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# CURRENT STATE AND TRANSLATIONAL DIFFICULTIES OF AN INSULIN TRANSDERMAL DELIVERY DEVICE BASED ON MICRONEEDLES

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**Abstract**
A metabolic disorder called hyperglycemia characterises diabetes mellitus. Insulin therapy is crucial for those with type 1 diabetes and severe type 2 diabetes. The most frequent delivery technique is still subcutaneous injection. Due to their advantages in reducing patient's discomfort, worry, and tension, non-invasive insulin delivery systems are being researched. The simplicity of administration and lack of hepatic first-pass metabolism make transdermal delivery techniques extremely popular. One of the most promising methods is microneedle technology, which uses painless, minimally invasive needles to inject insulin through the stratum corneum of the skin. This article will examine the development of MNs for transdermal delivery of insulin, including hollow MNs, dissolving MNs, which allow for precise control of insulin dosage.Insulin was localised using dissolving polymeric microneedle (MN) patches made of gelatin and sodium carboxymethyl cellulose (CMC). The ability of their in vitro skin implantation was tested by staining the skin after the patches were removed with tissue-marking dye. Optical coherence tomography (OCT) was utilised to track the MNs' current penetration depth, and scanning electron microscopy (SEM) was employed to analyse changes in the MNs over time. Thus demonstrates that using a gelatin/CMC MN patch for insulin delivery results in satisfactory relative bioavailability compared to a conventional hypodermic injection and can be a promising delivery method for medications containing poorly permeable proteins, such as those used to treat diabetes.
**Keywords:** Insulin loaded , Diabetes mellitus, Transdermal, Polymer,Carboxymethyl cellulose and Dissolving microneedles

## 1. Introduction

Since it was first discovered about 1500 BCE, diabetes, once known as "honey urine," has been recognised as a lethal and devastating ailment for more than 2000 years[1, 2] According to the International Diabetes Federation (IDF) Diabetes Atlas 9th Edition 2019[3], around 463 million people aged 20 to 79 throughout the world currently have diabetes, and this figure is projected to climb to 700 million by 2045. A group of metabolic diseases characterised by persistent hyperglycemia are collectively referred to as "diabetes mellitus." Diabetes pathophysiology may be impacted by poor insulin production, poor insulin action, or both. [4]

Patients who have type 1 diabetes must use insulin (insulin dependence). Patients with severe type 2 diabetes mellitus (insulin resistance) also require insulin to maintain blood glucose homeostasis. The study found that human insulin has a molecular weight of 5.8 kD and is composed of an A chain with 21 amino acids and a B chain with 30 amino acids.[5]

Subcutaneous (SC) injection using a syringe, insulin pen, or insulin pump is still the most common

way to give insulin treatment because it is less expensive, more effective at delivering insulin, and has a greater bioavailability.[6, 7] Patients still require to inject 2-4 times day even if long-acting insulin (up to 24 h) has been developed. Numerous injections might result in pain and discomfort as well as edoema, illness, and local tissue necrosis at the injection sites.[8, 9]

Furthermore, real-time adjustments to the injection dosages are required to induce fast hypoglycemia after a meal and moderate but sustained blood glucose reduction before bed. Due to the difficulties in precisely giving the necessary dosage, hyperglycemia and hypoglycemia are frequent. Furthermore, due to its low stability as a biological peptide, insulin must be stored between 2 and 8 °C for distribution and shelf life, which makes transporting and storing it in some underdeveloped nations more challenging.[10]

Despite having comparable limitations, the IM version is frequently utilised for bolus and quick computations. Today's improvements in insulin medication concentrate on creating insulin formulations that are more reliable, practical, pleasant, long-acting, and glucose-monitoring. In 1998, the first microneedles (MNs) were created as a trimmer way of pharmaceutical administration.[11] In healthcare settings, intravenous (IV), intramuscular (IM), subcutaneous, or transdermal (topical) usage are the only authorised methods for providing parenteral medicine. The best bioavailability and dosage control are provided by the IV approach, which has the disadvantages of discomfort, contamination, and complication in maintaining venous access for the administration of opioids, antipsychotics, and peptide vaccines.

The subcutaneous method is preferable for administering medications like insulin or certain immunotherapy treatments, but it has several disadvantages, including discomfort, irregular pharmcokinetics, and low absorption. Alternative delivery methods, such nasal or aerosolized distribution, usually raise concerns about dose repeatability and regional effects.

