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(54) Title: COSMETIC PROCESS USING MICRONEEDLE SHEET

(57) Abstract: The present invention relates to a cosmetic process for a keratin substance such as the skin or the lips, comprising the steps of: applying onto the keratin substance a microneedle sheet comprising a substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer; and applying onto the microneedle sheet a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water. The cosmetic process according to the present invention can rapidly dissolve or disintegrate the substrate sheet.

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## DESCRIPTION

## COSMETIC PROCESS USING MICRONEEDLE SHEET

## 5 TECHNICAL FIELD

The present invention relates to a microneedle sheet comprising a plurality of microneedles which can be used for cosmetic treatments of a keratin substance such as the skin and the lips.

## 10 BACKGROUND ART

The stratum corneum (SC) constitutes the main barrier to exogenous substances including small molecular weight materials. In general, exogenous substances permeating the skin must diffuse through the highly organized intercellular lipid bilayers of the stratum corneum. This intercellular microroute, which is lipophilic, is the primary pathway for exogenous substances to pass through the SC barrier by passive diffusion along a concentration gradient between a delivery vehicle and the SC. It is difficult for some exogenous substances to penetrate into the skin.

20 In order to provide exogenous substances deeper into the skin, it is possible to perform injections using a conventional needle. However, such injections cause pain, and need to be performed by a professional such as a doctor. Thus, injections using a conventional needle are not common for cosmetic purposes.

25 The concept of using a micro-structured device with a plurality of microneedles to breach the stratum corneum (SC) barrier was first proposed in the 1970s. The production of microneedle arrays has been described in the art, for example in WO 2008/139786, WO 2009/040548, WO 2015/147040 and WO 2016/076442. Microneedles have an advantage of potentially penetrating the SC without pain caused by the use of conventional needles for injections, and can be self-administered.

## DISCLOSURE OF INVENTION

35 In general, microneedles are arrayed on a substrate sheet to form a microneedle sheet. A microneedle sheet is applied on a keratin substance such as the skin for some time so that the microneedles can be dissolved or disintegrated in the keratin substance by the moisture or water inside the keratin substance.

40 However, even after the dissolution or disintegration of the microneedles, the substrate sheet remains and may provide an uncomfortable feeling to the touch.

An objective of the present invention is to provide a cosmetic process using a microneedle sheet with microneedles on a substrate sheet wherein the substrate sheet can rapidly dissolve or disintegrate.

45 The above objective can be achieved by a cosmetic process for a keratin substance such as the skin or the lips, comprising the steps of:  
applying onto the keratin substance a microneedle sheet comprising a substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer; and

applying onto the microneedle sheet a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water.

The microneedle may have a height of from 50 to 1000 microns, preferably from 100 to 750 microns, and more preferably from 150 to 500 microns.

The microneedle may be in the shape of a cone.

The base of the cone of the microneedle may have a diameter of from 50 to 350 microns, preferably from 100 to 300 microns, and more preferably from 150 to 250 microns.

The ratio of (the height of the cone)/(the diameter of the base of the cone) of the microneedle may be 1 or more, preferably 1.5 or more, and more preferably 2.0 or more.

The water-soluble or water-dispersible polymer may be selected from hyaluronic acids, monosaccharides, disaccharides, oligosaccharides, polysaccharides, dextrans, dextrins, polyethylene glycols, polyvinyl alcohols, poly(methylvinylether/maleic anhydride), polyvinylpyrrolidone, poly(methyl/vinyl ether/maleic acid) (PMVE/MA) and esters thereof, poly(methyl/vinyl ether/maleic anhydride) (PMVE/MAH), and mixtures thereof.

The water-soluble or water-dispersible polymer may have a molecular weight of from 10,000 to 200,000 Dalton, preferably from 30,000 to 150,000 Dalton, and more preferably from 50,000 to 100,000 Dalton.

The conjugated fiber may comprise a fiber body comprising at least two polymers, preferably two apolar polymers, and more preferably two polyolefin polymers.

The conjugated fiber may have at least one coating.

The coating may comprise at least one polymer, preferably at least one hydrophilic polymer, and more preferably at least one hydrophilic acrylic polymer.

The porous sheet may be a woven or nonwoven fabric, preferably a nonwoven fabric, and more preferably a nonwoven fabric prepared by a thermal bonding process.

At least one of the microneedles may comprise at least one cosmetic active ingredient.

The present invention also relates to a kit comprising:

a microneedle sheet comprising a substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer;

and

a porous sheet comprising at least one conjugated fiber, preferably further comprising water, and more preferably packaged in a container with water.

The present invention also relates to a process for dissolving a substrate sheet of a microneedle sheet comprising the substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer,

comprising the step of:

applying a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water, onto the substrate sheet.

The present invention also relates to a use of a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water, in order to dissolve a substrate sheet of a microneedle sheet comprising the substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer.

## BEST MODE FOR CARRYING OUT THE INVENTION

After diligent research, the inventors have discovered that it is possible to provide a cosmetic process using a microneedle sheet with microneedles on a substrate sheet wherein the substrate sheet can rapidly dissolve or disintegrate.

Thus, one aspect of the present invention is a cosmetic process for a keratin substance such as the skin or the lips, comprising the steps of:

applying onto the keratin substance a microneedle sheet comprising a substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer; and

applying onto the microneedle sheet a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water.

According to the present invention, the substrate sheet can rapidly dissolve or disintegrate. In other words, the substrate sheet can dissolve or disintegrate in a short period of time. Thus, the substrate sheet, which may provide an uncomfortable feeling to the touch, can disappear easily, and does not remain on the keratin substance for a long period of time.

Therefore, the cosmetic process according to the present invention can be performed in a relatively short period of time.

Since microneedles do not cause any pain, the cosmetic process according to the present invention can provide cosmetic treatments without pain.

The present invention is convenient for cosmetic or non-therapeutic treatments.

Hereafter, the cosmetic process, kit, and the like according to the present invention will be described in a detailed manner.

### [Cosmetic Process]

The cosmetic process according to the present invention for a keratin substance such as the skin or the lips, comprises the steps of:

applying onto the keratin substance a microneedle sheet comprising a substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer; and

applying onto the microneedle sheet a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water.

