REVIEW ARTICLE

The Growing Role of Hydrogel Microneedles in Transdermal Drug Delivery

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ABSTRACT

Microneedles represent a new promising approach that can be applied to enhance drug delivery. Various types of microneedles are available, including solid, coated, hollow, dissolving, and more recently, hydrogel microneedles. This review focuses on the benefits offered by hydrogel microneedles and their applications in transdermal drug delivery. Hydrogel microneedle arrays possessing several advantages over other types of microneedles, including a higher safety profile. Since they are removed intact from the skin following insertion; therefore, no polymer residue remained within the skin.

Furthermore, because they swell shortly after insertion, they cannot be inserted again and thus prevent the reuse of microneedles. In addition, hydrogel microneedles can deliver drugs with different molecular weights at higher concentrations due to the presence of a reservoir attached to the microneedle array that can be loaded with larger amounts of drugs. Another important property of hydrogel microneedles is their ability to deliver drugs in a sustained release manner. This depends on the crosslinking density of the polymers forming the hydrogel matrix and on the degree of swelling achieved. The swelling decreased as the crosslinking between the polymers increased, resulting in a sustained drug release. Therefore, controlling the degree of crosslinking of the polymers forming hydrogel microneedles can be utilized to obtain a sustained transdermal drug delivery.

Keywords: Hydrogel microneedles, Sustained drug release, Swelling, Transdermal drug delivery.

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MICRONEEDLES (MNs)

Hypodermic needles and transdermal patches are frequently used for the systemic delivery of drugs across the skin. However, hypodermic needles can cause pain and phobia that decrease patients' compliance and adherence to the treatment protocol.[1] On the other hand, due to the formidable nature of the skin barrier that hampers the transport of the drug molecules across the skin, there is a limited number of drugs with suitable physicochemical properties that can be delivered passively to the transdermal patches across the skin to achieve desired therapeutic effect.[2] Therefore, various attempts have been performed to enhance the delivery of the drug through the skin using active enhancement techniques such as microneedles, which can deliver drugs transdermally at therapeutic concentrations.[3] Microneedles merge the advantages of simple and easy use of a transdermal patch with the efficiency of delivery accomplished by conventional hypodermic syringe.[4]

Microneedles are minimally invasive devices that painlessly bypass the *Stratum corneum,* which is the main barrier to topically applied drugs.[5] Microneedles are composed of needles in micron size (50–900 μm) arranged in an array that can overcome the issue of pain sensation associated with hypodermic needles since their tips are very sharp and they do not penetrate deep into the lower dermis containing nerves, and hence they are considered as painless technology with increased patient compliance. In addition, microneedles can deliver a variety of small and large molecular weight drugs because of the formation of microchannels within the skin through which drug molecules can pass readily to the dermal microcirculation for systemic absorption.[6]

TYPES OF MICRONEEDLES

Microneedles can be divided into different types as shown in Figure 1 according to the way they deliver drugs into the skin,[7] these are:

A. Solid microneedles ('poke and patch'): They first puncture the skin, followed by the application of the drug formulation to the skin surface, allowing the drug to diffuse through the formed microchannels. They can be used as skin pre-treatment.[8]
B. Coated microneedles ('coat and poke') are typically coated with a water-soluble drug, with the subsequent

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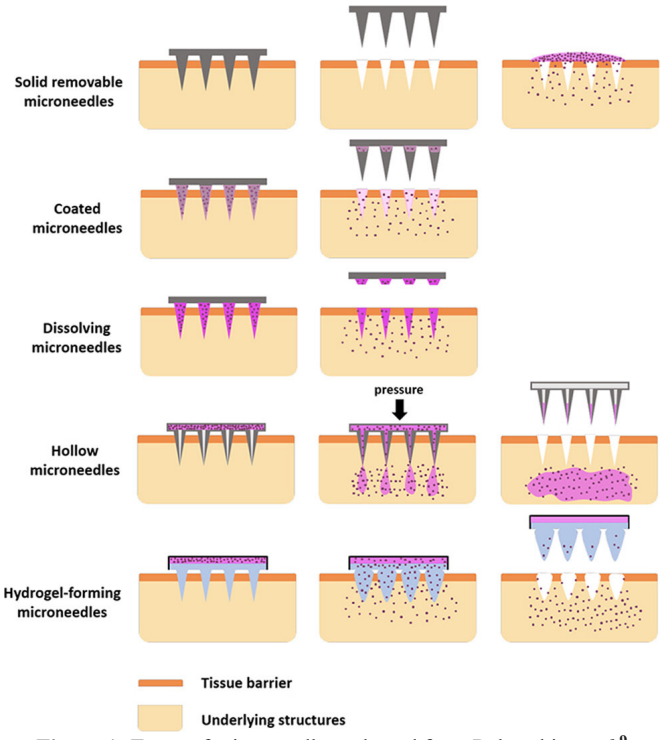

