Fabrication and testing of porous Ti microneedles for drug delivery

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Porous metal microneedles were fabricated by an incorporated process of cutting and wet etching. Each microneedle is comprised of many connecting microholes that can deliver drugs into organisms conveniently and efficiently. The microneedle height is larger than 400 μm, the pitch distance is about 800 μm and the microholes in each microneedle are about 20 μm in diameter. In force testing, the microneedles could resist large shear forces and pierce into skins easily; in the in vivo experiment, the insulin was efficiently injected into rats by a patch of the microneedles. The testing and the experiment demonstrated that the microneedles could deliver drugs into organisms to treat diseases without fracture.

1. Introduction: Drugs conveyed into organisms play an important role in treating all kinds of diseases for human health. Diverse delivering ways, including ancient oral and modern injecting, have been invented to deliver the drugs into the organism. However, the former usually results in low absorption efficiency for the drugs and the latter often brings pain. While considering these conditions, a new method called transdermal drug delivery has been designed. Transdermal drug delivery includes three ways: intact skin dissolves drugs [1], chemical ways convey drugs [2] and physical ways pierce into skins to deliver drugs [3, 4]. All of them are in the ascendant, respectively, such as little pain and high efficiency for drug absorption. However, the intact skin only permits small molecule drugs through it [5]. Microneedle piercing, as one of the physical ways, is often employed by destroying the intact skin to deliver modern advanced drugs, such as protein and peptide. Microneedles, which are often 0.1–0.5 mm in length [6], can reach into the superficial dermis that connects the recycle system and has few nerve cells. Therefore they can achieve high absorption of drugs and cause little pain.

The materials in microneedles include silicon, metal, polymer and so on. These materials can be shaped into solid or hollow microneedles by varied fabrication processes. Solid microneedles are fabricated easily, but have no continuity resulting from delivering a limited dose of drugs [1, 7–9]. Hollow microneedles have holes that can make the drugs flow through the skin continuously, therefore the dose of drugs is unlimited [10–13]. Usually, each hollow microneedle with one channel results in a fabrication process that is complex and costly. In this letter, a type of porous titanium microneedles (PTM) for continuous drug delivery is proposed. Each microneedle has many interconnecting microholes as channels in its whole body that make them easy to fabricate.

The microneedles were fabricated by combining mechanical cutting and wet etching. First, one patch containing microcolumns is cut from a porous Ti wafer. Then, wet etch is used to etch the microcolumns to shape tapered microneedles. In force testing, microneedles are sheared and inserted into the skin; in the in vivo experiment, microneedles were employed to inject insulin into rats to test its ability in treating diseases.

2. Fabrication process: A mixture of acids (HNO_3, HF and H_2O) can etch the Ti by following the isotropic etching principle. Therefore the Ti microcolumns can be formed into tapered structures. The detailed fabrication process of the PTM is shown in Fig. 1: a porous Ti wafer with a diameter of 75 mm and a thickness of 2 mm was proposed (Fig. 1*a*); then, wire-electrode cutting was employed to form microcolumns with $500 \times 500 \times 500\ \mu m^3$ (Fig. 1*b*); and finally, the isotropic wet etching in the mixture acid solution (HNO_3: HF: H_2O = 5: 2: 7) took about 10 min to sharpen and smoothen the microcolumns to obtain the final tapered microneedles (Fig. 1*c*).

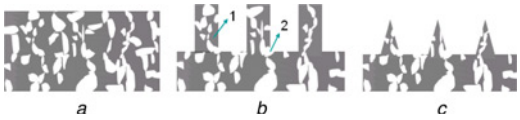


Figure 1 *Fabrication process*
a One wafer was proposed
b Microcolumns were cut by wire-electrode cutting
c Tapered microneedles were formed by wet etching: 1 is Ti, and 2 is microhole

The SEM of the cut microcolumns and the etched microneedles are shown in Fig. 2. After being cut, the numerous microholes in the cut microcolumns were blocked using metal chips and dust (Fig. 2*a*); the wet etching can etch the microcolumns to form tapered microneedles, and can enlarge the microholes and eliminate the chips and dust to make the microholes connect again (Fig. 2*b*). The microholes in the PTM are about 20 μm in diameter, the length of the PTM is about 400 μm and the pitch distance is about 800 μm.

