

TITLE: MICRONEEDLE PATCHES COMPRISING CORTICOSTEROID

Field of the Invention

The present invention generally relates to home-based treatments for skin conditions. More particularly, the present invention pertains to drug-laden microneedle patches having tailored shapes for treating chronic skin conditions such as keloids, etc.

Background of the Invention

Keloid scars are a common skin disorder with significant morbidity. Prominent symptoms include pain and itch which can significantly impact the quality of life. The undesirable, disfiguring appearance can also lead to emotional distress and psychosocial burden. Current therapeutic options are limited. The first-line option is intra-lesional corticosteroid injections which, due to the sensitivity of keloids, is painful and precludes treatment in many patients. Moreover, there is a high recurrence rate of near 50%. Other commonly employed therapies include cryotherapy, radiotherapy and occlusive dressings which have poor efficacy rates, low patient adherence and a high rate of recurrence.

At the National Skin Centre (NSC) in Singapore, in 2012, there were 675 new cases of keloids seen. Statistics show that keloids account for 11.5 – 34.5 million surgical procedures globally and represent a SGD \$7billion market size. Given the incidence of keloids both locally and worldwide

and the limitations with current treatment, there is clearly an unmet need for more effective, tolerable and reliable therapy.

The current treatment is direct injection of corticosteroid into the keloids using syringes, which is painful. If the keloids cover a large area on the skin, multiple injections are performed to spread the corticosteroid over the entire keloids as uniform as possible. This requires great dexterity and dermatological experience and is normally carried out by a specialist or medical personnel. The shortcomings of the present practice are that the parenteral injection is painful and it is almost impossible to spread the drug evenly across the keloid, even with experienced medical personnel.

Over the past decade, microneedle technology has been increasingly tried for the treatment of skin conditions. The decreased likelihood of causing pain, infection, and injury makes microneedles a great platform for self-administration of drugs. In recent years, drug-loaded dissolving hyaluronic acid microneedles have received extensive attention in transdermal drug delivery. In contrast to drug-coated microneedles, they do not have the risk of leaving foreign material in the skin if broken, can encapsulate sensitive biomolecules within the needle shafts to deliver a specific dosage of drugs, and may have a higher drug-loading capacity.

In particular, microneedle patches are advantageous in treating keloids because the microneedles can deliver the corticosteroid into the keloids painlessly and easily without needing the help of trained medical personnel. Moreover, the microneedle patches can be custom-made into individual keloids' shapes so that the corticosteroid is delivered to and spread evenly over the keloids' site, without spilling over to the normal skin, as corticosteroid is harmful to normal skin. It should be noted that keloid is a general term referring to a targeted skin site, and its meaning should be extended to any other skin conditions in addition to keloids.

US patent 9,539,418 B2 awarded to Cosmed Pharmaceutical reported a microneedle patch made of proteoglycan; US patent 8,167,152 B2 awarded to Cosmed Pharmaceutical reported a microneedle patch made of hyaluronic acid and collagen. Both patents report dissolving microneedles but they do not contain drug for treating skin conditions such as keloids.

PCT patent application WO 2015/122838A1 awarded to Lim et. al. reported a rapidly dissolvable microneedle and the fabrication method thereof, which is reference in its entirety in this present invention.

To our knowledge, there is no published data on the use of drug-embedded dissolving microneedles in the treatment of keloids. As such, the motivation of the present invention is to provide a home-based solution where a custom-shaped microneedle patch loaded with corticosteroid can be applied by a patient at home on daily or weekly basis. The present invention bring forth a is translates to less pain, improved efficacy, feasibility for self-administration, better patient adherence and a lower risk of systemic absorption and local side effects of steroid therapy.

Summary of the Invention

The current practice in treating chronic skin conditions which require constant injection of drugs on the affected skin sites, poses several problems as follows:

- (a) the trauma they experience during the intradermal injections,
- (b) the inconvenience they endure for every visit to the hospital for such injections,
- (c) the uneven delivery of drug across the skin sites (e.g. keloids) by hands,

Considering these problems, there is a long-felt need for a drug delivery system to provide certain desirable features such as:

- (a) painlessness,
- (b) self-administration, and
- (c) precision in drug delivery in terms of depth and affected area.

Now the preferred embodiments of the present invention will be provided to solve the current problems of chronic skin conditions by providing the desirable solutions mentioned above.