The availability of a fairly limited number of medications, many of which are utilised in dermatology, limits the use of topical methods. The pharmacologic agent's capacity to diffuse through the stratum corneum, the top layer of skin, largely limits this route.[12] It is recognised that physical and chemical characteristics of a molecule, such as its molecular weight, ionisation, carrier nature, and dilution ratio, can impact how well it can permeate the skin.[13] Other characteristics like hydrophilicity and lipid solubility might also be influential. Microneedles can pierce the stratum corneum at the top of the epidermis, but they cannot penetrate the dermis deep enough to activate the nociceptive nerve terminals.[14] Additionally, they have shorter, narrower geometries that make it easier to avoid discomfort.[15]

MNs can also control how chemicals are delivered to the dermis, which has a lot of lymphatic and vascular perfusion. For systemic applications, the various pharmacokinetic and pharmacodynamic characteristics of this layer are also being studied.[16]

Drug delivery most frequently makes use of various MNs systems. Solid MNs have the potential to pierce skin and open pores. In order to aid in dispersion following removal, the region is subsequently coated with a transdermal patch or gel formulation. Skin that has previously been covered with the material can likewise be treated with MNs.[17] Drug-filled biodegradable MNs are usually designed to break under the skin and deliver controlled drug release.[18] Drugs are delivered

through hollow MNs in a way comparable to injection, but with the aid of physical forces such as diffusion and pressure.[19] Numerous materials, including silicon, metal, biodegradable or non-biodegradable polymers, glass, and others, have been used to create microneedles.[20]
Their small size limits both the total dose that can be administered to them and the amount of time it takes for that dose to be absorbed by the dermis.[18] As a result, drug compositions must be carefully altered. According to past research, the two-step manufacturing process for MN patches offers a number of advantages.[21,22] We created and used diabetic mouse and human cadaveric skin models to assess the capability of a patch constructed of two-layer dissolving MN patches made of gelatin and sodium carboxymethyl cellulose (CMC) for medicine administration.[23]
Fewer research have looked at the effects on human cadaveric skin, despite the fact that several studies have proposed novel techniques for making MN patches and evaluated their effects using animal models. Fewer research have looked at the effects on human cadaveric skin, despite the fact that several studies have proposed novel techniques for making MN patches and evaluated their effects using animal models. This work achieved many notable goals, including the publication of preliminary data on MN usage on human skin, the application of conventional techniques to evaluate MN effects, and the suggestion of an acceptable anatomic area of human skin for future clinical MN patch application. MNs' main goal is to develop clinical applications.

## 2. Materials and Methods

### 2.1 Substances

Commercial MN patches were obtained from 3MTM (3M, St. Paul, MN, USA), and polydimethulsiloxane negative moulds were produced (PDMS; Sylgard 184, Dow Corning, Belgium). The following chemicals were bought from Sigma-Aldrich: gelatin (porcine skin, type A, 90-110 Bloom), CMC (MW 90 kDa), rhodamine 6G (R6G; MW 470.01 Da), fluorescein 5(6)-isothiocyanate (FITC; MW 389.38 Da), and insulin (from bovine pancreas, 25 U/mg; MW about 5.73 kDa) (St. Louis, MO, USA).

### 2.2 Making Dissolving Gelatin/CMC MN Patches,

The master templates for the 3MTM MN patches were utilised to produce the negative mouldings that were used to fabricate the MN patches.[22] In a nutshell, a modified two-step procedure was utilised, in which a 10% gelatin solution was loaded with a medication and placed into each PDMS mould. The mould cavities were then filled by centrifuging the mixture at 4000 rpm for 30 minutes. After removing any remaining solutions from the mould surface, 10% CMC solution devoid of drugs was added on top of 10% gelatin, and the mixture was centrifuged for 10 minutes at 4000 rpm. The two-layered gelatin/CMC MN patch moulds were all dried the next day at room temperature.[24,25]

### 2.3 Manufacturing of MN Patches Containing Drugs

In this work, R6G, a water-soluble red fluorescent dye, served as a low-molecular-weight model medication. A stock solution of 0.5 mg/mL of the dye was prepared by dissolving oit in deionized water. A 50 mL stock solution was added to each polymer solution. To create insulin-containing gelatin solutions, insulin-FITC that had been dissolved in 0.1 M HCl was added to the gelatin

solutions and mixed in a consistent ratio. The shapes of the drug-laden MNs were examined using an inverted fluorescent microscope, which also served to verify that the medications had been correctly loaded into the needle points of the MN patches.

2.4 Mouse Skin Ex Vivo Penetration Tests

Patches of MN were applied to mouse cadaveric skins using a homemade applicator and 9 N of force (about equivalent to that applied by the thumb) for 10 minutes in order to assess the insertion capabilities of the suggested gelatin/CMC MNs. After that, they were taken out, and scanning electron microscopy was used to track the MNs in the patches as they underwent morphological changes over time (SEM; S-3000N, Hitachi, Tokyo, Japan).

