Introduction

Recently, health care technology and product development is positioning itself as a major national growth factor due to its large social and economic impact as social demands for longer life expectancy and better quality of life, and the associated environment, change. Accordingly, in the pharmacological environment, where there is a transition taking place from expensive and time-consuming development of new drugs to development of generic medicine, intelligent and personalized medicine is being developed actively as drug delivery technology leads the way. Drug delivery systems (DDSs) use existing formulations and optimize drug treatment in order to reduce adverse drug reactions, increase our body’s compliance, and maximize efficacy and effectiveness, via effective delivery of drug. DDSs are developed for purposes such as improved bioavailability and treatment efficacy, reduced adverse reactions, and increased patient compliance.

DDSs are classified into oral administration, transdermal administration, injection, pulmonary inhalation, and transmucosal administration, based on route of administration. Among these, transdermal administration is most commonly used because of its low level of patient discomfort and ease of use. The attempt to deliver drug through the skin has a long history, as the skin accounts for the largest area of the human body. However, early transdermal drug delivery (TDD) systems were attempted for localized action on a damaged area, because the skin had been perceived as a layer impenetrable to drugs, protecting the human body against the invasion of various harmful substances, microorganisms, or chemical substance. However, development of TDD systems accelerated, as the Transderm-Scop patch, a painkiller, developed for administration of scopolamine, was approved by FDA in 1979. Thereafter, patches for delivery of small lipophilic drugs, such as nitroglycerine, nicotine, and fentanyl, were developed. TDD has the advantages of markedly low adverse drug reaction compared to oral administration, and noticeable increase in user convenience compared to hypodermic drug injection. Moreover, TDD has advantages of no gastrointestinal disorder, a low absorption variation between individuals, no risk of loss by drug metabolism, long-lasting effect of single application, and sustaining delivery of drugs with short half-lives, and ease of discontinuation of administration in the event of adverse reaction.
The skin is composed of three layers: stratum corneum, viable epidermis, and dermis. The outer skin layer, stratum corneum, is dead tissue, of 10–15 μm in thickness. The stratum corneum is a primary barrier in drug delivery. The tissue with living cells and nerves underneath the stratum corneum layer, the viable epidermis, is about 50–100 μm in thickness, and does not have blood vessels. Finally, the tissue underneath the viable epidermis, the dermis, has living cells, nerves, and blood vessels. As mentioned earlier, because the stratum corneum hinders drug delivery in TDD, many researchers have developed chemical methods that use peptide enhancers and liposomes, and physical methods that use ultrasound, thermal ablation, electroporation, laser microdrilling, and microneedles in order to enhance skin permeability of drugs. Fig. 1 shows a schematic diagram of the chemical and physical techniques to enhance the efficiency of TDD.

In particular, the microneedle technique is heavily researched due to the advantage that it can be easily mass-manufactured thanks to advances in micromachining technologies, and because it can enhance skin permeability without auxiliary devices such as power source, frequency source, and laser source. TDD based on microneedles can effectively deliver various sizes of drugs into the body because it penetrates stratum corneum layer, a primary barrier in drug transport, using microneedles, and it is possible to deliver drugs without pain by adjusting the height of the microneedles.

The microneedles used in TDD can be manufactured with various biocompatible materials including ceramics (silicon, silicon dioxide, etc.), metals (nickel, stainless steel, etc.), and polymers (poly-lactic acid, poly-glycolic acid, carboxyl-methyl-cellulose, maltose, poly-vinyl-pyrollidone, etc.). Microneedles can be classified into solid needles and hollow needles. This review paper will introduce various TDD methods using microneedles, and various manufacturing methods of microneedles.