In the preferred embodiment of the present invention, a patch of dissolving microneedles loaded with active ingredients to be applied to skin for treating skin conditions is provided. As seen in Fig. 1, the dissolving microneedle patch **10** comprises a substrate **12** and a plurality of microneedles **14** which extends from the substrate. The dissolving microneedle patch **10** is made of a matrix material and at least one active ingredient such as a corticosteroid, namely triamcinolone (TAC). The matrix material is made of bio-compatible materials such as hyaluronic acid (HA), polyvinylpyrrolidone (PVP), or mixture of them, which dissolve rapidly when they are in contact with the inner skin. The active ingredient is loaded onto individual patches with the desirable dosage ranging from 0.01mg - 1.0mg.

The dissolving microneedle patch **10** may be accompanied by a skin protection coating **20** which has a hole tailored to the target keloid's shape so that the active ingredient can be effectively delivered into the keloid while the excess will be masked out by the skin protection coating **20**. As mentioned previously, 'keloids' is herein referred to not only keloids but any targeted skin site that requires drug delivery. The skin protection coating **20** is made of inert material including but not

limited to woven or non-woven fabrics, wax, polymer films, etc. and is adhered on the targeted skin site to only expose the keloid to the dissolving microneedle patch **10**.

For delivering the active ingredients loaded in the microneedles, the dissolving microneedle patch **10** is applied on the affected skin site (such as a keloid) and is held on with mild pressure for a length of time, e.g. from 10 seconds to 10 minutes.

The application of the dissolving microneedle patch can be carried in several modes, including using a spring applicator and a handle.

There is another preferred embodiment of the present invention in which the dissolving microneedle patch **30** is affixed on a skin adhesive **32**. The skin protection coating **40** is an external separate piece that is applied on the skin beforehand to expose only the keloid to the dissolving microneedle patch **30**. This adhesive dissolving microneedle patch **30** is applied on the skin with fingers and it is adhered on the skin for a length of time. The patient may use his fingers to exert mild pressure on the patch from time to time.

Brief Description of the Figures

Fig. 1 shows a dissolving microneedle patch **10** comprising a substrate **12** from which a plurality of microneedles **14** extends.

Fig. 2 shows an external skin protection coating **20** having a through hole for only exposing a targeted skin site such as a keloid. The coating **20** comprises a bottom surface **22** having an

adhesive coating for affixing onto the skin, a top surface **24** for receiving the microneedles, and a hole **26** to expose a keloid while masking out the normal skin.

Fig. 3 shows a dissolving microneedle patch **30** and a microneedle template **32** having a cavity **34** and a plurality of microneedle cavities **36**.

Fig. 4 shows a spring applicator **40** which can be used to apply the dissolving microneedle patch on the skin, comprising a transparent compressor cap **42** and a trigger button **44**.

Fig. 5 shows schematically the application of a dissolving microneedle patch **50** onto a skin site such as a keloid **52** which is masked out by a skin protection coating **54**.

Fig. 6 shows the chart summarizing the volume of keloids treated with the dissolving microneedles at baseline, 4 weeks after treatment, and after another 4 weeks of withheld treatment, as compared to controls.

Detailed Description of the Invention

It is the objective of the present invention to provide a drug delivery solution for the current intradermal injection practice for treating chronic skin conditions such as keloid scars. Currently, patients with keloid scars have to visit dermatologist regularly for the intradermal injections of corticosteroid such as triamcinolone (TAC). As mentioned earlier, a dissolving microneedle patch laded with TAC provides a home-based alternative for the patients because this patch is painless and easy to use. The present invention aims to cater to the uniform delivery of active ingredients across a targeted skin site, including but not limited to a keloid, by plurality of dissolving

microneedles. Fig. 1 shows an example of such a drug-laden dissolving microneedle patch **10**. As shown in the figure, the patch comprises a substrate **12** from which a plurality of dissolving microneedles **14** extend. The microneedles are typically 100um to 1,000um tall, with the peak-to-peak distance of 500um to 3,000um. For example, a 10x10 array of microneedle patch with a 500um peak-to-peak distance will have roughly a 5mm x 5mm = 25mm² in area. Due to manufacturing convenience, the dissolving microneedle patch **10** normally has rectangular shapes in sizes, typically ranging from 5mm x 5mm to 100mm x 100mm. The active ingredient is loaded onto individual patches with the desirable dosage ranging from 0.001mg - 1.0mg per mm², or more particularly 0.001mg – 0.01mg per mm².

