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A Review on Microneedle Microneedles: A Smart Approach for Transdermal Drug Delivery System

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ABSTRACT:

Transdermal delivery has the advantage of bypassing the frst-pass efect and allowing sustained release of the drug. However, the drug delivery is limited owing to the barrier created by the stratum corneum. Microneedles are a transdermal drug delivery system that is painless, less invasive, and easy to self-administer, with a high drug bioavailability.Area covered The dose, delivery rate, and efcacy of the drugs can be controlled by the microneedle design and drug formulations. This review introduces the types of microneedles and their design, materials used for fabrication, and manufacturing methods. Additionally, recent biological applications and clinical trials are introduced.Expert opinion With advancements made in formulation technologies, the drug-loading capability of microneedles can be improved. 3D printing and digital technology contribute to the improvement of microneedle fabrication technology. However, regulations regarding the manufacture of microneedle products should be established as soon as possible to promote commercialization.

Keywords: Microneedles, Solid Microneedles, Dissolving Microneedles, Hydrogel Microneedles

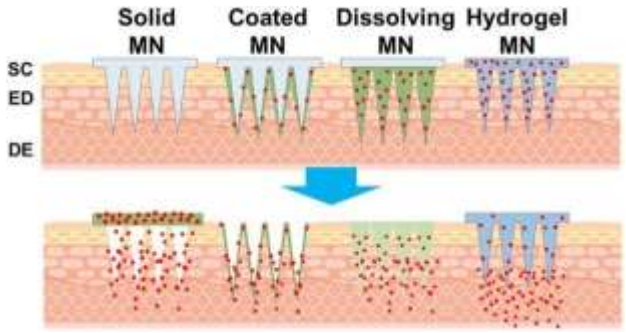
Introduction:

The efficacy of pharmaceuticals depends on not only the properties of the active drug component but also the mechanism underlying its delivery to the body (Tibbitt et al. 2016). Therefore, it is critical to investigate an optimal method for drug delivery in accordance with the characteristics of the drug. Oral administration is a simple and convenient drug delivery method because the patient can self-administer the drug; however, its application to biopharmaceuticals is challenging (Homayun et al. 2019). Injections result in high bioavailability and rapid onset of drug action. However, expertise is required for administration and patient compliance is low (Prausnitz 2017). Therefore, the ideal drug delivery method should be as simple as oral administration and should exhibit high bioavailability as with injection. Transdermal delivery has the advantage of bypassing the frst-pass efect and allowing sustained release of the drug. However, drug delivery is difcult due to the barrier created by the stratum corneum (Dharadhar et al. 2019). Microneedles are a platform for transdermal drug delivery; it is easy to self-administer, and it exhibits a high drug bioavailability (Prausnitz 2017).[1] In addition, it is a painless and less invasive method that enables the drug to directly pass through the stratum corneum, which is the largest barrier of the skin (Ye et al. 2018; Kim et al. 2012; Ma and Wu 2017; Prausnitz et al. 2008). The advantages and disadvantages of microneedles as a transdermal delivery system are summarized in Table 1. The dose, delivery rate, and efcacy of the drugs can be controlled by the microneedle design and drug formulation. Till date, studies have been conducted on microneedles formulated using various manufacturing methods and materials for delivering drugs and cosmetics (Donnelly et al. 2010; Ma et al. 2017). The efcacy and safety of microneedles have been demonstrated through animal experiments and clinical trials (Bhatnagar et al. 2017; Queiroz et al. 2020). In this review, we summarize the types of microneedles required for microneedle design, materials used for fabrication, and manufacturing methods.

Types of Microneedles

Although the microneedle design varies depending on the delivery method, type of microneedle, and action of the drugs to be delivered, most patches have certain common features. A typical microneedle has the shape of a tapered sharp tip with a length of 150– 1500 μm, a width of 50–250 μm, and a tip thickness of 1–25 μm (Waghule et al. 2019).