**Procedure of TDD Based on Microneedle Patch**

Microneedles can be classified into solid microneedles, which can be manufactured easily, and the hollow microneedles, which are difficult to manufacture, but similar to conventional syringe needles in shape and means of use. TDD systems using solid microneedles can be divided into three types, as shown in Fig. 2 based on the procedure by which drugs are injected. The first type is “poke, detach, and drug diffuse,” as shown in Fig. 2a, which involves creating micro-holes in the stratum corneum layer using a microneedle patch in the “poke” step, followed by removing the microneedle patch from the skin in the “detach” step, and finally, injecting the drug by adhering a drug patch on the micro-holes created in the skin in the “drug diffuse” step. The second type of drug delivery system uses a microneedle patch manufactured with biodegradable polymer; the procedure is shown in Fig. 2b. The sequence of the drug injection can be expressed as “poke, dissolve, and drug diffuse.” In the method, drugs are inserted in the microneedles when they are manufactured with biodegradable polymer, and when the microneedle patch is adhered to the skin for the microneedles to penetrate the stratum corneum layer (“poke” step), as biodegradable polymer dissolves (“dissolve” step), drugs are delivered into the body (“drug diffuse” step). The last method of TDD using solid microneedles is “poke with drug patch, and drug diffuse” as shown in Fig. 2c. This method takes advantage of the fact that through-holes are bound to occur when manufacturing solid microneedles using metal sheet. When using the microneedle patch manufactured with metal sheet and the drug patch in layers, micro-holes are created by the metal microneedle patch, and the drug contained in the drug patch attached to the back of the metal microneedle patch is delivered through the through-holes.

Unlike solid microneedles, hollow microneedles are used to replace conventional syringe needles. Therefore, hollow needles are used in combination with drug chambers. Fig. 2d shows the “poke,
and drug injection” technique to perform TDD using hollow microneedles. The method involves poking hollow microneedles integrated with drug chambers in the skin, followed by injecting the drug using various methods in the “drug injection” step.

In the following sections, research cases of TDD using solid microneedles will be reviewed first, and then the method of using hollow microneedles will be reviewed.

**Solid Microneedle**

1. Solid microneedle for the poke–detach–diffuse method

1) Silicon solid microneedle

The first study that manufactured microneedles using micro-machining technologies and applied them to drug delivery was conducted by S. Henry et al.\(^5\), which was designed to increase TDD efficiency. Fig. 3a shows the scanning electron microscope (SEM) image of the solid silicon microneedle manufactured in their study. They manufactured microneedles on the surface of a silicon wafer using the Black Silicon Method based on the reactive ion etching (RIE) process developed at the University of Twente. The microneedles shown in Fig. 3a were manufactured as a 20×20 array, with a microneedle bottom diameter of 80 μm height of 150 μm. Radius of curvature of the microneedle tip is very sharp, at no more than 1 μm. It has been reported that the diameter and height of the microneedle can be controlled by adjusting the flow rate ratio of SF\(_6\) and O\(_2\) gas used in the RIE process\(^5\). Fig. 3b shows the calcein permeability measured after poking the human skin using the manufactured solid silicon microneedle. In all experimental conditions (keeping the patch on, removing the patch after 10 sec, and removing the patch after 1 hr) of poking the human skin with the microneedle patch, the
use of needle patch showed much higher calcein (623 Da; 0.6 nm radius) permeability than the condition without the use of the patch, resulting in a 25,000-fold increase to permeability.

Fig. 4a shows a solid microneedle array in the shape of a pyramid on a single crystalline silicon wafer using the wet etching technique\textsuperscript{9}. Fig. 4b shows the magnified image of a single SEM. S. Hashmi et al.\textsuperscript{9} conducted anisotropic etching of silicon using potassium hydroxide solution in manufacturing of pyramid-shape microneedles. According to S. Hashmi et al., the height of the microneedles manufactured by the method ranges from tens to hundreds of μm, and the microneedle tip is extremely sharp, with the radius of curvature of no more than 0.1 μm. They used the manufactured solid silicon microneedles in the experiment to inject genes into plant, nematode, and mammalian cells.

Fig. 5a shows a 26-gauge hypodermic needle, and Fig. 5b shows the SEM image of a solid silicon microneedle array\textsuperscript{5} at the same magnification rate. The comparison of Figs. 5a and 5b demonstrates how small microneedles are. Fig. 5c is a magnified SEM image of Fig. 5b. Fig. 5d shows the SEM image of a blunt-tipped microneedle array\textsuperscript{10}. The blunt-tipped microneedle array was manufactured using the silicon wet etching technique shown in Fig. 4, the blunt-tipped microneedles were used for "skin scrape" instead of "skin poke". Their experiment involved causing micro-abrasion on the skin surface by scraping the skin many times using the blunt-tipped microneedle patch, and delivering DNA vaccine through the micro-abrasion. Their report indicated a 2,800-fold increased rate of drug delivery by the scraping.