Figure 1: Types of microneedles, adapted from Rzhevskiy *et al.*[9]

dissolution of the drug after insertion into the skin and then the microneedles can be removed intact. This approach solves the problem of the two-step application of solid microneedles. They have the advantage of delivering a fixed amount of drug, but this amount is very small due to the small dimensions of the microneedle tip. In addition, the remaining microneedles are dangerous because they can be reused again by other patients with the possibility of infection.[9]

C. Hollow microneedles ('poke and flow') are similar to a conventional syringe of short length in shape, allowing liquid medication to be injected directly into the skin layers. Furthermore, they can be used as an alternative approach in the sampling of fluids from patients without causing pain or bleeding for the therapeutic drug monitoring and an assay of biomarkers from interstitial fluid, such as in the case of glucose monitoring.[10]

D. Dissolving microneedles ('poke and release') where the drugs are encapsulated within a dissolving biodegradable microneedle array. They dissolve when the microneedles are inserted into the skin, releasing the drug in microneedles. Dissolving microneedles improve the disadvantages of the coated microneedles by loading larger doses of a drug. Additionally, they have the advantages of elimination of the need for sharps disposal and the likelihood of accidental reuse of microneedles.[11]

E. Hydrogel microneedles are recently discovered by Donnelly *et al.*[12] They are prepared from polymers that form a hydrogel. Hydrogel microneedles can be used for several purposes and have several advantages, as discussed in the following sections.

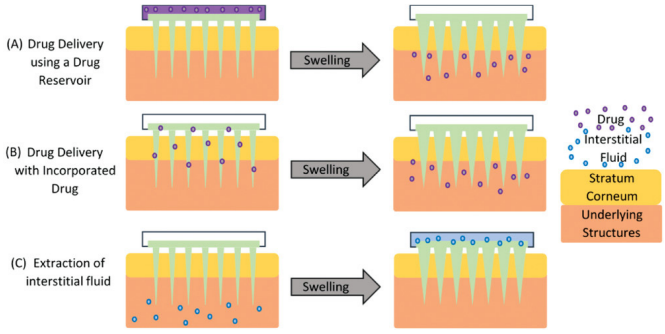

Figure 2: An illustration of the mechanism of transdermal drug delivery and extraction of interstitial fluid from the skin using hydrogel MNs, adapted from Turner *et al.* [21].

HYDROGEL MICRONEEDLES

Hydrogel MNs are type of microneedles that could pierce the skin to create microchannels for drug delivery. These microchannels resist the closure while the hydrogel MNs are in their place due to the swelling of the needles resulting from absorbing skin interstitial fluid.[13] Hydrogels are polymers with a three-dimensional structure that exhibit the ability to swell in water and keep a significant amount of water within their structure. They can be divided into natural hydrogels and synthetic ones. Natural hydrogels include methylcellulose, chitosan, starch, hyaluronic acid, agarose, and collagen. Synthetic hydrogels such as polyvinyl alcohol, sodium polyacrylate, acrylate polymers, and copolymers with an abundance of hydrophilic groups such as polyethylene glycol and polymethyl vinyl ether/maleic acid (Gantrez®).[14] To obtain an excellent swelling of the hydrogel MNs, sodium carbonate Na_2CO_3 can be added to the hydrogel polymers formula since it acts as a pore-forming agent, which enables the hydrogel matrix to absorb more liquid.[15] The polymers used in the fabrication of hydrogel MNs should be non-toxic, biocompatible, have a suitable swelling property to aid in releasing drugs from the MNs, and preferably having an antimicrobial effect.[16]