The cosmetic process according to the present invention may be intended for cosmetic treatments of a keratin substance such as the skin or the lips, preferably the skin, and more preferably the skin of the face.

5 The cosmetic process according to the present invention may be used to improve the aesthetic appearance of a keratin substance, for example, by reducing the appearance of wrinkles or by providing the keratin substance with any cosmetic active ingredient, if present, in the microneedles.

10 A reduction in the amount of matrix, such as epidermis, in the skin tends to lead to a decrease in skin thickness and deterioration of skin elasticity, causing the formation of wrinkles. The microneedles can increase the amount of matrix in the skin to cause an increase of skin elasticity which results in the reduction of wrinkles on the skin.

15 If the microneedle, in particular the distal end portion, is swellable, it can swell in the skin to further increase the volume of the microneedle along with its absorption of, for example, water in the skin. Such volume expansion beneath the skin surface of a wrinkle site can effectively push the wrinkles from inside the skin and makes the wrinkles become shallower and wider. Thus, the wrinkles can be reduced or made less noticeable.

20 Thus, it is preferable that the cosmetic process according to the present invention comprise the step of pressing onto the keratin substance the microneedle sheet to securely insert the microneedles of the microneedle sheet into the keratin substance such as the skin.

25 In a particular embodiment, the cosmetic process according to the present invention can be used to apply semi-permanent or permanent cosmetic treatments to a keratin substance such as the skin.

30 Hereafter, the microneedle sheet and the porous sheet used for the cosmetic process according to the present invention will be explained in a detailed manner.

#### {Microneedle Sheet}

35 The microneedle sheet to be used for the process according to the present invention comprises a substrate sheet and a plurality of microneedles on a substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer.

40 The microneedle sheet to be used for the present invention may be a cosmetic device, preferably a cosmetic device for a keratin substance, and more preferably a cosmetic device for the skin, in particular the skin of the face, as well as the lips.

#### (Microneedles)

45 The microneedle sheet to be used for the present invention comprises a plurality of microneedles.

The microneedles are present on the surface of a substrate sheet. The microneedles may be present on 50% or more, preferably 70% or more, and more preferably 90% or more of the surface of the substrate sheet.

50

It is preferable that the microneedles be present on one of the surfaces of a substrate sheet.

It is preferable that the microneedles of the microneedle sheet to be used for the present invention be designed to penetrate or enter into the stratum corneum of the skin, in particular the skin of the face, as well as the lips.

A microneedle can be any suitable size and shape to puncture the stratum corneum. It may be preferable that the microneedles be designed to pierce and cross the stratum corneum. The microneedles may be capable of creating openings in the stratum corneum.

If necessary, the height of the microneedles may be altered so as to allow penetration into the epidermis and/or dermis of the skin, preferably into the upper dermis, and more preferably into the lower dermis.

The shape of the microneedles is not limited as long as the shape is a "needle". It will be apparent to those skilled in the art that the microneedles for the present invention can take any reasonable shape, including, but not limited to, cones, rods and/or pillars. As such, the microneedles may have the same diameter at the tip as at the base or may taper in diameter in the direction from the base to the tip.

For example, the shape of the microneedle may be in the form of a triangular pyramid, a square pyramid or a pentagonal pyramid. Alternatively, the microneedle may be in the form of a cylinder preferably with a tip which may be formed by diagonally cutting the cylinder.

Thus, reference is made to "microneedles" as a type of microprotrusion or microprojection which is being employed. It will be understood by persons skilled in the art that in many cases the same inventive principles apply to the use of other microprotrusions or microprojections to penetrate the skin. Other microprotrusions or microprojections may include, for example, microblades as described in U.S. Patent No. 6,219,574 and Canadian Patent Application No. 2,226,718, and edged microneedles as described in U.S. Patent No. 6,652,478.

The height or length of the microneedle of the microneedle sheet to be used for the present invention may be from 50 to 1000 microns, preferably from 100 to 750 microns, and more preferably from 150 to 500 microns.

According to one embodiment of the present invention, the microneedle is in the form of a cone.

The cone may comprise a distal end such as a tip and a base. The shape of the base may be a circle or oval.

The height or length of the cone of the microneedle of the microneedle sheet to be used for the present invention may be from 50 to 1000 microns, preferably from 100 to 750 microns, and more preferably from 150 to 500 microns.

The base of the cone of the microneedle of the microneedle sheet to be used for the present invention may have a diameter or width of from 50 to 350 microns, preferably from 100 to 300 microns, and more preferably from 150 to 250 microns. If the base of the cone of the microneedle of the microneedle sheet to be used for the present invention is in the shape of an

oval or ellipse, the length of the major axis or width of the oval may be from 50 to 350 microns, preferably from 100 to 300 microns, and more preferably from 150 to 250 microns.

The microneedle may have an aspect ratio (length/width at base) of at least about 3:1, at least about 2:1, or at least about 1:1. The ratio of (the height of the cone)/(the diameter of the base of the cone) of the microneedle may be 1 or more, preferably 1.5 or more, and more preferably 2.0 or more.

Preferably, the microneedles do not fracture by force when a pressure of insertion of less than 50.0 N/cm<sup>2</sup>, for example less than 20.0 N/cm<sup>2</sup>, such as less than 10 N/cm<sup>2</sup> is exerted on the microneedles along their length.

It is also preferable that the microneedle sheet to be used for the present invention, in particular the microneedles of the microneedle sheet, have a Young modulus of 50 N/mm or more, preferably 55 N/mm or more, and more preferably 60 N/mm or more.

It may be preferable that the microneedle be capable of penetrating into a keratin substance, such as the skin or the lips, to a depth of 200 microns or less, preferably 180 microns or less, and more preferably 160 microns or less.

The microneedle can be dissolvable or non-dissolvable. It is preferable that the microneedle be dissolvable.

The “dissolvable microneedle” is meant that the microneedle can be broken down or disintegrated inside a keratin substance such as the skin or the lips by, for example, a natural moisturizing factor or external moisture.