Quite often the targeted skin sites have irregular shapes. By applying the rectangular shaped dissolving microneedle patches, the surrounding normal skin will also be injected with the active ingredients, which is not desirable because the normal tissues will be damaged. In order to prevent this undesirable event from happening, the present invention provides a skin protection coating which basically covers the surrounding normal skin with inert material and prevents the dissolving microneedles from penetrating it. Fig. 2 shows an external skin protection coating **20**, which comprises a bottom surface **22** coated with skin adhesive, a top surface **24** for receiving the microneedles, and a hole **26** made to expose a keloid. The external skin protection coating **20** is a thin layer of inert material such as woven or non-woven fabric, wax, polymer films, etc. that adheres to the skin before the dissolving microneedles are applied to the skin. The external skin protection coating **20** can take the form of a film that can be worn on a keloid, or it can take the form of a liquid like wax, which takes a liquid form when it is applied on the skin with a brush but rapidly solidifies into a solid layer which firmly adhere to the skin to mask out the normal skin and protect it from delivery of TAC by the microneedles.

The fabrication of the dissolving microneedle patch is reported in patent document WO 2015/122838A1, which is reference in its entirety herein. Fig. 3 shows the process flow of making a dissolving microneedle patch **30** on a microneedle template **32**. The microneedle template **32** comprises a cavity **34** and a plurality of microneedle cavities **36**. The dissolving microneedle patch **30** is made of a matrix material and at least one active ingredient such as a corticosteroid, namely triamcinolone (TAC). The matrix material is made of bio-compatible materials such as hyaluronic acid (HA), polyvinylpyrrolidone (PVP), or mixture of them, which dissolve rapidly when they are in contact with the inner skin. The active ingredient triamcinolone acetone TAC is only mildly soluble in water.

Fabrication of Dissolving Microneedle Patch

In one example, the active ingredient TAC is pre-mixed with the matrix material and the mixture is cast onto the microneedle template **32** (Fig. 3) to form the dissolving microneedle patch. The microneedle template has a cavity **34** with dimensions of 8mm x 8mm x 1mm (height), or 64ul in volume, which further comprises a plurality of microneedle cavities **36**. The matrix material is HA 0.6g/ml and the active ingredient is TAC 10mg/ml. The mixing ratio is HA:TAC = 5:1. 64ul of the mixture is loaded into the cavity **34** and the microneedle template **32** is subjected to a centrifugal force at 3,000 – 5,000 RPM for 1-2 minutes. The centrifugal force will push the mixture comprising TAC into the microneedle cavities **36**. Since TAC is not soluble in water, a considerable amount of TAC in the cavity **34** is forced to fill the microneedle cavities **36**.

Alternatively, the active ingredient and the matrix material can be loaded individually into the cavity **34** of the microneedle template **32**. The matrix material may be 50ul of HA at 0.6g/ml and the active ingredient may be 10ul of TAC at 10mg/ml, which makes up 0.1mg per patch. The loaded microneedle template **32** is then subjected to a centrifugal force of 3,000 RPM to 5,000 RPM for 1-2 minutes to fill up the microneedle cavities **36**. Due to the fact that TAC is insoluble, the centrifuging step distributes TAC across the microneedle cavities **36** evenly and pushes TAC into the microneedle cavities **36**. Subsequently, the filled microneedle template will be left in a controlled environment so that the microneedle patch solidifies. The solidification duration in room temperature typical ranges from 4 -16 hours. Finally, the solidified dissolving microneedle patch **30** is de-moulded from the microneedle template **32**.

Application of Dissolving Microneedle Patches on the Skin

The application of dissolving microneedle patches on the skin can be achieved by several methods. Fig. 4 shows a spring applicator **40** which is used for applying a dissolving microneedle patch on the skin. The spring applicator **40** comprises a transparent compressor cap **42** for fixing and tensioning the skin site prior to application and a trigger button **44** is pushed to release the spring for applying the dissolving microneedle patch **46** onto the skin at high speed. The penetration speed of the spring applicator **40** is roughly 2m/s and the impact force is 1.0 – 1.6N. The use of spring applicator warrants consistency and repeatability of the application of dissolving microneedle patches.