3. Experimental: The microneedles should be safe when they are employed to insert into the skin. The fractured shear force of the fabricated PTM could be tested conveniently by a machine called RHESCA-PTR-1101 (Rhesca company, Japan): a patch of PTM was fixed on a glass slide with a diameter of 75 mm and a thickness of 2 mm; then the machine with continuous variable forces was used to shear the microneedles tip until the microneedles were fractured (Fig. 3*a*). The method to test the ability of the microneedles in piercing the skin has been reported [14], the principle is shown in Fig. 3*b*: (1) pigskin (the thickness is 1–2 mm) was fixed on a platform; (2) constant inserting speed of 1 mm/min and (3) loading axial forces ranging from 0 to 50 N were loaded on the microneedles patch.

As the fabricated PTM would be used to deliver drugs, the in vivo drug delivery experiment can evaluate their ability in this usage. The experiment employs a device that consists of a patch of PTM and a syringe, as shown in Fig. 4*a*: the two parts were

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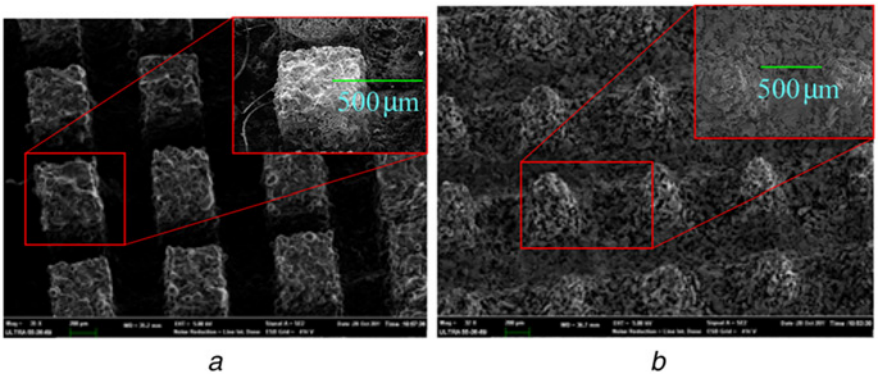


Figure 2 *SEM of the tapered microcolumns and the fabricated results*
a Cut microcolumns with few microholes
b Shaped PTM with numerous microholes

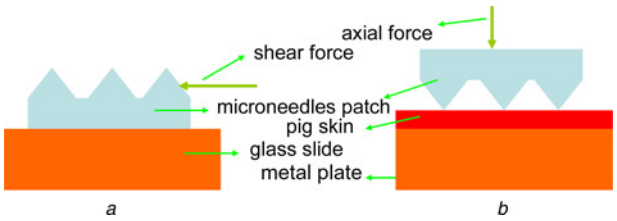


Figure 3 *Principle of the testing instrument*
a Testing principle of the shear force
b Testing principle of the ability of the PTM in piercing skin

connected by glue; however, for preventing the leakage of liquids from the PTM body, a bottle of glue was used to seal around the body. When the water was delivered into this device, the liquid flowed through the PTM (Fig. 4*b*) indicating that most of the liquid could flow through the sealed body without leakage. This device was deployed to inject the insulin into a rat's body through the skin to assess the PTM's ability in drug delivery. This testing is called glucose tolerance test by detecting the blood glucose concentration (BGC) [15]. Three rats numbered 1 (36 g), 2 (33 g) and 3 (36 g) were prepared with water and without food for 12 h. The rats were given free access to food and water ad libitum unless otherwise noted. All the procedures were approved by the Laboratory Animal Use Committee of Shanghai Jiao Tong University School of Pharmacy. All possible efforts were made to reduce the number of animals used, minimise their suffering and employ alternatives to the in vivo techniques, if available. The

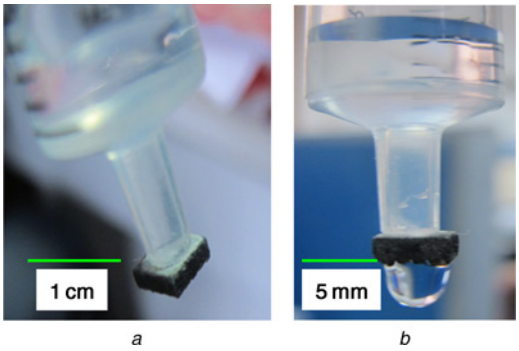


Figure 4 *The device and the liquid flow testing*
a The device consists of a microneedles patch and a syringe
b The liquid flow testing

experimental study groups were assigned randomly, and the researcher was blinded for the behaviour tests.

No. 1 rat was injected with glucose (0.5 g/ml) only, No. 2 rat was injected with insulin (0.8 IU/ml) and glucose by hypodermic injection (HI) and No. 3 rat was injected with insulin and glucose by the device.

