Mechanical Properties of Dissolvable Microneedles Arrays for Transdermal Drug Delivery

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Abstract:
Dissolvable microneedles have been used for transdermal drug delivery. They are usually fabricated from water-soluble biocompatible materials such as biocompatible polymers and sugars. Here, we have investigated the correlation between hyaluronic acid (HA)/polyvinylpyrrolidone (PVP) composite and properties of the fabricated microneedles. Stereomicroscope is used to observe the morphology whereas compression strength of the microneedles was measured by universal testing machine. We observed that the microneedles with high PVP content possessed a higher compressive strength. Dissolution rate of microneedles was measured in situ of the porcine ear skin. The results indicate that the microneedles with high PVP content showed the faster dissolving rate in the porcine ear skin than the microneedles with high HA content.

1. Introduction
Transdermal drug delivery is an alternative to oral deliver drug and hypodermic injection. It has several advantages. For examples, it can enhance dosage efficacy, patient compliance, and reduced systematic side effects. Unfortunately, only low molecular drugs (<600 Da) can be passively delivered into the skin across the stratum corneum that is the outer most layer of the skin. Microneedles is one of the strategies to overcome this skin barrier. It is a minimally invasive method to deliver drugs. It can pierce the stratum corneum and generate reversible microchannels which the drugs can passively diffuse into the skin. Microneedles can be designed with an appropriate length and shape. It usually has needles height of less than 1000 µm to deliver in an appropriate depth without stimulating nerves and damaging blood vessels.

There are four types of microneedles. 1) Solid microneedles; usually made of metal (e.g. stainless-steel and titanium), silicone, and ceramics. The needle is used to make temporary holes at the surface of the skin. Then, the drug can be applied and diffuse through the holes. 2) Coated microneedles; it is a solid microneedles that the needles are coated with drugs. The drug is quickly delivered into the skin during the application of the needles though the skin. 3) Hollow microneedles; this type of microneedles is similar to hypodermic needle only with shorter length of the needle. It allows the drugs to be injected into the skin through the hollow. 4) Dissolvable microneedles; it is made from water-soluble polymers with drugs incorporated in the polymer matrix. When these microneedles are embedded the skin, the material will dissolve and release the pre-loaded drugs.

Recently, dissolvable microneedles have received considerable attention because it has advantages over other types of microneedles such as it can deliver a wide range of therapeutics, is easy to use, is inexpensive, and leave no sharp waste after use. There are a wide range of polymers that have been used to fabricate dissolvable microneedles such as hyaluronic acid (HA), carboxymethylcellulose (CMC), polyvinyl alcohol (PVA), and
polyvinylpyrrolidone (PVP). The difference polymers would affect their skin penetration ability, mechanical property of the needles, and the dissolution rate of microneedles.

HA is a natural water-soluble polymer composed of repeated units of β-1,4-D-glucuronic acid and β-1,3-N-acetyl-D-glucosamine. It can be found in all tissues and body fluid. It is widely used as a cosmetic ingredient and an injectable cosmetic filler.

The cross-linked HA is used to fabricate microneedles in order to improve the mechanical properties. However, it takes longer time to dissolve, possesses higher risks of clogging capillary and rejection by the body. Crosslinked-HA microneedles need to be pressed on the skin for a long time until they dissolve. This can cause the uncomfortable feeling and skin irritation. PVP has also been used for fabricating microneedles. It has a rapid dissolution rate. By combining HA and PVP, microneedles with sufficient strength to penetrate skin and suitable dissolution rate can be obtained.

Here we have developed a dissolvable microneedles patches made of HA and PVP of various ratios. HA/PVP microneedles were prepared using a micromolding process. Compression strength of the HA/PVP microneedles was measured by universal testing machine. Ex vivo skin penetration of HA/PVP microneedles was analyzed and dissolution rate of microneedles was measured in situ of the porcine ear skin.

2. Materials and Methods

2.1 Materials for the preparation of HA/PVP microneedles

The commercial microneedles molds were purchased from Micropoint Technologies Pte, Ltd. (Singapore), hyaluronic acid (cosmetic grade, MW 2 MDa) was purchase from Shandong Focuschem Biotech Co., Ltd. (Shandong Sheng, China), polyvinylpyrrolidone (analytical grade, MW 40 kDa) and polyvinyl alcohol (analytical grade, MW 31-50 kDa) were purchased from Sigma-Aldrich (Missouri, USA).

2.2 Fabrication of HA/PVP microneedles patches

Polydimethylsiloxane (PDMS) microneedles mold consisted of 100 (10 × 10) pyramidal needles of 300µm×300µm×850µm (W×L×H) with tip-to-tip spacing of 500 µm. Five difference composites of 10% polymer solution, HA/PVP (100:0, 75:25, 50:50, 25:75, 0:100) were prepared, then poured into the PDMS mold. The microneedles patches were dried in desiccator at room temperature overnight. Finally, adhesive tape was pasted on the microneedles as a supporting layer and the needles were pulled out from the mold. Morphologies of HA/PVP microneedles patches were investigated using stereomicroscope (Olympus DP22, Olympus Corporation, Tokyo, Japan).