The microneedle of the microneedle sheet to be used for the present invention may comprise at least one water-soluble or water-dispersible polymer. Here, the terms “water-soluble” and “water-dispersible” mean soluble and dispersible, respectively, when being in contact with water. A single water-soluble or water-dispersible polymer may be used. Two or more water-soluble or water-dispersible polymers may be used in combination.

It is preferable that the water-soluble or water-dispersible polymer be soluble or dispersible in the skin or the lips. Thus, in one embodiment of the present invention, the water-soluble or water-dispersible polymer is capable of being dissolved or dispersed after insertion into a keratin substance such as the skin or the lips. Due to the solubility or dispersibility of the polymer, the microneedle of the microneedle sheet to be used for the present invention can effectively release an agent or agents, if present, in the microneedle. Optional external water combined with the application of the microneedle sheet can be used to accelerate the dissolution or dispersion of the microneedle.

It is preferable that the water-soluble or water-dispersible polymer be dissolvable in the surface layer of a keratin substance such as the skin or the lips.

The water-soluble or water-dispersible polymer may be selected from hyaluronic acids (in particular lower molecular weight hyaluronic acid), monosaccharides, disaccharides, oligosaccharides, polysaccharides (including derivatives thereof such as hydroxymethylcellulose), dextrans, dextrans, polyethylene glycols, polyvinyl alcohols, poly(methylvinylether/maleic anhydride), polyvinylpyrrolidone, poly(methyl/vinyl

ether/maleic acid) (PMVE/MA) and esters thereof, poly(methyl/vinyl ether/maleic anhydride) (PMVE/MAH), and mixtures thereof.

The water-soluble or water-dispersible polymer may have a molecular weight of from 10,000 to 200,000 Dalton, preferably from 30,000 to 150,000 Dalton, and more preferably from 50,000 to 100,000 Dalton.

The low molecular weight hyaluronic acid may have a molecular weight of 100 kDa or less, preferably 70 kDa or less, and more preferably 50 kDa or less.

The polyvinylpyrrolidone may have a molecular weight between 1 kDa and 300 kDa, preferably between 5 kDa and 200 kDa, and more preferably between 7 kDa and 100 kDa.

The poly(methyl/vinyl ether/maleic acid) (PMVE/MA) and esters thereof, and poly(methyl/vinyl ether/maleic anhydride) (PMVE/MAH) are known as Gantrez-type polymers.

The amount (solid basis) of the water-soluble or water-dispersible polymer(s) in the microneedle of the microneedle sheet to be used for the present invention may be 50% by weight or more, preferably 60% by weight or more, and more preferably 70% by weight or more, relative to the total weight of the microneedle. The amount (solid basis) of the water-soluble or water-dispersible polymer(s) in the microneedle of the microneedle sheet to be used for the present invention may be 100% by weight or less, preferably 90% by weight or less, and more preferably 80% by weight or less, relative to the total weight of the microneedle. Thus, the amount (solid basis) of the water-soluble or water-dispersible polymer(s) in the microneedle of the microneedle sheet to be used for the present invention may be from 50% to 100% by weight, preferably from 60% to 90% by weight, and more preferably from 70% to 80% by weight, relative to the total weight of the microneedle.

It may be possible that the microneedle of the microneedle sheet to be used for the present invention comprise at least one material which is swellable, more preferably water-swellable, and even more preferably swellable in a keratin substance such as the skin or the lips. The above material may be a polymer which is swellable, more preferably water-swellable, and even more preferably swellable in the keratin substance. Here, the term "water-swellable" means swellable when being in contact with water. The above swellable material or polymer may have a high swellability such that it can swell to at least over 10 times in a 1-hour *in vitro* incubation in a physiological saline solution or phosphate buffered saline, preferably at least 20 times in 1-hour incubation, more preferably at least 30 times in 1-hour incubation, even more preferably at least 40 times in 1-hour incubation, and most preferably about 45-55 times in 1-hour incubation.

It may be preferable that at least the distal end portion of the microneedle swell upon insertion into the keratin substance, more preferably within less than 1 hour, and even more preferably to at least 2 times within 24 hours after insertion into the keratin substance.

The above swellable material, preferably the above swellable polymer, may have a high viscoelasticity such that it can form a gel after the *in vitro* incubation in a physiological saline solution or phosphate buffered saline. The gel exhibits a high elastic modulus  $G'$ , a high viscous modulus  $G''$ , a Tangent ( $\delta$ ) ( $\text{Tangent } (\delta) = G''/G'$ ) of less than 1, and a high

consistency  $G^*$  ( $G^{*2}=G'^2 + G''^2$ ) even at low frequency (0.01 Hz) in a dynamic frequency sweep test with a Rheometer.

In one embodiment, the above swellable material, preferably the swellable polymer, is not water-soluble or not water-dispersible.

In another embodiment, the above swellable material, preferably the swellable polymer, may be a hydrogel-forming polymer.

The above swellable polymer may be selected from high molecular weight hyaluronic acids, cross-linked hyaluronic acids, cross-linked polyethylene glycol, polyethylene glycol cross-linked poly-lactic acid or poly-glycolic acid or poly-lactic-co-glycolic acid or poly dioxanone, poly(styrene)-block-poly(acrylic acid), polyethylene glycol cross-linked PMVE/MA, cross-linked polyvinylpyrrolidone, sodium starch glycolate; cellulose; natural and synthetic gums; alginates; sodium polyacrylate PEG-crosslinked poly(methyl/vinyl ether/maleic acid) (PMVE/MA) and esters thereof, PEG-crosslinked poly(methyl/vinyl ether/maleic anhydride) (PMVE/MAH) and esters thereof, and mixtures thereof.

The high molecular weight hyaluronic acid may have a molecular weight of more than 500 kDa, preferably more than 1000 kDa, and more preferably more than 2100 kDa, and preferably less than 10000 kDa.

Unless otherwise defined, the molecular weight here means a number average molecular weight.

The poly(methyl/vinyl ether/maleic acid) (PMVE/MA) and esters thereof, and poly(methyl/vinyl ether/maleic anhydride) (PMVE/MAH) are known as Gantrez-type polymers.