Microneedles are usually made of metal, silicon, polymer, glass, or ceramic. The drug is generally placed in or on the microneedle tip, which is fxed to the base substrate underneath to form an array. The microneedle array is attached to the patch backing for ease of use; this backing includes a skin adhesive to improve contact with the skin. The microneedles are typically classifed into four types (Fig. 1). Solid microneedles are primarily made of metal and silicon, which provide strong mechanical properties and do not contain drugs. Therefore, after applying the microneedles, it is necessary to further apply the drug to the area. In contrast, when coated microneedles are applied on the surface of the skin, the drug is delivered simultaneously with the application. In dissolving microneedles, the drug can be included in the biodegradable matrix, in which case no sharp waste is produced after microneedle application. Hydrogel microneedles allow drugs to be delivered slowly because the drug is contained in all areas such as the tip of the microneedle and the patch backing. Since the characteristics of microneedles vary with the type, a suitable design should be selected for the microneedles according to the drug dose, onset of action, delivery period, delivery efciency, packaging, sharp waste, and patch-wearing time.[2]



[fig.1 Types of microneedles]

1) Solid Microneedles

Solid microneedles are an array containing microscale tapered sharp tips composed of a single material without any drugs or excipients, They are inserted into the skin, creating micron-sized pores on the skin surface (Fig. 2a). When the drug is placed on the treated area, the drug passes through the stratum corneum, the largest barrier of the skin, through these pores; it is easily transferred to the capillaries in the superfcial dermis, increasing the bioavailability of the drug (Henry et al. 1998). The agent may be formulated.

2) Coated Microneedles

In coated microneedles, the surface of a solid microneedle is coated with a water-soluble matrix so that the drug dissolves rapidly into the skin after microneedle insertion (Fig. 2b) (Haj-Ahmad et al. 2015; Jiang et al. 2007). The coating formulation should form a flm on the surface of the microneedle and maintain adhesion during storage and insertion into the skin. To achieve this purpose, the coating formulation should have adequate viscosity. The location where the coating formulation is placed should be considered. Generally, it iseconomical to place the drugs only at the tip where the microneedle enters the actual skin. In the case of dip coating, the drug-coated area can be controlled via regulating the depth to which the microneedle is dipped into the coating formulation (Gill et al. 2007a; Gill et al.2007b; Shakya et al. 2019). The drug-coated area can be determined by controlling the surface tension of the coating formulation, thus regulating the spreading of the microneedle. In coated microneedles, the drug can quickly dissolve in the skin, resulting in a fast onset of drug action. The thickness of the coating can be increased by repeating the formulation coating; however, it is not suitable for drug delivery as it requires a large dose due to dose limitations.[4]

3) Dissolving Microneedles

Microneedles themselves can be made of water-soluble or biodegradable materials that contain the drugs and possess sufcient mechanical strength to penetrate the skin (Fig. 2c) (Sullivan et al. 2010). Insertion of a dissolving microneedle into the skin does not generate sharps waste because it rapidly dissolves or disintegrates upon contact with the skin fuid (Edens et al. 2015; Hirobe et al. 2015; Quinn et al. 2015). Dissolving microneedles are primarily manufactured using a water-soluble biodegradable polymer via a solvent casting method. Biodegradable, cellulose-based polymers such as carboxymethyl cellulose (CMC) and methyl cellulose are frequently used. Saccharides (e.g. trehalose and sucrose) are also included in the microneedles; they promote disintegration of the formulation and stabilize biomolecules (Mistillis et al. 2015; Raphael et al. 2016). The formulation of the drug- containing tip should exhibit compatibility with the drug, provide mechanical strength, and have a sufciently low viscosity for flling the microscale mold space well without air bubbles. The base substrate containing no drug may have a higher viscosity than the tip, may be mechanically weak, or may be a water-insoluble material (Prausnitz 2017).Recently, several studies have been conducted for shortening the microneedle patch-wearing time via separating the microneedle tips rapidly from the base substrate without needing the tips to fully dissolve in the skin. Li et al. reported a microneedle patch capable of rapidly separating after skin insertion by shearing force. The mechanical strength of the microneedle was controlled by trapping a droplet on the microneedle (Li et al. 2019a). In addition, the microneedle tip was separated within 2 min from the base substrate, which was composed of a foamable material (Li et al. 2019b). Jun et al. developed insertion-responsive microneedles for immediate separation of the microneedle after skin application (Jun et al. 2018). A small single wall was designed on the side of the microneedle base; the structure enabled rapid mechanical separation of the tip from base. However, as with dissolving and coated microneedles, this system is disadvantageous for delivering large doses; studies are being conducted for increasing the amount of drug that can be incorporated in these microneedles.