2) Polymer solid microneedle

The advantage of the manufacturing method of the polymer solid microneedle over silicon solid microneedle manufacturing method is price competitiveness. Polymer solid microneedles

\begin{figure}[h]
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\caption{The first solid microneedles\textsuperscript{5}. (a) Image of scanning electron microscope of silicon microneedles made by the reactive ion etching technique, (b) permeability of human skin treated with different microneedle protocols in vitro.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Silicon solid microneedle array\textsuperscript{9}; (a) image of scanning electron microscope of silicon microneedles fabricated by silicon anisotropic etching technique, (b) a single microneedle used to deliver genes to plant, nematode, and mammalian cells and across vascular tissue.}
\end{figure}
are generally manufactured by the replication process called the molding process\textsuperscript{2,11}. The molding process is the method of manufacturing microneedles by creating cavities in the shape of microneedles and filling them with the polymer with the desired physical and chemical properties. Therefore, mass manufacturing is possible because the microarrays in the same shape can be continuously replicated, as long as the mold is not damaged. This makes the manufacturing cost of the silicon microneedles lower than that of polymer microneedles. In general, microneedle molds can be manufactured with the lithography technique with a photoresist, which can easily produce microstructures with high aspect ratio, such as SU-8. Alternatively, the previously described silicon solid microneedle can be replicated with polymer and used as a mold. The material most commonly used as a mold in the replication process for solid polymer microneedles is polydimethylsiloxane (PDMS)\textsuperscript{11}. The reason for such high use of PDMS is its advantages such as easy-handling, cost effectiveness, and high flexibility.

Fig. 6a shows an SEM image of a beveled-tip microneedle array, which was replicated using the polyglycolic acid (PGA) and the microneedle mold manufactured using lithography process with SU-8 photoresist and the RIE process\textsuperscript{11}. A 20×6 array on a 9×9 mm area was manufactured with a total of 120 PGA microneedles, each of which was 600 μm in height and 100 μm in bottom diameter. Using the poke–detach–diffuse method, permeability of calcein (623 Da; 0.6 nm radius) and bovine serum albumin (BSA, 66 kDa; 3.5 nm radius) were measured; the results are shown in Fig. 6b. The experiment was conducted with human cadaver skin. The study reported over 1,000-fold increase in permeability in both calcein and BSA when the 100 PGA microneedle patch was used compared to non-use.

2. Dissolving polymer solid microneedle for poke–dissolve–diffuse method

As shown in Fig. 1b, the solid microneedles used in the poke–dissolve–diffuse method need to be manufactured with biodegradable polymer because they must be gradually dissolved by water when they are inserted in the body. Dissolving polymer microneedles must be selected from biodegradable polymers considering factors including form ability, dissolving speed, biocompatibility, cost effectiveness, and mechanical strength. Among the polymers that meet these requirements, commonly used polymers include polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), and carboxymethyl cellulose (CMC)\textsuperscript{11–14}.

Fig. 7 shows the dissolving polymer microneedle array manufactured with CMC, and its experimental results\textsuperscript{12}. Fig. 7a shows

![Fig. 5](image)

**Fig. 5.** (a) Scanning electron micrographs of a 26-gauge hypodermic needle, (b) a silicon microneedle\textsuperscript{5} array shown at the same magnification as the hypodermic needle, (c) higher magnification of silicon microneedle of (b); (d) solid microneedles (microenhancer array\textsuperscript{10}, 200 μm tall) chemically etched from a silicon wafer were dipped in plasmid DNA solution for vaccine delivery in vivo.