The amount (solid basis) of the swellable material(s) in the microneedle of the microneedle sheet to be used for the present invention may be 1% by weight or more, preferably 5% by weight or more, and more preferably 10% by weight or more, relative to the total weight of the microneedle. The amount (solid basis) of the swellable material(s) in the microneedle of the microneedle sheet to be used for the present invention may be 30% by weight or less, preferably 25% by weight or less, and more preferably 20% by weight or less, relative to the total weight of the microneedle. Thus, the amount (solid basis) of the swellable material(s) in the microneedle of the microneedle sheet to be used for the present invention may be from 1% to 30% by weight, preferably from 5% to 25% by weight, and more preferably from 10% to 20% by weight, relative to the total weight of the microneedle.

If the microneedle of the microneedle sheet to be used for the present invention comprises at least one swellable material, preferably at least one swellable polymer, the microneedle may be swellable such that it can improve the aesthetic appearance of a keratin substance, preferably the skin, and more preferably the skin of the face, by reducing the appearance of wrinkles.

In other words, if the microneedle is swellable, it can swell in the skin to further increase the volume of the microneedle along with its absorption of, for example, water in the skin. Such volume expansion beneath the skin surface of a wrinkle site can effectively push the wrinkles

from inside the skin and makes the wrinkles become shallower and wider. Thus, the wrinkles can be reduced or made less noticeable.

The apical separation distance between each of the individual microneedles on a substrate sheet can be modified to ensure the penetration of the skin or the lips by the microneedles while having a sufficiently small separation distance to provide high transdermal transport rates.

In one embodiment, the range of apical separation distances between microneedles can be in the range of 10-1000  $\mu\text{m}$ , such as 30-800  $\mu\text{m}$  or 50-600  $\mu\text{m}$ . This may allow a compromise to be achieved between efficient penetration of the stratum corneum by as many microneedles as possible and the necessary margin for possible swelling of the microneedles if they are swellable.

In one embodiment, the density of microneedles may be from 100 to 2000 microneedles/ $\text{cm}^2$ , preferably 200 to 1000 microneedles/ $\text{cm}^2$ , and even more preferably 200 to 500 microneedles/ $\text{cm}^2$ .

(Cosmetic Active Ingredient)

According to one embodiment, at least one of the microneedles of the microneedle sheet used for the present invention may comprise at least one cosmetic active ingredient. A single cosmetic active ingredient may be used. Two or more cosmetic active ingredients may be used in combination.

The type of the cosmetic active ingredient is not limited. For example, an anti-aging agent may be used as the cosmetic active ingredient.

As examples of the anti-aging agent, mention may be made of anti-oxidant, moisturizers, free-radical scavengers, keratolytic agents, vitamins, anti-elastase and anti-collagenase agents, protides, fatty acid derivatives, steroids, trace elements, bleaching agents, extracts of algae and of planktons, enzymes and coenzymes, flavonoids and ceramides, and mixtures thereof.

The amount of the cosmetic active ingredient(s) in the microneedle of the microneedle sheet used for the present invention is not limited, and may be from 0.01% to 10% by weight, preferably from 0.05% to 5% by weight, and more preferably from 0.1% to 1% by weight, relative to the total weight of the microneedle.

It is also possible that the amount of the cosmetic active ingredient(s) in the microneedle of the microneedle sheet to be used for the present invention be less than 0.01% by weight, relative to the total weight of the microneedle. In one embodiment, the microneedle of the microneedle sheet according to the present invention may include no cosmetic active ingredient.

(Substrate Sheet)

The microneedle sheet according to the present invention comprises a substrate sheet on which the microneedles are present or placed.

The substrate sheet of the microneedle sheet to be used for the present invention is dissolvable in water or disintegrable in water.

The substrate sheet of the microneedle sheet to be used for the present invention comprises at least one water-soluble or water dispersible polymer, as explained above. In other words, the above explanations for the water-soluble or water-dispersible polymer which may be comprised in the microneedles of the microneedle sheet can apply to the water-soluble or water-dispersible polymer comprised in the substrate sheet.

For example, the amount (solid basis) of the water-soluble or water-dispersible polymer(s) in the substrate sheet of the microneedle sheet to be used for the present invention may be 50% by weight or more, preferably 60% by weight or more, and more preferably 70% by weight or more, relative to the total weight of the substrate sheet. The amount (solid basis) of the water-soluble or water-dispersible polymer(s) in the substrate sheet of the microneedle sheet to be used for the present invention may be 100% by weight or less, preferably 90% by weight or less, and more preferably 80% by weight or less, relative to the total weight of the substrate sheet. Thus, the amount (solid basis) of the water-soluble or water-dispersible polymer(s) in the substrate sheet of the microneedle sheet to be used for the present invention may be from 50% to 100% by weight, preferably from 60% to 90% by weight, and more preferably from 70% to 80% by weight, relative to the total weight of the substrate sheet.

The substrate sheet and the microneedles may be separated or integrated.

For example, the substrate sheet and the microneedles may comprise at least one common water-soluble or water dispersible polymer. Thus, in one embodiment, the substrate sheet and the microneedles can be a single element comprising at least one common water-soluble or water-dispersible polymer. Preferably, the single element can be prepared by using the same water-soluble or water-dispersible polymer(s).

On the other hand, the substrate sheet may be different or distinct from the microneedles. For example, the substrate sheet and the microneedles may be made from different materials. In this case, the substrate sheet may be, for example, chosen from masks, wipes, patches, and in general all types of porous substrate sheets. Preferably, these substrate sheets have an oblong structure, namely with a thickness smaller than the dimensions of the plane in which they are defined.

The substrate sheet may be cut so as to be in the form of a patch, a disc, a mask, a towel, a glove, a precut roll, or any other form suitable for a cosmetic use.

#### (Preparation)

There is no limitation regarding how to prepare the microneedle sheet to be used for the present invention. It is possible to prepare the microneedle sheet to be used for the present invention based on conventional technology such as molding, 3D printing and droplet born air blowing.

The microneedle sheet to be used for the present invention can be prepared, for example, by a process comprising the steps of molding a composition comprising at least one water-soluble or water-dispersible polymer, as explained above.