4) Hydrogel Microneedles

In hydrogel microneedles, the drug is contained in all areas of the microneedle tip, base substrate, and patch backing and is released at a slow rate while the patch is applied to the skin (Fig. 2d). The microneedle patches are primarily composed of hydrogel, and when they encounter fuids in the skin, they are hydrated but not dissolved (Al Sulaiman et al. 2019; He et al. 2020; Yu et al. 2015). A high amount of the drug in the hydrogel is delivered to the skin through difusion (Migdadi et al. 2018; Courtenay et al. 2020). Since the drug can be incorporated in the entire microneedle patch, this system is suitable for large dose delivery; however, its disadvantage is that the patch-wearing time is long because the drug delivery rate is slow.

Materials for Microneedles

Various materials, from metal to polymer, are used in microneedles, depending on the design or components of the patch. Generally, microneedle materials should have sufcient mechanical strength for skin insertion (Dharadhar et al. 2019). Non-dissolving microneedles are inert, biocompatible, and sufciently strong for skin insertion without causing an immune response. In contrast, the matrices of the coated and dissolving microneedles should generally be water-soluble and biocompatible. In addition, it should dissolve or disintegrate in the body without inducing toxicity. Compatibility between the matrices and drugs is critical during the manufacturing process, storage, and transportation of the microneedle patches. The characteristics of various materials used in microneedles are described below.

1) Silicon

Silicon has sufcient mechanical strength for skin insertion; therefore, it is often used for manufacturing solid and coated microneedles (Hoang et al. 2015; McGrath et al. 2011). Silicon microneedles can be precisely manufactured with small sharp tips with lengths of 100 μm or less using deep reactive ion etching and photolithography (Donnelly et al. 2009; Henry et al. 1998; Li et al. 2019c). However, the equipment used is expensive, the process is expensive, and the production speed is slow (Banga 2009). The silicon microneedle can cause safety problems when it breaks from the skin and fragments remain in the tissue (McGrath et al. 2011). Recently, silicon is being used in reverse master molds rather than in solid microneedles (Lutton et al. 2015).

2) Metal

Metal materials exhibit high mechanical and tensile strength; therefore, they can easily pass through the skin. They are used to produce solid, coated, and hollow microneedles. In general, stainless steel (Gupta et al. 2011) and titanium (Ti) (Choi et al. 2013; McCarthy et al. 2011; Skoog et al. 2015) are typical metal materials used in microneedles. Stainless steel is the most used metal material for microneedle production; however, it exhibits a faster corrosion rate than Ti alloy (Amalraju et al. 2012). Ti alloys possess stronger mechanical strength than stainless steel; however, they are more expensive (Amalraju et al. 2012).

3) Polymer

The polymers used for microneedle manufacture should be water-soluble, biocompatible, and mechanically strong for skin insertion (Praustniz 2017). The most common method for producing polymer microneedle is the solvent casting method. This method involves obtaining an inverse mold from the microneedle structure, pouring a polymer formulation on it, drying it, and peeling it from the inverse mold. Dissolving or hydrogel microneedles are manufactured using the solvent casting method with various types of polymers such as hydroxypropyl methylcellulose (Kim et al. 2016), hyaluronic acid (Du et al. 2019), CMC (Mistillis et al. 2015), polyvinyl pyrrolidone (Cafarel-Salvador et al. 2015; Tang et al. 2018; Tas et al. 2017), and poly(lactic-co-glycolic acid)

4) Glass

Glass microneedles are primarily hollow and prepared using wet etching or micropipette puller (Dharadhar et al. 2019; Martanto et al. 2006). It exhibits sufcient strength for skin insertion, enabling easy processing of the tapered shape. It is easy to sterilize because it is stable at high temperature and pressure; the material itself is biocompatible. However, it breaks easily; specifcally, if the tip of the microneedle is broken and it remains in the skin tissue, it can cause infammation or granulomas.

