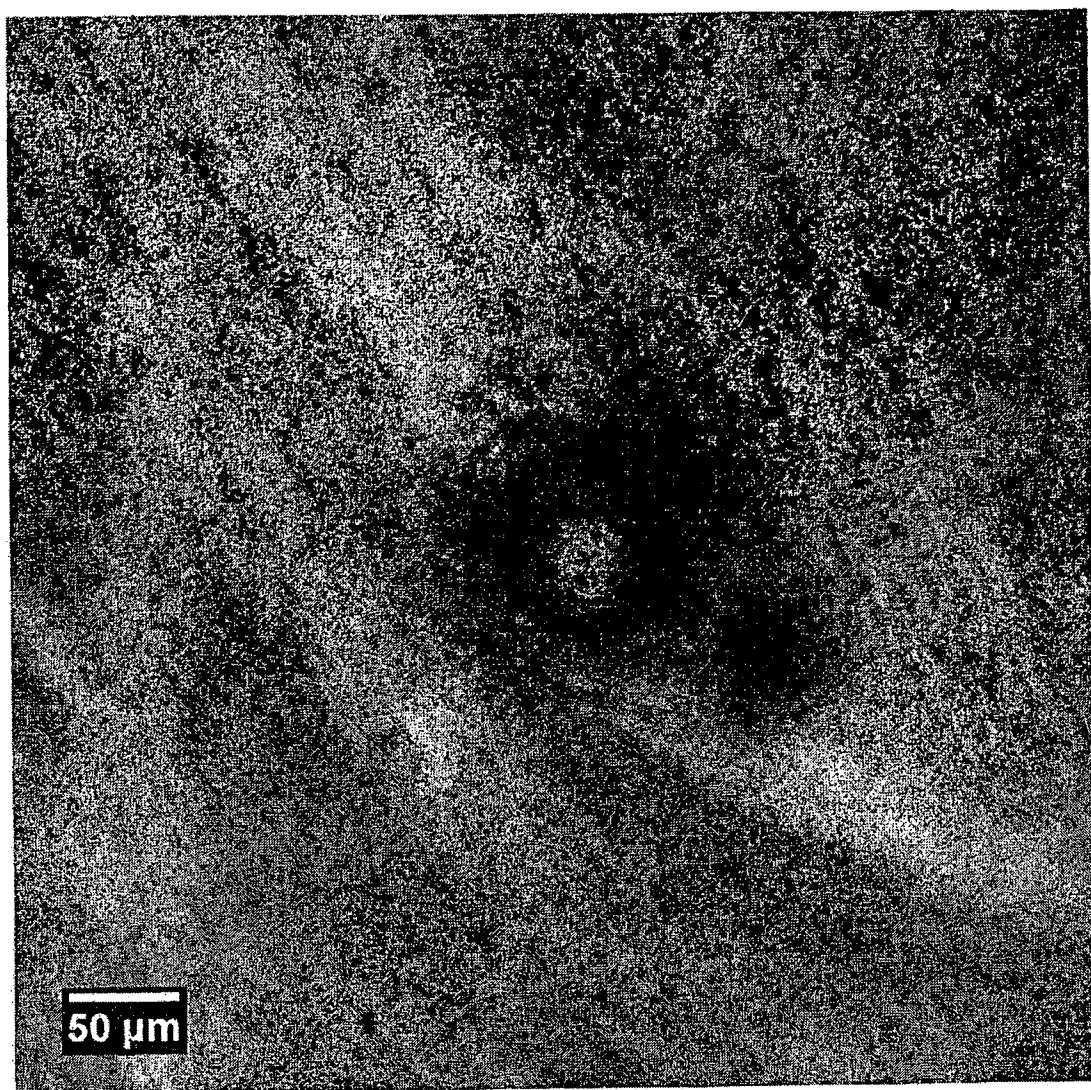


图7d

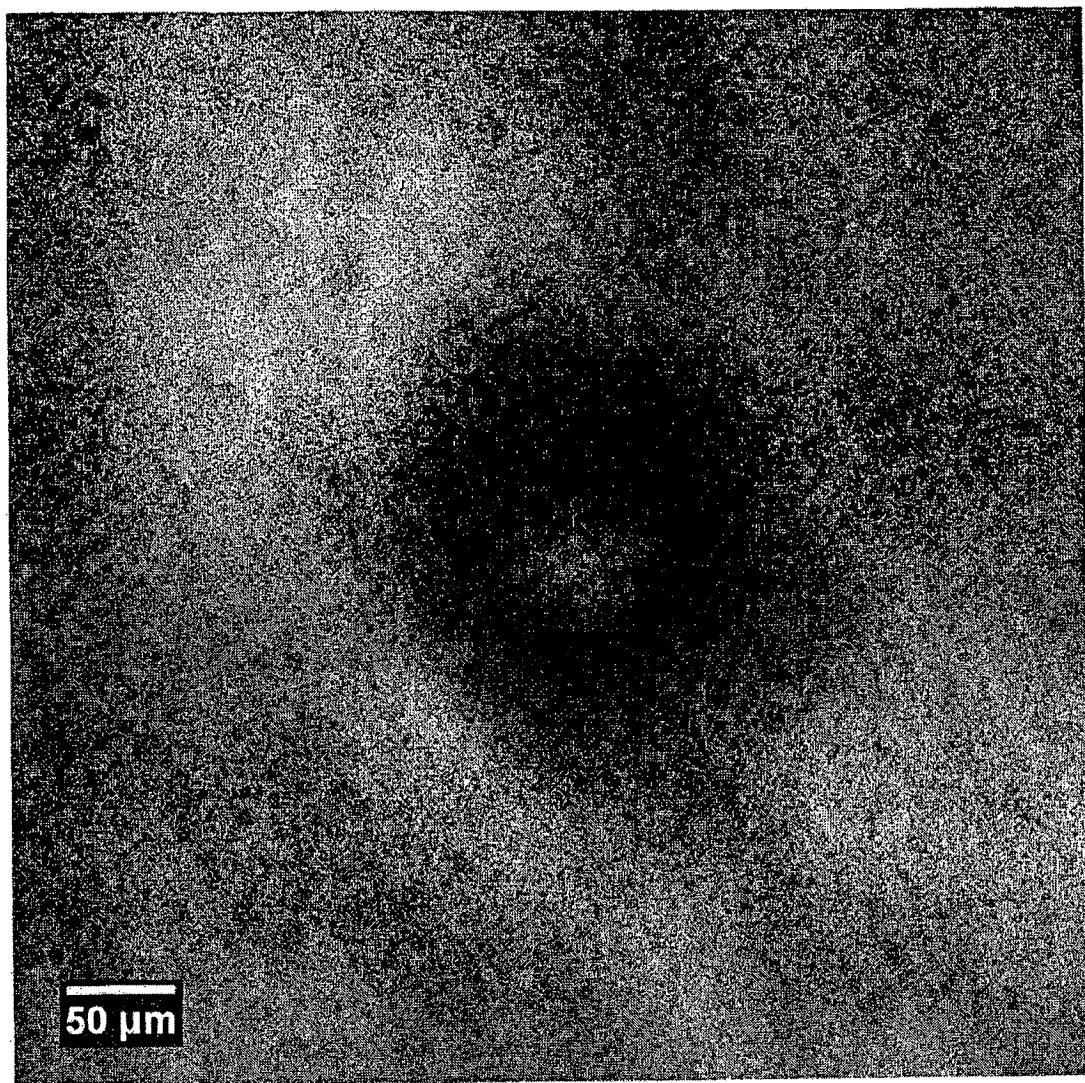


图7e

Abstract

The present invention relates to a microneedle patch composition comprising one or more microneedles each comprising: (a) a tapered tip portion containing a therapeutically active ingredient dispersed in a matrix of a biodegradable polymer capable of providing sustained release of the therapeutically active ingredient over a period of at least two days after insertion of the microneedle or microneedles into the skin, and (b) a fast dissolving microneedle backing layer portion containing a water-soluble polymer overlayering the tip portion, said microneedle or microneedles being attached to and extending from an adhesive surface of a removable substrate.