Hydrogel MNs can deliver drugs into the skin without any polymeric residue in the skin since they are removed intact from the skin after a certain period of time which is considered as an advantage to hydrogel MNs. In addition, a higher drug loading can be achieved by the use of hydrogel MNs because they are attached to a drug reservoir and can provide a sustained release of drugs with improved patients compliance.[17] The way of drug incorporation into MNs depends on the dose of the drug used; if the drug has a low dose, it can be incorporated within the MNs hydrogel matrix polymer. While drugs with a high dose can be prepared as a patch attached to the hydrogel MNs.[18] Additionally, hydrogels can also be classified as conventional hydrogels that do not exhibit any significant volume transition due to environmental changes (pH, temperature, photo field, ion concentration, and composition of the solvent)) and intelligent hydrogels that can change their volumes abruptly in response to the changes of the external environmental factors such as fabrication of hydrogel

microneedles contain ibuprofen with light responsive polymer. The drug was released when exposed to light.[19] Moreover, hydrogel MNs can be used in biomedical analysis, such as the uptake of interstitial fluid as a biomarker, for example, to measure blood glucose in the human body[20] as demonstrated in Figure 2.

Hydrogel MNs mechanism of drug release, as illustrated in Figure 2 can differ from other types of MNs because it depends on the degree of swelling of polymers used. The swelling of the hydrogel matrix increases with an increase in the percentage of a pore-forming agent, such as sodium carbonate concentration used in the fabrication of hydrogel MNs. Another factor that influences the swelling of hydrogel MNs is the degree of crosslinking between polymers; when it increased, the hydrogel network becomes more rigid, and the swelling will decrease. This property of hydrogel swelling and the degree of polymers crosslinking enable the drug incorporated in MNs to be released in a sustained manner by controlling the percentage of polymers used in their preparation.[13]

DIMENSIONS OF HYDROGEL MICRONEEDLES

Hydrogel MNs can be fabricated in various sizes depending on the material used and the type of microneedle. Microneedles dimensions can vary between 150–1500 μm needle length, 50–250 μm width, and between 1–25 μm tip diameter. The shape of the tip can be cylindrical, triangular, pointed, and pentagonal.[22] Microneedle dimensions would influence several factors. First, is the pain accompanied with application of MNs, because when the length of needles increases above 500 μm there is a greater chance to reach the dermal layer and can trigger pain receptors to cause pain that results in patient discomfort.[23] The second one is the strength of MNs; it decreased when the needle length increased and may cause needle fracture and damage during application. The third factor is the needle width; there is a higher opportunity for needle damage when the needle width is very thin.[24]

Examples of Using Hydrogel Microneedles in Drug Delivery

There are several examples of hydrogel MNs applications, including:

1. Hydrogel MNs can deliver drugs with different molecular weights. Thus, resolving the problem of transdermal drug delivery of large molecular weight drugs. For example, hydrogel MNs have been used to deliver a high dose of the antidiabetic drug (metformin) in a sustained release profile with a decrease in the GIT side effects that may occur when metformin is administered orally.[25]
2. Delivery of monoclonal antibody transdermally in a sustained release profile and improve patient compliance by eliminating the need for needle injection.[26]
3. Hydrogel MNs can be accompanied by materials that respond to light. For example, the release of a drug in response to external triggers (light) and the amount of drug released depends on the power of energy applied.[27]
4. Enhancement of the delivery of antidepressant drugs such as esketamine and thus providing a suitable alternative to parenterally administered drug.[28]
5. Hydrogel MNs have been used as a minimum invasive device to detect specific nucleic acid and biomarker present in skin interstitial fluid.[29]

ADVANTAGES OF HYDROGEL MICRONEEDLES[30-32]

1. Larger amounts of drugs can be loaded with hydrogel MNs in comparison with other microneedles types.
2. Ease of fabrication from biocompatible polymers with cost-effectiveness.
3. One-step application with self-administration.
4. Ability to deliver drugs in a sustained release manner by controlling the degree of crosslinking between polymers forming hydrogel MNs.
5. Unlike dissolving MNs, hydrogel MNs were removed intact from the skin following insertion with no polymer deposition within the skin.
6. They swell shortly after insertion and thus cannot be inserted again, consequently preventing the reuse of microneedles.
7. Due to swelling of the MNs, they maintain microconducts formed following their insertion opened for a longer period of time, permitting greater amounts for a drug to be absorbed.
8. They can be used for the extraction of interstitial skin fluid because of the swelling capacity of hydrogel polymers.