In the case where the targeted skin site is a large area, the spring applicator is not able to apply large patches. Therefore, large patches can only be applied by hands. However, as mentioned earlier, large patches may overreach the normal skin area and deliver corticosteroid to the normal skin site, which is undesirable. Fig. 5 shows a schematic process flow of how a dissolving microneedle patch **50** and an external skin protection coating **52** are applied to target only the affected skin sites such as keloids **54**. ‘Keloid’ in Fig. 5 shall include other targeted skin site which requires drug delivery. The external skin protection coating **52** masks out the normal skin and only exposes the keloid to receive the microneedles. The external skin protection coating **52** can take the form of a skin adhesive, which has one surface having skin adhesive for affixation on the skin and another open surface for receiving microneedles. Alternatively, the external skin protection coating **52** can take the form of a wax, which can be in liquid form and is applied onto the skin with a brush, and rapidly solidifies to form a rigid layer on the skin to receive microneedles.

Clinical Trial

The dissolving microneedle patches were made and loaded with 0.1mg of TAC and were applied with the spring applicator. The trial was carried out at National Skin Centre in Singapore. This was a single-blinded, intra-individual randomized controlled clinical trial where two keloids on each subject were randomized to the following treatment groups:

1. Control group: No treatment
2. Dissolving microneedles group: Triamcinolone-embedded, dissolving hyaluronic acid microneedles

At baseline, volume measurements and patient assessments of pain and itch were recorded. Subjects were treated with the dissolvable microneedles over 4 weeks and measurements were repeated. A final visit was scheduled at 4 weeks post-treatment and measurements taken again (Table 1).

Table 1. Study Schedule

Visits	Action taken
Baseline (Week 0)	Patient assessment and randomization Measurements
1 st Visit (Week 4)	Review – conclusion of treatment Measurements
2 nd Visit (Week 8)	Review and measurements

A total of 28 patients, comprising of 24 (85.7%) males and 4 (14.3%) females were enrolled into the study. Majority were Chinese (n = 22, 78.6%), Malay (n = 5, 17.9%) and others (n = 1, 3.6%). Twenty-seven subjects completed the study and 1 subject defaulted without treatment. After applying the treatment for 4 weeks, significant reduction in mean keloid size was seen in the Dissolving microneedles group from 117.6 mm³ in Visit 1 to 108.5 mm³ in Visit 2 (p-value 0.001). The reduction in the Dissolving group (mean change: -9.1 ± 15.4 , p-value = 0.038) was greater than the Control group (mean change: 7.2 ± 25.7). In the subsequent 4 weeks, when no treatment was given from Visit 2 to Visit 3, it was observed that the keloids treated in the Dissolving microneedles group (p-value = 0.017) grew back in size (Table 2). In terms of pain, the Dissolving microneedles group (mean change: -0.5 ± 1.1 , p-value = 0.007) experienced lesser pain after 4 weeks of treatment (Table 3). There were no significant changes in itch score in both groups after 4 weeks of treatment.

Table 2: Keloid Size (mm³) by Visit and Intervention

	Visit 1 (n = 27)	Visit 2 (n = 27)	Visit 3 (n = 27)	Change from Visit 1 to 2 (n = 27)	Change from Visit 2 to 3 (n = 27)	Change from Visit 1 to 3 (n = 27)
Keloid Size (mm3)						
Control Group						
mean ± sd	148.6 ± 204.4	155.7 ± 221.9	155.8 ± 223.9	7.2 ± 25.7	0.05 ± 11.7	7.2 ± 29.0
median (min, max)	49.3 (2.5 , 855.0)	44.0 (1.5 , 979.0)	48.0 (2.5 , 1001.0)	0.7 (-23.7 , 124)	-0.33 (-29.7 , 24.7)	0.3 (-11.3 , 146)
p-value for comparing each visit and subsequent visit for Control group				0.104	0.983	0.101
Dissolving microneedles group						
mean ± sd	117.6 ± 280.8	108.5 ± 271.9	114.9 ± 285.3	-9.1 ± 15.4	6.4 ± 14.2	-2.9 ± 12.4
median (min, max)	30.7 (1.4 , 1467.3)	25.7 (1.6 , 1419.3)	34.3 (1.1 , 1488.0)	-5.0 (-56.7, 10.3)	2.2 (-4.3 , 68.7)	-1.7 (-43.7 , 20.7)
p-value for comparing each visit and subsequent visit for Dissolving group				0.001	0.017	0.312
p-value for comparing the difference between each visit and subsequent visit between Dissolving microneedles and Control groups				0.038	0.415	0.046

Note: Keloid Size (mm3) was based on the mean of 3 measurements.