In one embodiment, the microneedle sheet to be used for the present invention can be prepared by a process comprising the steps of

- (a) providing a mold with cavities corresponding to a negative of the microneedles,
- (b) filling a composition comprising at least one water-soluble or water-dispersible polymer, as explained above, into the cavities,
- (c) solidifying the composition, for example, by drying at room temperature (and optionally heating) for a period of time such as several hours to form the microneedles, and
- (d) removing the microneedle sheet from the mold.

The mold may be made from organic materials such as polyamides and silicones and inorganic materials such as aluminum and iron.

At least one evaporable liquid ingredient may be included in the above composition, if necessary, in order to enhance the fluidity of the composition. Examples of the evaporable liquid ingredient are not limited, but may preferably be water and alcohol such as ethanol.

The amount of the evaporable liquid ingredient(s) may be 10% by weight or more, preferably 20% by weight or more, and more preferably 30% by weight or more, relative to the total weight of the composition. The amount of the evaporable liquid ingredient(s) may be 98% by weight or less, preferably 95% by weight or less, and more preferably 90% by weight or less, relative to the total weight of the composition. Thus, the amount of the evaporable liquid ingredient(s) may be from 10% to 98% by weight, preferably from 20% to 95% by weight, and more preferably from 30% to 90% by weight, relative to the total weight of the composition.

The amount of the water-soluble or water-dispersible polymer(s) in the above composition, which is preferably capable of flowing, and more preferably is in the form of a liquid, may be from 2% to 90% by weight, preferably from 5% to 50% by weight, and more preferably from 5% to 30% by weight relative to the total weight of the composition.

If necessary, the above composition may include at least one additional polymer such as the above-explained swellable polymer and/or at least one cosmetic active ingredient as explained above.

The shape of the microneedle sheet to be used for the present invention is not limited, and it may be any shape such as the shape of the lips or a shape suitable for application under the eyes, depending on the application target of the microneedle sheet.

#### {Porous Sheet}

The porous sheet to be used for the cosmetic process according to the present invention comprises at least one conjugated fiber.

The conjugated fiber comprises a body made from at least two polymeric materials. The body may comprise a core and a sheath. In one embodiment, the core comprises at least one polymeric material, and the sheath comprises at least one polymeric material.

In a preferred embodiment, the conjugated fiber is a bi-component fiber. Thus, it is preferable that the body comprise two polymers each of which forms a core and a sheath. In one

embodiment, the polymers of the body, in the cross section of the fiber, are arranged as sheath/core side by side. In one embodiment, the polymers of the body, in the cross section of the fiber, are arranged as concentric or eccentric sheath/core.

- 5 In one preferred embodiment, the body comprises a core having a higher melting point (melting temperature) and a sheath having a lower melting point (melting temperature).

Within the meaning of the present invention, the melting point corresponds to the temperature of the most endothermic peak observed by thermal analysis (DSC) as described in ISO 1  
10 1357-3. The melting point can be measured using a differential scanning calorimeter (DSC), for example the calorimeter sold under the name "MDSC 2920" by TA Instruments.

In one embodiment, the melting point of the core of the body is higher than 150°C. In one  
embodiment, the melting point of the core of the body is higher than 230°C. In one  
15 embodiment, the melting point of the core of the body ranges from 150°C to 300°C. In one  
embodiment, the melting point of the core of the body ranges from 230°C to 300°C.

In one embodiment, the melting point of the sheath of the body is lower than 230°C. In one  
embodiment, the melting point of the sheath of the body is lower than 150°C. In one  
20 embodiment, the melting point of the sheath of the body ranges from 100°C to 230°C. In one  
embodiment, the melting point of the sheath of the body ranges from 100°C to 150°C.

In one preferred and specific embodiment, said conjugated fiber comprises a body comprising  
a core formed by a first polymer and a sheath formed by a second polymer, wherein said first  
25 polymer has a melting point higher than the second polymer.

Non-limiting examples of polymers which can be used as one of the polymers for said body  
are selected from the group consisting of polyesters such as polylactic acid, derivatives of  
polyesters, polyamides such as Nylon 6 and Nylon 66, polyolefins such as polypropylene and  
30 polyethylene, polystyrenes, and any mixtures thereof.

In one embodiment, non-limiting examples of polymers which can be used as one of the  
polymers for said body are selected from the group consisting of low density polyethylene  
(LDPE), polypropylene (PP) high density polyethylene (HDPE), ultra-high molecular weight  
35 polyethylene (UHMW), polypropylene (PP), polyvinylidene fluoride (PVDF),  
polytetrafluoroethylene (PTFE), polyester, and polyethersulfone (PES), and any mixtures  
thereof.

In one embodiment, the core of the body is selected among polypropylene (PP), and the  
40 sheath of the body is selected among polyethylene (PE), wherein said polypropylene has a  
melting point higher than said polyethylene.

Some common examples of combinations of two fibers are shown below:

- Polyester core (250°C melting point) with copolyester sheath (melting points of  
45 110°C to 220°C)
- Polyester core (250°C melting point) with polyethylene sheath (130°C melting point)
- Polypropylene core (175°C melting point) with polyethylene sheath (130°C melting  
point)

In a preferred embodiment, the conjugated fiber may comprise a fiber body comprising at least two polymers, more preferably two apolar polymers, and even more preferably two polyolefin polymers such as polyethylenes and polypropylenes.

5 In a preferred embodiment, the conjugated fiber has at least one coating.

In one embodiment, the coating comprises at least one polymer. Preferably, the polymer in the coating comprises a hydrophilic polymer, and more preferably at least one hydrophilic acrylic polymer. The hydrophilic polymer may preferably be selected from the group  
10 consisting of any commercially available hydrophilic polymers. Non-limiting examples for such polymers may be selected from acrylic acid, methacrylic acid, glutamic acid,  $\beta$ -carboxyethyl acrylate, maleic acid, monoesters of maleic acid, etc. More preferably, said hydrophilic polymers are acrylic or acrylate polymers.