5) Ceramic

Since ceramic materials such as alumina, calcium phosphate, and calcium sulphate exhibit biocompatibility and provide sufcient mechanical strength, studies have explored their use in the preparation of microneedles (Ita 2018) (Figure. 3).[8]

Microneedle Fabrication Techniques

When designing a microneedle, the objective of the microneedle is considered frst. The drug type and dose, desirable pharmacokinetics/pharmacodynamics, and targets for use are considered. Next, the most optimized microneedle design and materials are determined.
The manufacturing method for microneedles varies depending on the design or material. When focusing on the economic aspect, a method such as solvent casting, which is easy to set up, is used. In contrast, if the focus is on the accuracy, precision, and reproducibility of needle production, production of metal or silicon microneedles based on MEMS technology can be considered. We have summarized various methods reported till date for microneedle manufacture

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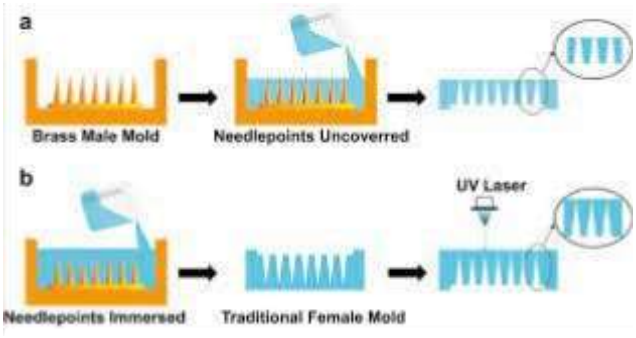

[Fig.2]

TechniquesLaser cutting

Laser cutting is primarily used for manufacturing a metal or polymer microneedle; the most used material is stainless steel (Banks et al. 2010; Martanto et al. 2004; McAllister et al.

2003). The 2D shape of a microneedle is generated through cutting on a fat metallic sheet using a laser. The size and orientation of the microneedle array is designed through a computer-aided design (CAD) software. The microneedle drawn in 2D is bent by 90 degrees to create a 3D microneedle. Needle tips or rough surfaces can be cleaned using electropolishing (Gill et al. 2007a; Gill et al. 2007b; Shakya et al. 2019).

Laser ablation

Laser ablation is also used for fabricating metal or polymer microneedles (Nejad et al. 2018). Laser cutting involves cutting a metal or polymer plate into a 2D shape, whereas laser ablation engraves the plate into a 3D shape. Basically, when the substrate is irradiated with a laser beam (e.g., CO2 laser ment of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC)http://creativecommons.org/licenses/by- nc/4.0/. **Reprinted/adapted from [Tang et al., Science Advances 2018 4:eaat9365] © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC)

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Photolithography

Photolithography is used to elaborately create solid or hollow microneedles. This method is used to manufacture silicon microneedles or dissolving/hydrogel microneedles via making an inverse mold based on the microneedle structure. When fabricating silicon microneedles using photolithography, a sacrifcial layer is deposited in the form of a thin flm on cleanly treated silicon. Subsequently, a photoresist, a photosensitive polymer, is coated on the silicon via spin coating. If the photomask with desirable pattern is aligned on the substrate and exposed to strong UV radiation, the desired pattern is generated in the part exposed or not exposed. The pattern is generated in the photoresist through the development process; subsequently, the exposed substrate without the photoresist is etched through the etching step. Consequently, a desirable pattern is transferred from the photomask to the photoresist to the silicon (Dardanoet al. 2015; Dharadhar et al. 2019).

Etching

When a microneedle is fabricated using general photolithography, etching is an important process for determining the tapered shape of the microneedle tip. Before the etching process, the size of the microneedle base and the gap among the microneedles are determined. Subsequently, the length and shape of the microneedles are determined through the etching process (Wilke et al. 2005). The etching process is classifed as dry etching and wet etching. It results in isotropic or anisotropic etching, depending on the method utilized.

Dry etching

Dry etching is primarily used to create solid or hollow microneedles. It is classifed into physical methods and chemical methods. Physical methods include ion milling and sputtering (Indermun et al. 2014; Kim et al. 2012). In dry etching, an inert gas (e.g., Ar or SF6) is ionized by high energy and unidirectional electrodes. Because the ions strike the silicon substrate at a high speed in a single direction, anisotropic etching is performed. In the manufacturing process, the area protected by the oxide flm (sacrifcial layer) or photoresist is hardly etched, while the area exposed on the silicon is etched. Chemical methods include high pressure plasma etching, in which a chemically reactive plasma gas is generated using strong energy. The plasma reacts with the surface of the substrate, and it is converted into a volatile material, which is blown away, thereby resulting in isotropic etching of the substrate. Reactive ion etching combines physical and chemical methods; both plasma and sputter etching can be used to control isotropic and anisotropic etching (McAllister et al. 2003). Through the optimization of this process, a precise microneedle sharp tip can be manufactured (Henry et al. 1998).