![Fig. 6](image)

**Fig. 6.** Beveled-tip polymer solid microneedles\textsuperscript{11}: (a) scanning electron microscope images of a portion of a 120-needle array of PGA microneedles, (b) skin permeability of human cadaver skin treated with the solid microneedle patch.
anSEM image of pyramidal microneedles used as the master-mold, which was manufactured with the lithography process using SU-8 photoresist. The pyramidal microneedle has bottom width, tip width, and height of 300 μm, 25 μm, and 600 μm, respectively. The microneedles shown in Fig. 7b can be manufactured by creating a female-mold master-mold of pyramidal microneedles (Fig. 7a) using PDMS, and using it to perform the replication process with CMC. Fig. 7c is the microscopic image of the solid microneedles that were encapsulated with red-color fluorescent dye, sulforhodamine-B. Fig. 7d shows the image of the microneedles manufactured as in Fig. 7c, then adhered to the pig cadaver skin, and then taken with a microscope in five minutes. As Fig. 7d shows, as CMC microneedles were dissolving for five minutes, the sulforhodamine-B encapsulated on the microneedles dissipated toward the tissue, performing the coloring. Fig. 8 shows the microscopic image demonstrating dissolution kinetics of CMC microneedles over time after inserting the CMC microneedle patch in the pig cadaver skin. Fig. 8 shows the degree that CMC microneedles were dissolved before insertion and 10 sec, 1 min, 15 min, and 60 min after insertion, respectively. In this experiment, CMC microneedles were completely dissolved in about 60 min, and the dissolving rate can be adjusted through modification of size or material of microneedles.

A typical method of solid polymer microneedle manufacturing is the method illustrated above involving the manufacturing of master-mold for solid microneedles and replication of microneedles using the molding process. This method requires solid microneedle as a prototype. The method to be introduced below is the thermal drawing technique for direct manufacturing of microneedles without a prototype. Figs. 9a, 9b, and 9c show an image of manufacturing PLGA microneedles using the thermal drawing technique. Figs. 9d and 9e are the images of the step of loading drug in PLGA microneedles via dip coating and drug-loaded microneedles, respectively. Fig. 9f shows the image of dissolving polymer microneedle patch, which was made to bend for application to vascular injuries. Microneedles were manufactured in a 3×3 array, and each microneedle had a bottom diameter of about 270 μm and height of about 600 μm. In an in vivo animal study with 38 male New Zealand white rabbits, K. Lee et al. reported that the bent dissolving microneedle patch demonstrated about a 100-fold higher rate of drug delivery than the conventional film-type drug delivery.
3. Metallic solid microneedles for poke-diffuse method

The last TDD method that uses solid microneedles uses the metallic microneedle patch. Metallic solid microneedles can not only be used in the poke-detach-diffuse method shown in Fig. 2a, but also be used with a drug patch as in Fig. 2c. This is possible because penetrated holes are the by product of manufacturing microneedles using a metal sheet. A typical method of manufacturing metallic solid microneedles involves making metal sheet into needle shapes using the laser cutting technique or chemical etching technique, followed by bending up the microneedles[8,16-18].

Fig. 10a shows the SEM image of metallic microneedles manufactured by W. Martanto et al.[16] by manufacturing the 75 μm-thick stainless steel 304 sheet into 1,000 μm-high 200 μm-wide triangular shape tips, which were then bent perpendicular. By performing transdermal delivery of insulin using the manufactured metallic microneedles, W. Martanto et al. demonstrated the transdermal delivery potential of the macromolecular drug. In their study, the metallic microneedle patch was applied to TDD based on the poke-detach-diffuse method. Fig. 10b shows the microneedle patch manufactured with a titanium sheet, placed next to a 25-gauge needle. According to J. Matriano et al.[18], the titanium microneedles array was manufactured by the chemical etching technique, and had the height of 330 μm, and contained 190 needles in a 1 cm² area. The TDD study was conducted using the poke-diffuse method with the metallic microneedle array with its surfaced coated with protein antigen for vaccine delivery.

Hollow Microneedle

TDD with hollow microneedles is used in two ways. The first use is to replace conventional needles, mainly for pain-reduction and fear-reduction purposes. The second use is to extend the drug injection time by combining hollow microneedle and drug reservoir, as shown in Fig. 2d[3] As discussed earlier, the manufacturing process is more complex for hollow microneedles than solid ones, although both types can be manufactured with ceramics, metals, or polymers.