15 Acrylic or acrylate polymers containing carboxyl groups are commercially available. In one particular embodiment, said hydrophilic polymer is poly(acrylic acid). For example, poly(acrylic acid) can be obtained from, among other sources, Polycryl AG, Bohler, Postfach, CH-6221 Rickenbach, Switzerland (trade name: Polycryl); Stockhausen, 2401 Doyle Street, Greensboro, N.C., 27406-2911; and BFGoodrich, Four Coliseum Centre, 2730 West Tyvola Rd., Charlotte, N.C. 28217-4578 (trade name: Carbopol).  
20

The polymer for the conjugated fiber (either for the body or the coating) designates a polymer made on the basis of a single monomer or of two or more monomers. Accordingly, the term polymer is broad in the sense of the present invention and includes homopolymers and  
25 copolymers unless indicated otherwise. Copolymers designate random and alternating copolymers, without limitation except that it is suitable for the present invention.

The polymer for the conjugated polymer may be linear or branched.

30 In one specific embodiment, the conjugated fiber may comprise a PP core and a PE sheath in the body, and poly(acrylic acid) in the coating.

In one specific embodiment, the conjugated fiber may consist of a body consisting of a PP core and a PE sheath, and of a coating consisting of poly(acrylic acid).  
35

It is preferable that the conjugated fibers be entangled. The porous sheet may be a fibrous sheet, preferably a woven or nonwoven fabric, and more preferably a nonwoven fabric.

The porous sheet, such as a nonwoven fabric, may have pores formed in between the  
40 nonwoven fibers. In one embodiment, the porous sheet may comprise conjugated fibers having a linear mass density ranging from 0.1 to 100 dtex, preferably from 0.3 to 10 dtex, and more preferably from 0.5 to 8 dtex.

One technical advantage of the porous sheet is the light weight of the porous sheet.  
45

The size and shape of the porous sheet depend on, for example, the application target. For example, the porous sheet may have a surface area ranging from 0.25 cm<sup>2</sup> to 500 cm<sup>2</sup>, preferably from 200 cm<sup>2</sup> to 450 cm<sup>2</sup>. The solid substrate typically has a density (grammage) of 5 g/m<sup>2</sup> to 400 g/m<sup>2</sup>, preferably 5 g/m<sup>2</sup> to 80 g/m<sup>2</sup>. In one specific embodiment, the porous

sheet has a density (grammage) of 5 to 40 g/m<sup>2</sup>, preferably 10 to 30 g/m<sup>2</sup>, and more preferably 15 to 25 g/m<sup>2</sup>. Gram/square meter or g/m<sup>2</sup> is also known as gsm.

The porous sheet may be prepared by a thermal bonding process.

The porous sheet, such as a nonwoven fabric, may be prepared by a process comprising:

- (i) extruding at least two polymeric materials;
- (ii) forming a plurality of conjugated fibers comprising said at least two polymers, preferably two apolar polymers, and more preferably two polyolefin polymers;
- (iii) coating said conjugated fibers by at least one polymer, preferably at least one hydrophilic polymer, and more preferably at least one hydrophilic acrylic polymer; and
- (iv) bonding said plurality of conjugated fibers by a bonding process.

In one embodiment, said bonding process (iv) comprises carding and thermal bonding of said plurality of conjugated fibers.

In one embodiment, said process comprises (i) extruding at least two polymers in the same spinneret, and (ii) forming a plurality of conjugated fibers comprising said at least two polymers, one polymer forming a core of the fiber body and another polymer forming a sheath of the fiber body.

In one embodiment, the process comprises carding said plurality of conjugated fibers comprising said at least two polymers passing hot air through the nonwoven web of fibers.

This is referred to as a hot air process or thermal bonding process.

In a preferred embodiment, the temperature for the hot air process for making a porous sheet is selected in a way that only the sheath of the fiber body is melted and the core of the fiber body remains in non-melted form. Accordingly, said thermal bonding is advantageously performed at a temperature for melting the sheath of the fiber body but not melting the core of the body fiber.

In one embodiment, said bonding process (iv) is performed at a temperature in the range of 100°C to 230°C.

Advantageously, this hot air process results in a consoled material, and gives the porous sheet a fluffy soft feel required in particular for topical applications, especially for cosmetic applications. Because of non-melting of the fiber body, preferably the core thereof, the prepared sheet remains in open structure, which gives it advantageously a fluffy and soft feel.

The porous sheet to be used for the cosmetic process according to the present invention comprises water. The amount of water is not limited. However, it is preferable that the amount of water be 50% or more, preferably 70% or more, and more preferably 90% or more of the water-holding capacity of the porous sheet. It is most preferable that the porous sheet be saturated with water.

In one embodiment, the porous sheet may be in the form of a face mask. In a preferable embodiment, the porous sheet may comprise at least one cosmetic active ingredient as explained above.

In another embodiment, the porous sheet may be a wipe.

In one embodiment, the porous sheet may have a rounded shape, for example a circular or oval shape. In another embodiment, the porous sheet may have a polygonal shape.

5

In one embodiment, the porous sheet may be in the form of a face mask capable of defining at least one central through opening, intended to receive the nose of a user, and at least two upper through openings for placement in front of the eyes of the user.

10

Advantageously, the porous sheet may comprise at least two through openings intended to be placed facing the eyes of a user, and another through opening intended to be placed facing the mouth of a user. In a particular embodiment, the face mask may also comprise a slit delimiting a flapper intended to be pushed away by the nose of the user, to delimit a nose insertion through opening. In a variant, the slit delimits a through opening without a flapper.

15

In a particular embodiment, the porous sheet is deformable to the touch, to adapt to the conformation of the body or face surface.

#### [Kit, Process, and Use]

20

The present invention also relates to a kit comprising:

a microneedle sheet comprising a substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer;

and

25

a porous sheet comprising at least one conjugated fiber, preferably further comprising water, and more preferably packaged in a container with water.

The porous sheet in the kit according to the present invention may be dry. In this case, the porous sheet is made wet before being used.

30

It is preferable that the porous sheet in the kit according to the present invention comprise water. In other words, it is preferable that the porous sheet in the kit according to the present invention be wet.

35

It is more preferable that the porous sheet in the kit according to the present invention be packaged in a container including water.

The container may include not only water but also at least one cosmetic active ingredient as explained above.

40

The container may preferably be a bag or sachet made from any material, preferably a plastic or metal film. Aluminum foil, in particular a laminated aluminum foil, is more preferable as the material for the bag or sachet.