FABRICATION OF HYDROGEL MICRONEEDLES

Hydrogel MNs are frequently prepared by molding or casting method using a mold. The molds had various shapes and sizes in micrometers. Polydimethylsiloxane (PDSM) mold is commonly used because it is easy to use, inert, and repeatedly reused without damage. The polymers solution was first prepared and then mixed until a clear solution is obtained. The bubbles that may occur can be removed by centrifugation. After that, the solution was poured over the mold, which was then placed in a centrifuge or sonication bath to allow the solution of polymers to enter the mold cavities. Following this, the mold was kept under a vacuum in a desiccator for 48 hours for complete drying. The formed microneedle arrays were heated in an oven for 24 hours at 80°C to allow the crosslinking (esterification reaction) to occur between polymers to produce the final hydrogel MNs.[33]

CHARACTERIZATION OF HYDROGEL MICRONEEDLES

1. Visual Inspection and Microscopic Examination

The prepared MNs are tested visually and examined under a digital microscope to detect the proper formation of the needles and identify if any defect is present in their morphology.[34]

2. Scanning Electron Microscopy (SEM) Imaging

Scanning electron microscopy (SEM) imaging was performed to show the surface morphology and dimensions of microneedle arrays using SEM instrument.[35]

3. Evaluation of MNs Mechanical Strength

The mechanical characteristics of the microneedle arrays could be assessed to show the axial fracture force of the MNs by using a texture analyzer instrument in compression mode to show the strength of the microneedle tips. Known axial compression forces (forces applied perpendicular to the baseplate of MNs) were applied to the microneedle arrays to investigate the needle strength. A digital microscope visualized a microneedle array before and after the application of force to show the effect of force on the needle shape.[36]

4. Swelling Property of Hydrogel Microneedles

This test is performed by weighing the array at the zero time point in the dry state (m0), and after that, it is placed into a specific volume of fluid. The array is then removed at specific time points, the surface fluid was removed by wiping with a filter paper, and the mass of the swollen array was recorded (mt). The percentage swelling of the film can be determined using the following equation.[37]

$$\% \text{ swelling} = \frac{mt - m0}{m0} \times 100\%,$$

Where:

m0: is the initial weight of the MNs.

mt: is the weight of the MNs after swelling.

5. *In vitro* Release Study

This test is performed using Franz diffusion cells, and the liquid used in the receptor chamber should provide the required sink conditions for the drug release. The vehicle's temperature is maintained at 37 ± 1°C with continuous stirring at 400-600 rpm. HPLC analyzes the samples collected because it represents an accurate, quick, quantitative and versatile method for the determination of drug concentration.[38]

6. Detection of MNs Insertion

Parafilm (PF) was used as a validated skin model for MNs insertion experiments. Microneedle arrays were applied perpendicularly into an eight-sheet PF laminate (approximately 1mm in total thickness) using the texture analyzer instrument. Microneedle arrays were then carefully removed from the PF, the sheets unfolded, and the number of holes created in each layer counted using a digital microscope. Optical coherence tomography (OCT) can also be used to image the pores on PF created by MNs.[39] Another method for detecting pores created by MNs is the use of dye staining protocol, for example, the use of methylene blue or gentian violet dyes to stain the MNs pores. Furthermore, histological examination of the cross-sectioned skin samples can be applied to highlight the depth of microchannels formed by MNs insertion.[40]

7. *Ex vivo* Permeation Study

In this test, human or animals' skin is used to assess drug permeation into/across the skin. Microneedle arrays were applied to the skin, which is then fixed between Franz cells' donor and receptor chambers. A stainless-steel weight was placed over the MNs to prevent their repulsion from the skin. The temperature of the receptor fluid was kept at 37 ± 1°C, and the stirring speed was maintained at 400–600 rpm. Samples were withdrawn from the receptor fluid and replaced with the same volume of the liquid to maintained sink condition. All the samples were analyzed for drug content by HPLC.[18]

8. *In vivo* Study

In this test, laboratory animals are used to determine the permeation of a drug from the microneedle arrays. The animals are anesthetized to apply the microneedle arrays on their skin and then blood samples are collected at definite time intervals to be analyzed by HPLC.[41]

CONCLUSIONS

Owing to the several advantages offered by hydrogel MNs in enhancing transdermal delivery of drugs, there was a growing interest in their application in this field reflected by the increasing number of research articles dealing with their multiple application in drug delivery. It is thought that hydrogel MNs can overcome many drawbacks associated with other MNs types, especially regarding their ability to deliver higher amounts of drugs in a sustained release manner. However, further quality-control tests and *in vivo* investigations are required to pave the way towards their commercialization and clinical use.

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