1. Ceramics

Fig. 11a shows the SEM image of the microneedle array manufactured with silicon dioxide (glass)[19]. The microneedle array manufactured with silicon dioxide was 30 μm in height and 5 μm in diameter, for the purpose of injecting DNA into plant or animal cells. Fig. 11b shows the SEM image of glass microneedle array covered with cell membrane debris. K. Chun et al.[19] manufactured glass microneedles by creating micro-holes with silicon using the reactive ion etching technique, and then growing silicon dioxide on the surface of micro-holes using the oxidation process, followed by removing the silicon using the chemical etching.
technique. The glass microneedles manufactured through the process are too small and brittle to apply to TDD.

Fig. 12a shows the hollow silicon microneedles (MicronJet) manufactured for TDD; Figs. 12b and 12c show the magnified SME images of microneedles\textsuperscript{20}. As shown in Fig. 12a, the hollow microneedles manufactured by V. Damme et al. were manufactured for intradermal vaccination, replacing conventional hypodermic needles. "MicronJet" consists of four 450 μm-high hollow silicon microneedles. The hollow silicon microneedles were manufactured by the combination of the silicon RIE technique and silicon anisotropic chemical etching technique. "MicronJet" was developed by NanoPass Technologies Ltd. in Israel, approved by FDA, and is commercially available.

2. Polymers

Hollow polymer microneedles can be manufactured by various methods including X-ray lithography of polymethylmethacrylate (PMMA) sheet\textsuperscript{21}, laser machining and injection molding\textsuperscript{22}, and UV lithography of SU-8 photoresist\textsuperscript{23}. Figs. 13a and 13b show the polymer hollow microneedle array and single microneedle manufactured by 3M, respectively, and the prototype was manufactured with the name of hollow Microstructured Transdermal System (hMTS)\textsuperscript{24}. hMTS is reported to have 18 hollow microneedles in 27 cm\textsuperscript{2} with microneedle height of 500–900 μm, and diameter of the cannula where the drug goes through can be manufactured at 10–40 μm. Fig. 13c shows an image of the experiment where 3M hMTS was used to inject methylene blue into the swine skin, showing the tissues underneath the stratum corneum layer were successfully dyed blue with the injection that penetrated the stratum corneum layer using hMTS.

3. Metals

Metal hollow microneedle patches are usually manufactured by creating microneedle-shaped cavities using polymer followed by electro-deposition of metal on top of them\textsuperscript{25-29}. Figs. 14a and 14b show the SEM images of the first metallic hollow manufactured
Kim BH, Seo YH. Fabrication of Microneedles for Transdermal Drug Delivery

In 1999, according to D. McAllister et al., skin permeability increased up to 100,000-fold by hollow microneedles. Fig. 14c shows the SEM images of the metal hollow microneedles manufactured by S. Davis et al. by creating micro-holes on 500 μm-thick PMMA sheet using excimer laser, followed by electrodeposition of nickel, alongside the image of 27-gauge hypodermic needle. S. Davis et al. measured the insertion force of the manufactured nickel hollow microneedle through the skin, and found it was 1.65 N. This is a similar force to that of a person pressing a finger slightly. In addition, the fracture force of the nickel hollow microneedle was measured at about 4 N, which is more than twice the insertion force, suggesting that fracture of the nickel hollow microneedle would not occur while it is inserted into the skin.

Fig. 15a shows an SEM image of the 37 hollow microneedle array manufactured with NiFe, alongside a 26-gauge hypodermic needle. The manufacturing method for the hollow microneedle array involved creating solid microneedles using the silicon RIE technique, and creating a female-mold for silicon solid microneedles using SU-8 photoresist, followed by electrodeposition of NiFe. Using the manufactured hollow microneedles, skin permeability testing for calcein, insulin, BSA, and nanospheres (25 nm) was conducted.

Conclusion

In this review paper, methods of transdermal drug delivery based on microneedle patches, and fabrication methods of solid and hollow microneedles. Microneedles can be made of silicon, metal, and polymers in various geometries. Microneedles can provide several thousand times improvement of skin permeability for the macromolecular chemicals. In additions, the size of microneedle is less than 1 mm, thus pain-reduction and fear-reduction are expected. Microneedles will play an important role in future development of low cost and high efficiency transdermal drug delivery systems.

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