45

Thus, the porous sheet may be folded before being contained in the container.

The kit can preferably be used for performing a cosmetic process according to the present invention.

The present invention also relates to a process for dissolving a substrate sheet of a microneedle sheet comprising the substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer,

5 comprising the step of:

applying a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water, onto the substrate sheet.

10 The present invention relates to a use of a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water, in order to dissolve a substrate sheet of a microneedle sheet comprising the substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer.

15 According to the above process and use according to the present invention, the substrate sheet of the microneedle sheet can rapidly dissolve or disintegrate. In other words, the substrate sheet of the microneedle sheet can dissolve or disintegrate in a short period of time. Thus, the substrate sheet, which may impart an uncomfortable feeling to the touch, of the microneedle sheet can disappear easily, when the microneedle sheet is used, and does not remain on a  
20 keratin substance for a long period of time.

Therefore, the above process or use according to the present invention can reduce the time required for a cosmetic or non-therapeutic treatment process using a microneedle sheet.

25 The above explanations for the microneedle sheet and the porous sheet for the cosmetic process according to the present invention can also apply to those in the kit, process, and use according to the present invention.

## EXAMPLES

30 The present invention will be described in a more detailed manner by way of examples. However, these examples should not be construed as limiting the scope of the present invention. The examples below are presented as non-limiting illustrations in the field of the present invention.

35 [Microneedle Patch]

A microneedle sheet was prepared using sodium hyaluronate with an average molecular weight of 70,000 Dalton. The microneedle sheet had a plurality of microneedles on a  
40 substrate sheet with a density of 324 needles/cm<sup>2</sup>. Each microneedle had the shape of a cone with a length or height of 200 μm and a base diameter of 200 μm. The pitch of the microneedles was 60 μm.

45 The microneedle sheet was prepared by a standard mold casting process. Sodium hyaluronate was dissolved in water, and an aqueous solution of sodium hyaluronate thus obtained was poured into the cavities of a mold which correspond to the shape of microneedles. After drying at room temperature to remove water, microneedles in the cavities were removed from the mold as a microneedle sheet having a plurality of microneedles on a substrate sheet.

The microneedle sheet was cut such that it had the shape of a patch to be applied under the eyes.

[Fibrous Patches]

A nonwoven fibrous sheet to be used for Example 1 was prepared by using bi-component fibers with a core composed of polypropylene (PP) and a sheath composed of polyethylene (PE). The bi-component fibers were treated with an acrylic polymer, and then converted into a nonwoven fibrous sheet having a basis weight of 20 g/m<sup>2</sup> using a thermal bonding process. The temperature of the thermal bonding process was 125°C, so that the sheath part of the bi-component fibers was melted but the core part of the bi-component fibers was still remaining non-melted and resulted in fibrous substrate.

The nonwoven fibrous sheet to be used for Comparative Example 1 was prepared by using 50% cellulose fibers and 50% viscose rayon fibers. The basis weight of the nonwoven fibrous sheet was 50 g/m<sup>2</sup>.

The nonwoven fibrous sheet to be used for Comparative Example 2 was prepared by using PET fibers. The basis weight of the nonwoven fibrous sheet was 50 g/m<sup>2</sup>.

The features of the above three nonwoven fibrous sheets are shown in Table 1.

Table 1

|                       | Preparation Process     | Fibers                                          | Basis Weight (g/m <sup>2</sup> ) |
|-----------------------|-------------------------|-------------------------------------------------|----------------------------------|
| Example 1             | Thermal Bonding Process | Core (PP)/Sheath (PE) bi-component fibers       | 20                               |
| Comparative Example 1 | Spunlace Process        | 50% cellulose fibers + 50% viscose rayon fibers | 50                               |
| Comparative Example 2 | Spunlace Process        | 100% PET fibers                                 | 50                               |

Each of the three nonwoven fibrous sheets shown in Table 1 were cut such that it had the shape of a patch to be applied under the eyes, and each nonwoven fibrous sheet patch was packaged in a sachet including 2 g of a liquid formulation including the ingredients shown in Table 2 for 24 hours.

Table 2

| Ingredients      | % (w/w) |
|------------------|---------|
| Water            | 89.2    |
| Glycerin         | 5       |
| Butylene glycol  | 3       |
| Pentylene glycol | 2       |
| Phenoxy ethanol  | 0.5     |
| Xanthan Gum      | 0.3     |

Next, each of the nonwoven fibrous sheets was taken out from the sachet, and the weight of the liquid formulation remaining in the sachet was measured. Thus, the amount of the liquid

formulation absorbed by each of the nonwoven fibrous sheets was determined. The results are shown in Table 3.

Table 3

|                                                      | Example 1 | Comparative Example 1 | Comparative Example 2 |
|------------------------------------------------------|-----------|-----------------------|-----------------------|
| Initial Amount of Liquid Formulation in Sachet (g)   | 2         | 2                     | 2                     |
| Remaining Amount of Liquid Formulation in Sachet (g) | 0.29      | 0.77                  | 0.66                  |
| Absorbed Amount of Liquid Formulation (g)            | 1.71      | 1.23                  | 1.34                  |

Table 3 shows that the nonwoven fibrous sheet patch for Example 1 had a larger liquid absorption capability more than those for Comparative Examples 1 and 2. Thus, the nonwoven fibrous sheet patch for Example 1 was able to provide a greater quantity of the liquid formulation than those for Comparative Examples 1 and 2. This was surprising in view of the fact that the basis weight of the fibrous patch for Example 1 was smaller than those of the fibrous patches for Comparative Examples 1 and 2, which meant that the fibrous patch for Example 1 appeared to have a smaller amount of absorbing material than those for Comparative Examples 1 and 2.

[Evaluations]

(Example 1)

The microneedle patch thus prepared as above was applied on an artificial skin sample (Bio-Skin®) provided by Beaulax. The microneedle patch was then covered with the fibrous patch for Example 1.

After 15 minutes, the fibrous patch was removed, and the residue of the microneedle patch was observed visually immediately and 45 minutes later (1 hour after the application of the fibrous patch).