2.3 Compression strength test

The mechanical strength of HA/PVP microneedles patched was measured by pressing microneedles against stainless-steel plate on a universal testing machine (Shimadzu EZ-S, Shimadzu Corporation, Tokyo, Japan). The stainless-steel plate was moved toward the sample at a rate of 1 mm/min until a maximum load of 100 N was obtained.

2.4 Ex vivo skin penetration test

Black food coloring (Greenhill Co., Ltd., Thailand) was mixed into the polymer solutions to give colored needles under microscope. The HA/PVP microneedles patch was applied to the porcine ear skin. The images of needles penetration were observed by stereomicroscope.

2.5 In situ dissolution rate of microneedles in porcine ear skin

Black food coloring (Greenhill Co., Ltd., Thailand) was mixed into the polymer solutions before fabricating the
microneedles patch to give a color under microscope. Only the composites with the ability to penetrate the skin, HA/PVP (50:50, 25:75, 0:100), were studied. The microneedles patch was applied to the porcine ear skin. The images of the needles in the skin were observed after submerging the skin in the release medium. The residual polymer from the skin surface was wiped with tissue paper every 5 minutes until the color completely disappeared. The samples were observed by stereomicroscope.

3. Results & Discussion
3.1 Fabrication of HA/PVP microneedles patches

Herein, mold with pyramidal microneedles was chosen because previous literature has revealed that pyramidal microneedles show better mechanical strength than conical type microneedles. This strength is required for the needles fabricated using mechanically weak biomaterials. Figure 1(a)-(e) shows the morphologies of the five ratios of HA/PVP microneedles patches. The images indicate that HA/PVP microneedles patches were successfully fabricated and had pyramidal shape.

Figure 1. Stereomicroscopic images of microneedles patches made of (a) HA, (b) HA/PVP at 75/25, (c) HA/PVP at 50/50, (d) HA/PVP at 25/75, (e) PVP

3.2 Compression strength of HA/PVP microneedles patches

Measurement of mechanical strength of each microneedles was carried out using a universal testing machine. A plot of force versus displacement was then constructed as shown in Figure 2. All the HA/PVP microneedles patches were not fracture during the compression test. In comparison to the patch without PVP, the microneedles with higher PVP content possessed a higher compressive strength. From previous study, backbone structure of the vinyl pyrrolidone monomer contains a ring that may increase intramolecular rigidity, and therefore PVP may provide a better mechanical strength than HA. The result also indicates that the use of PVP at 50% gave quite similar strength to that at 75%.

Figure 2. Mechanical characteristic of microneedles patches made of HA (blue), HA/PVP at 75/25 (yellow), HA/PVP at 50/50 (red), HA/PVP at 25/75 (green), and PVP (black)

3.3 Ex vivo skin penetration of HA/PVP microneedles patches

To investigate the skin penetration ability of HA/PVP microneedles, we loaded black food coloring into the microneedles and applied the microneedles to porcine ear skin. The skin was observed by stereomicroscope. Figure 3 (a)-(e) show the top view of skin post application of the needles made from HA, HA/PVP at 75/25, HA/PVP at 50/50, HA/PVP at 25/75, and PVP respectively. The picture indicates that HA microneedles cannot penetrate the skin. This suggests that uncrosslinked HA has insufficient strength to make microneedles. After increase the PVP content to 25%, Figure 3 (b), some needles can penetrate the skin. Needles made of HA/PVP at 50/50,
HA/PVP at 25/75, and PVP have enough strength to penetrate the porcine skin. Consequently, needles made of HA/PVP at 50/50, HA/PVP at 25/75, and PVP were further investigated for the dissolution rate in porcine skin.

3.4 In situ dissolution rate of HA/PVP microneedles in porcine ear skin

To evaluate the dissolution rate, black food coloring was loaded in the HA/PVP microneedles. Three composites of HA/PVP microneedles, HA/PVP of 50:50, 25:75, and 0:100, were studied. The HA/PVP microneedles patches were applied to porcine ear skin and observed under stereomicroscope every 5 mins until the needles were fully dissolved. Figure 4 (a1)-(c1) show the porcine skin after the microneedles were dissolved. The needles made of HA/PVP at 50/50, HA/PVP at 25/75, and PVP alone took 30 mins, 25 mins, and 10 mins respectively to completely dissolve in the skin tissue. It indicates that the microneedles with higher PVP content show the faster dissolving rate in the porcine ear skin. It is considered that the lower molecular weight of PVP comparing to HA should result in faster dissolution rate. Faster dissolution means that less time of the base to be on skin, the needles can detach from the base more quickly.

Figure 4. In situ dissolution rate in porcine ear skin of microneedles made of HA/PVP at 50/50 (a-a1), HA/PVP at 25/75 (b-b1), and PVP (c-c1). The top view picture of porcine ear skin after microneedles application (a-c) and after submerging the skin in the release medium for 10 mins (a1), 25 mins (b1), and 30 mins (c1).

4. Conclusion

A dissolvable HA/PVP microneedles patches were successfully fabricated. Non-cross-linked HA microneedles patch do not possess enough strength to penetrate the porcine ear skin. PVP can be used to combine with HA to achieve a better strength. At least, 50% of PVP is needed to achieve sufficient strength to penetrate the skin. By adding PVP, the microneedles tend to have faster dissolution rate in the skin tissue. This HA/PVP microneedles patches provide immediate and efficient delivery of drugs into the skin and may become an alternative tool for transdermal drug delivery.

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