Wet etching

Wet etching is also used for fabrication of metal or silicon microneedles (Wilke et al. 2005). In this process, a pattern is produced on the substrate using a chemical etchant. In the case of a silicon wafer, a potassium hydroxide aqueous solution is used; a sharp tip shape can be produced by applying diferent rates of etching, depending on the direction of the silicon crystals (Henry et al. 1998; Indermun et al. 2014). Wet etching is primarily isotropic etching via a chemical reaction; the etching rate is signifcantly faster than that in dry etching.

Although the cost required for the entire process is low, the poor accuracy of this method is a disadvantage for the fabrication of fne patterns .[9]

Drug Delivery by Microneedles

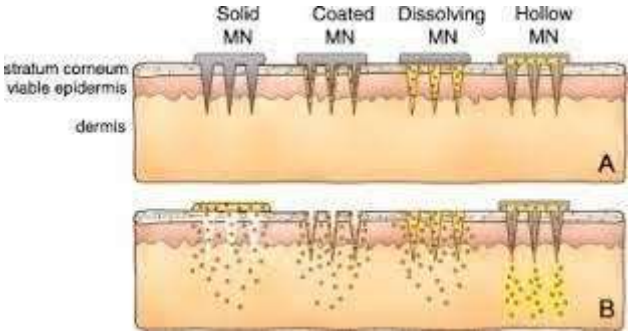

Fig.3.

1) Proteins

Protein drugs can be applied to various cancer treatments, vaccinations, and treatment of genetic diseases. Rapid development is expected; however, drug delivery is limited due to the problems of low stability and absorption. For example, during dosing and storage, protein denaturation, drug absorption efciency, and cellular permeability related to molecular size can lead to limited therapeutic efciency. Microneedle research is being conducted for improving the delivery efciency of protein drugs. For example, microneedle technology has been developed for proteins including insulin, desmopressin, erythropoietin, lysozyme, glucagon, glucagon-like peptide-1, parathyroid hormone, and growth hormone.

The selection of materials and formulations for preserving protein drug stability remains a difcult task, especially in large-scale storage planning and production chains for clinical use. Chen et al. reported a microneedle with glucose response and temperature stability that was developed using phenylboronic acid for insulin drug delivery in diabetes treatment (Chen et al. 2020). Lahiji et al. evaluated the efects of microneedle manufacturing parameters including manufacturing and storage temperature and drying conditions so that the combination of low temperature during manufacture, mild drying conditions, polymer concentration, and addition of protein stabilizer maintains lysozyme activity up to 99.8±3.8%. Additionally, they reported the importance of optimizing manufacturing parameters (Lahijiet al. 2018).[10]

2) Vaccines/antibodies

Current vaccines are usually limited to subcutaneous injection. Microneedles containing vaccines have been studied recently for induction of an antibody immune response. The advantage of microneedle vaccines is that they enable stronger local immunity compared to injectable formulations because they induce antigen presentation to dendritic cells residing in the skin. Currently, the availability of vaccines is often dependent on cold storage and transportation. Vaccine development using microneedles can preserve the long-term antigenic immunogenicity of the patch and allow fexible storage conditions. Additionally, monoclonal antibodies target specifc cells and modulate the immune system, rendering them useful in a wide range of diagnostic and therapeutic applications. Local delivery of monoclonal antibodies using microneedles was performed for alleviating excessive stimulation of autoreactive T cells and addressing side efects (Xu et al. 2017). Antibody delivery can pose various challenges, including loss of efcacy and risk of immunogenicity due to protein inactivation. To address this problem, stability of the antibody in the microneedle is important.[11]

Limitations and perspectives

Microneedles are a transdermal drug delivery system that is rapidly growing in research owing to the beneft of increasing patient access to drugs through replacing other routes of administration. Microneedles have been proven to improve drug stability and drug delivery efcacy through non-clinical and clinical studies. However, microneedles as a tool for drug delivery has limitations.[15]

1) Limited drug dose

Because of their small size, microneedles can deliver only a limited amount of drugs. Therefore, their application is difcult when a large dose or continuous drug release is required. To overcome this limitation, the immediate limitations can be overcome through applying several patches at once or periodically changing the microneedle patch. However, for expanding the scope of microneedles in medicine, research is needed on increasing the drug dose that can be incorporated in the microneedles.