Table 3: Pain score by Visit and Intervention

	Visit 1 (n = 27)	Visit 2 (n = 27)	Visit 3 (n = 27)	Change from Visit 1 to 2 (n = 27)	Change from Visit 2 to 3 (n = 27)	Change from Visit 1 to 3 (n = 27)
Pain (VAS)						
Control group						
mean $\pm$ sd	1.2 $\pm$ 2.0	1.0 $\pm$ 1.8	1.0 $\pm$ 1.9	-0.2 $\pm$ 1.0	-0.04 $\pm$ 0.8	-0.2 $\pm$ 1.3
median (min, max)	0.0 (0.0 , 6.0)	0.0 (0.0 , 5.0)	0.0 (0.0 , 7.0)	0.0 (-5.0 , 1.0)	0.0 (-2.0 , 3.0)	0.0 (-5.0 , 3.0)
p-value for comparing each visit and subsequent visit for Control group				0.344	0.796	0.256
Dissolving microneedles group						
mean $\pm$ sd	0.9 $\pm$ 1.5	0.3 $\pm$ 0.8	0.4 $\pm$ 1.1	-0.5 $\pm$ 1.1	-0.1 $\pm$ 0.9	-0.4 $\pm$ 1.1
median (min, max)	0.0 (0.0 , 5.0)	0.0 (0.0 , 3.0)	0.0 (0.0 , 4.0)	0.0 (-4.0 , 0.0)	0.0 (-2.0 , 4.0)	0.0 (-4.0 , 1.0)
p-value for comparing each visit and subsequent visit for Dissolving microneedles group				0.007	0.509	0.035

Fig. 6 shows the chart summarizing the volume of keloids treated with the dissolving microneedles at baseline, 4 weeks after treatment, and after another 4 weeks of withheld treatment, as compared to controls. It is clearly shown that the delivery of TAC into keloids by the dissolving microneedle patches is effective.

CLAIMS

What is claimed is:

1. A dissolving microneedle patch comprising a matrix material and an active pharmaceutical ingredient, wherein the active pharmaceutical ingredient is a corticosteroid.
2. A dissolving microneedle patch in claim 1, wherein the matrix material comprises hyaluronic acid.
3. A dissolving microneedle patch in claim 1, wherein the matrix material comprises polyvinylpyrrolidone.
4. A dissolving microneedle patch in claim 1, wherein the corticosteroid is triamcinolone acetonide.
5. A dissolving microneedle patch in claim 1, wherein the corticosteroid dose ranges from 0.01mg to 1.0mg per patch.
6. A dissolving microneedle patch in claim 1, further comprising an external skin protection coating for protecting the normal skin from receiving the microneedles.
7. A dissolving microneedle patch in claim 6, wherein the external skin protection coating further comprises a surface to be adhered to the skin and another surface for receiving the microneedles.
8. A dissolving microneedle patch in claim 6, wherein the external skin protection coating is made of wax which is in liquid form when applied on the skin but rapidly solidifies to form a protective layer.
9. A dissolving microneedle patch in claim 6, wherein the external skin protection coating is made of a skin adhesive having one surface coated with skin adhesive and another surface to receive the microneedles.
10. A method of fabricating a dissolving microneedle patch in claim 1, comprising:

- i. Providing a microneedle template, which comprises a cavity and a plurality of microneedle cavities;
 - ii. Loading of a matrix material and an active pharmaceutical ingredient into the cavity on the microneedle template, wherein the active pharmaceutical ingredient is a corticosteroid;
 - iii. Subjecting the loaded microneedle template to a centrifuging force so that the matrix material and the corticosteroid fill up the microneedle cavities;
 - iv. Drying of the filled-up microneedle template.
11. A method of fabricating a dissolving microneedle patch in claim 10, wherein the loading of matrix material and an active pharmaceutical ingredient is done separately.
12. A method of fabricating a dissolving microneedle patch in claim 10, wherein the matrix material comprises sodium hyaluronate, polyvinylpyrrolidone, or a mixture of both.
13. A method of fabricating a dissolving microneedle patch in claims 10, wherein the corticosteroid is triamcinolone acetonide.
14. A method of fabricating a dissolving microneedle patch in claim 12, wherein the concentration of sodium hyaluronate is 0.2 – 1.0 g/ml.
15. A method of fabricating a dissolving microneedle patch in claim 10 and 13, wherein the concentration of triamcinolone acetonide is 10 – 40 mg/ml.