4. Results and discussion: The experimental results are shown in Fig. 5. Fig. 5*a* depicts the fracture of the PTM, and Fig. 5*b* shows the fracture shear forces of the No. 1 and the No. 2 microneedles. The No. 1 microneedle fracture shear force is about 2.9 N, and the No. 2 microneedle force is about 2.6 N. Their fracture section radius is about 0.15 mm. Therefore we can estimate that the fracture section area A of a single microneedle is about 0.28×10^{-6} m^2 ($A = \Pi r^2$, $\Pi = 3.14$ and $r = 0.3$ mm). The required extreme pressure P for piercing the skin is about 3.18 MPa [6]. Therefore, for a single Ti microneedle, the calculated extreme shear force F is about 0.89 N ($F = P \times A$), which is far smaller than the testing shear force (2.9 and 2.6 N). It indicates that the PTM can be employed to insert into the skin without being fractured. The result of the ability of the PTM in piercing the skin indicates that the PTM can be inserted into pigskins (Fig. 5*c*).

The BGC testing results of the three rats are shown in Figure 5c: first, the BGC levels were tested by a glucose oxidase method by OneTouch® Ultra® 2 Blood Glucose Meter (Johnson & Johnson Company, Shanghai, China); then, the No. 1 rat was injected with 0.36 ml saline by HI (Fig. 5, black rectangular at 0 min), the No. 2 rat was injected with 0.33 ml insulin by HI (Fig. 5, red dot at 0 min), the No. 3 rat was injected with 0.36 ml insulin by the device (Fig. 5, blue triangle at 0 min); after 30 min, the BGC was tested again and the three rats were injected with 0.36, 0.33 and 0.36 ml glucose, respectively, (Fig. 5, at 30 min in each line); finally, the BGC levels were tested at 30 min, 1 h, and 3 h, respectively. The BGC levels with and without the insulin in the rats indicates that the PTM have the same effect as the metal needles in delivering drugs.

5. Conclusions: A new type of porous Ti microneedles has been designed and fabricated for delivering drugs. Each microneedle, which has numerous microholes on its surface, can control the dose of drugs and realise continuous drug delivery. The force testing indicates that it can pierce the skin easily without deformation and it can resist large shear force; the in vivo experiment manifests that if it is connected a syringe, it will inject the insulin into the organism successfully and efficiently. In the future, it could be connected to a micropump to constitute an automatic transdermal drug delivery system, or a syringe, to treat some diseases, such as diabetes.

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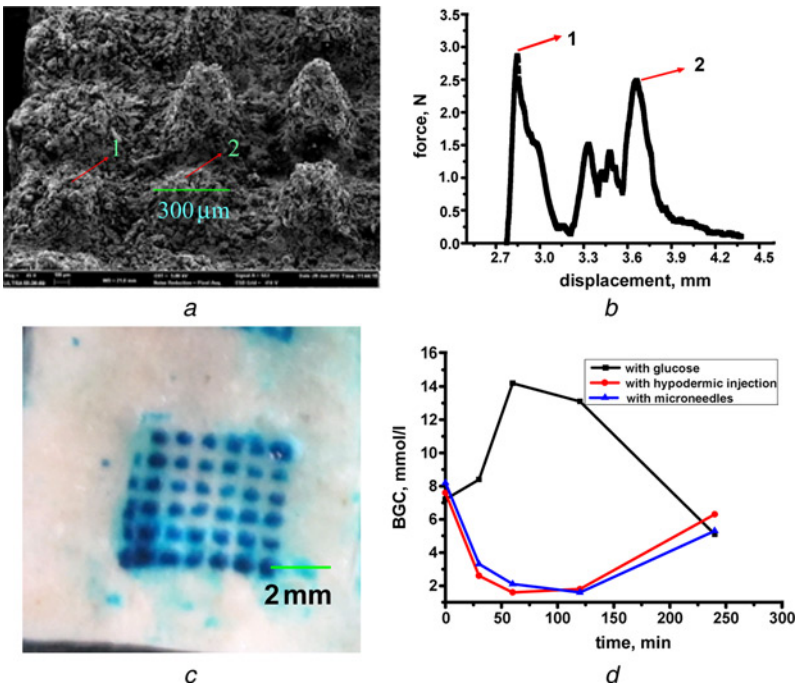


Figure 5 *Force test*
a Fracture of the PTM
b Testing fractured shear force
c Left holes in the pigskin, it is coloured by blue
d The BGC levels vary with the insulin injected into the rats by different injecting methods: the black line is the No. 1 rat; the red is the No. 2 rat; and the blue is the No. 3 rat

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