2) Solubilizing technology for poorly soluble drug

Solubilization of poorly soluble drugs is an essential technology for solving the problem of small-dose microneedles. Basically, sufcient drug solubility in an aqueous solution is required to apply the drug to a microneedle. However, since several drugs show low water solubility, only a small proportion of the drugs can be delivered (Kearney et al. 2019).

Increasing the solubility of a poorly soluble drug allows a large dose of the drug to be contained in the same formulation, enabling the incorporation of higher amounts of drugs in microneedles of limited size. Use of prodrugs for increasing solubilization is a representative technique for solubilizing poorly soluble drugs. In addition, there has been consistent research on improving the solubility of poorly soluble drugs using surfactants or liposomes, salt preparation of the drug, pH adjustment, and nanoparticle control technology.

3) Sustained drug-releasing technology

Till date, research on microneedle-based drug delivery has focused on demonstrating rapid dissolution of drug formulations from the microneedles into the body. Thus, although microneedles are efective for single drug administrations, they have limitations in continuous drug delivery. To demonstrate sustained drug release using microneedles, separable microneedles have been developed. Since Chu et al. frst developed separable microneedles (Chu et al. 2011), various studies on separable microneedles have been conducted for minimizing the patch-wearing time through rapidly separating the formulation from the microneedle. (Choi et al. 2018; Li et al. 2019a, 2019b). In addition, research is being conducted on introducing a sustained-release formulation technology for enabling long-term drug delivery of drugs separated from the microneedle to the body. Li et al. have developed a separable microneedle to release contraceptive hormones and maintain their levels within the therapeutic range for approximately a month (Li et al.

2019a, 2019b). Through research on formulation technology for long-term drug delivery, various drugs can be applied to microneedle patches and various incrementally modifed drugs can be developed by enabling efective drug delivery. In addition, it is necessary to develop an adhesive patch that does not cause toxicity even when wearing a microneedle patch for a long duration.[6]

4) Fabrication technology

Microneedle master molds are primarily manufactured by deep reactive ion etching for fabricating the small microneedle tips, the size of which ranges over several tens of micrometers with high accuracy and reproducibility. Because the instrument and maintenance are expensive, the barrier to enter the feld of microneedle research is high, and the technology of mass production has been limited to certain companies.[7]

5) 3D printing

As the technology for 3D printing advances, microneedle manufacturing has been conducted using entry-level 3D printers. Because the price and maintenance of 3D printers are inexpensive, they can be easily utilized for various applications. CAD software enables the design of novel shapes of microneedles. 3D printing can signifcantly shorten the product development time due to rapid fabrication and modifcation of the prototypes. However, there is a limit to the materials that can be used, and the low resolution of entrylevel 3D printers remains a problem. Although there are high-resolution 3D printers, the instrument price is high. Nevertheless, 3D printing studies have continued to overcome the limitations. It is expected that the 3D printing technology will enable us to produce customized microneedle patches depending on individual symptoms.

6) Regulations

Currently, the licensing of microneedle products is processed for each application rather than for a specifc microneedle system (product-specifc approval). Therefore, the licensing of microneedle products is delayed, which is a factor restricting the commercialization of microneedles. To address this problem, a microneedle-based licensing regulation including the shape, formulation, sterilization, and packaging of the microneedle must be defned.

Through the unifcation of cGMP and quality control, a microneedle licensing method based on quality by design should be established to promote the commercialization of microneedle products as pharmaceuticals.[13]

7) Convergence with digital technology

Current microneedles are designed as simple patches for delivering drugs; however, in the future, they can be developed as digital medicine through fusion with information technology. Convergence systems that provide information on the drug-loading amount, patch-changing time, or rate of controlled drug release can be developed. The convergence technology can contribute to maximizing the drug delivery application of microneedles and diversifying the products.[16]

Conclusion

Microneedles are a transdermal drug delivery system that is rapidly growing in research owing to the beneft of increasing patient access to drugs through replacing other routes of administration. Microneedles can be classifed as solid, coating, dissolving, and hydrogel formulations. They are composed of various materials such as silicon, metal, polymer, glass, and ceramic. Various manufacturing techniques are utilized for imparting unique shapes, sizes, and properties. Microneedles continue to evolve through clinical trials and utilize various drugs. Most studies have demonstrated favorable results using this system. This technique has the potential to provide therapeutic efects in multiple felds

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