(Comparative Example 1)

The microneedle patch thus prepared as above was applied on an artificial skin sample (Bio-Skin®) provided by Beaulax. The microneedle patch was then covered with the fibrous patch for Comparative Example 1.

After 15 minutes, the fibrous patch was removed, and the residue of the microneedle patch was observed visually immediately and 45 minutes later (1 hour after the application of the fibrous patch).

(Comparative Example 2)

The microneedle patch thus prepared as above was applied on an artificial skin sample (Bio-Skin®) provided by Beaulax. The microneedle patch was then covered with the fibrous patch for Comparative Example 2.

After 15 minutes, the fibrous patch was removed, and the residue of the microneedle patch was observed visually immediately and 45 minutes later (1 hour after the application of the fibrous patch).

5

(Results)

The amount of the residue of the microneedle patch on the artificial skin sample in Example 1 was smaller than that in Comparative Example 1 or Comparative Example 2, at the timing of both 15 minutes and 1 hour after the application of the fibrous patch.

10

This meant that the nonwoven fibrous patch composed of bi-component fibers was able to make the substrate sheet of the microneedle patch dissolve or disintegrate faster or in a shorter period of time than the conventional nonwoven fibrous patches did. This can be attributed to the delivery of a greater amount of the liquid formulation by the nonwoven fibrous patch composed of bi-component fibers.

15

## CLAIMS

1. A cosmetic process for a keratin substance such as the skin or the lips, comprising the steps of:  
5 applying onto the keratin substance a microneedle sheet comprising a substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer; and  
applying onto the microneedle sheet a porous sheet comprising at least one  
10 conjugated fiber, wherein the porous sheet comprises water.
2. The cosmetic process according to Claim 1, wherein the microneedle has a height of from 50 to 1000 microns, preferably from 100 to 750 microns, and more preferably from 150 to 500 microns.
- 15 3. The cosmetic process according to Claim 1 or 2, wherein the microneedle is in the shape of a cone.
4. The cosmetic process according to Claim 3, wherein the base of the cone of the microneedle has a diameter of from 50 to 350 microns, preferably from 100 to 300  
20 microns, and more preferably from 150 to 250 microns.
5. The cosmetic process according to Claim 3 or 4, wherein the ratio of (the height of the cone)/(the diameter of the base of the cone) of the microneedle is 1 or more, preferably 1.5 or more, and more preferably 2.0 or more.
- 25 6. The cosmetic process according to any one of Claims 1 to 5, wherein the water-soluble or water-dispersible polymer is selected from hyaluronic acids, monosaccharides, disaccharides, oligosaccharides, polysaccharides, dextrans, dextrans, polyethylene glycols, polyvinyl alcohols, poly(methylvinylether/maleic  
30 anhydride), polyvinylpyrrolidone, poly(methyl/vinyl ether/maleic acid) (PMVE/MA) and esters thereof, poly(methyl/vinyl ether/maleic anhydride) (PMVE/MAH), and mixtures thereof.
7. The cosmetic process according to any one of Claims 1 to 6, wherein the water-soluble or water-dispersible polymer has a molecular weight of from 10,000 to 200,000 Dalton, preferably from 30,000 to 150,000 Dalton, and more preferably from 50,000 to 100,000 Dalton.
- 35 8. The cosmetic process according to any one of Claims 1 to 7, wherein the conjugated fiber comprises a fiber body comprising at least two polymers, preferably two apolar polymers, and more preferably two polyolefin polymers.
- 40 9. The cosmetic process according to Claim 8, wherein the conjugated fiber has at least one coating.
- 45 10. The cosmetic process according to Claim 9, wherein the coating comprises at least one polymer, preferably at least one hydrophilic polymer, and more preferably at least one hydrophilic acrylic polymer.

11. The cosmetic process according to any one of Claims 1 to 10, wherein the porous sheet is a woven or nonwoven fabric, preferably a nonwoven fabric, and more preferably a nonwoven fabric prepared by a thermal bonding process.
- 5 12. The cosmetic process according to any one of Claims 1 to 11, wherein at least one of the microneedles comprises at least one cosmetic active ingredient.
13. A kit comprising:  
a microneedle sheet comprising a substrate sheet and a plurality of microneedles on  
10 the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer;  
and  
a porous sheet comprising at least one conjugated fiber, preferably further comprising water, and more preferably packaged in a container with water.
- 15 14. A process for dissolving a substrate sheet of a microneedle sheet comprising the substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer, comprising the step of:  
20 applying a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water, onto the substrate sheet.
- 25 15. A use of a porous sheet comprising at least one conjugated fiber, wherein the porous sheet comprises water, in order to dissolve a substrate sheet of a microneedle sheet comprising the substrate sheet and a plurality of microneedles on the substrate sheet, wherein the substrate sheet comprises at least one water-soluble or water-dispersible polymer.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/JP2019/025999

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K8/02 A61Q19/08 A61K8/73 A61K8/81 A61M37/00  
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 A61Q

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, 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         | US 2016/045720 A1 (SUZUKI MASAYUKI [US] ET AL) 18 February 2016 (2016-02-18)<br>paragraph [0001]<br>example 1<br>example 4<br>paragraphs [0047], [0069]<br>claim 9<br><br>----- | 1-6, 11,<br>14        |
| X         | JP 6 121674 B2 (KOSUMEDEI SEIYAKU KK) 26 April 2017 (2017-04-26)                                                                                                                | 1-7,<br>13-15         |
| Y         | paragraph [0001]<br>paragraph [0011]<br>paragraph [0025]<br>figure 2<br>paragraph [0054]<br>paragraph [0041]<br>claim 3<br><br>-----<br><br>-/-                                 | 8-12, 15              |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

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"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

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/JP2019/025999

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                 |                       |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                              | Relevant to claim No. |
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| Y                                                    | WO 2013/084989 A1 (LION CORP [JP])<br>13 June 2013 (2013-06-13)<br>tables 1-8<br>the whole document<br>-----                    | 8-12,15               |
| A                                                    | WO 2016/076615 A1 (SMALL LAB CO LTD [KR])<br>19 May 2016 (2016-05-19)<br>the whole document<br>-----                            | 1-15                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2019/025999

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|                                           |                     | WO 2016076615 A1           | 19-05-2016          |