2.5 Transdermal Delivery Imaging and Optical Coherence Tomography

Prior to the patches being removed, the depth of MN penetration into the mouse skins was evaluated in real-time using optical coherence tomography (OCT; Chang Gung University, Taiwan) (during the 10-min application time). In order to see the transdermal delivery under 9 N of force over 60 minutes, patches filled with R6G were also put on mouse skins. Confocal microscopy was used to measure the vertical depth of the skin from the surface to the dermis.

2.6 Insulin-Loaded MNs for In Vivo Transdermal Delivery

The epidermal penetration of insulin in live animals was seen using the in vivo imaging system (IVIS; Xenogen 200, Caliper Life Sciences, Alameda, CA, USA) as a non-invasive analytical instrument. Anesthetized diabetic mice were photographed 10 min, 1 h, and 3 h after receiving MN patches loaded with FITC-insulin or not (control). All fluorescence data from this investigation were analysed using the IVIS and shown as photon flux (photons sec1cm2 steradian1).[26]

2.7 Transdermal Insulin Delivery via MN Patches

We carried out the tests in accordance with the rules set out by the Chang Gung Memorial Hospital Laboratory Animal Center, and the Institutional Animal Care and Use Committee of Chang Gung Memorial Hospital approved the methods utilised in the animal investigations. The investigation was conducted using male C57BL/6 db/db mice that were eight weeks old. At the start of the trial, the average blood sugar level in each mouse was over 600 mg/dL. All diabetic mice (n = 6) were randomly assigned to one of three groups: the SC group, which received insulin injections (0.2 IU) subcutaneously into the abdominal skin using a hypodermic needle; the unloaded MN group; and the insulin-loaded MN group, which received insulin via unloaded MNs (0.2 IU per patch) applied to their backs and stabilised with tape. Following treatment, blood samples were taken at 0, 1, 2, 3, 4, and 6 hours. Based on the starting point, the percentage change in plasma glucose levels at each time point was computed.

2.8 Human Cadaveric Skin OCT Measurement and Tissue-Marking Dye Staining

Human cadaveric skin was collected from patients' various anatomical sites. An informed consent was signed by each patient. The Chang Gung Medical Foundation's Institutional Review Board has explicitly authorised this study (IRB Nos. 103-3234B and 104-0046C). After the skin was

harvested, the subcutaneous fat was removed, and the whole thickness of the skin was preserved at 20 °C until use. To show repeatability, several samples (including those from donors' dorsal ears, volar forearms, medial thighs, and lower abdomens) were utilised. Before usage, each skin was dabbed with clean tissue paper to remove extra moisture after being frozen to room temperature.

Using a handmade applicator, 9 N of force was applied for 10 minutes to human cadaveric skin to test the gelatin/CMC MN patches' ability to penetrate the skin. The insertion sites were visible after the patch was removed because the skin surface was exposed to a blue tissue-marking dye for 1 minute.[19] After that, the blue spots were examined with a stereomicroscope (P6000, Nikon, Tokyo, Japan), and pictures were taken. OCT measurements were also utilised to determine the penetration depth of the gelatin/CMC MN patches in human cadaveric skins when applied for 10 minutes with a 9 N force without peeled off.

### 3. MNs are used to administer insulin transdermally

Patients can self-administer, and MNs can increase patient compliance. It has enormous potential to replace conventional insulin therapy. Hydrogel and dissolving MNs can both be directly loaded with insulin for administration; this can considerably enhance the quantity of insulin delivered transdermally. Hollow MNs are an indirect auxiliary administration. Additionally, glucose-responsive MNs can practically deliver accurate insulin dose that is tailored to the person's blood sugar in real time.

### 3.1 Hollow MNs

In order to constantly inject the liquid formulation into the skin through the needle cavity (often at a rate of 10-100 L/min), hollow MNs are made up of an empty cavity needle (5-70 m wide) and an external auxiliary device, such as a syringe, pump, gas, or electrical support.[27,28] Hollow MNs share a fundamental construction with standard subcutaneous injection needles. When compared to other MN kinds, hollow MNs have a larger delivery capacity because their dose quantity and flow rate may be adjusted by an external auxiliary device, whereas coated or dissolving MNs can only be dosed according to the size of the needle and the number of needles.[29,30]

Hollow MNs may be created using a broad range of materials, including silicon, metal, glass, ceramic, and polymers (Fig. 1).[31,32] In recent years, interest has grown in polymers with good biocompatibility, including SU8 polymer, clay reinforced polyimide, and metal electroplated polymer.[33,34] Microelectromechanical systems (MEMS), such as lithographic moulding, X-ray photolithography, etching, and laser ablation/cutting, can be used to create hollow MNs.[32,35] To create a hollow MN array, Wang et al. used a polymer-based approach in conjunction with UV photolithography.

The entire procedure was broken down into two steps: First, a polydimethylsiloxane (PDMS) mould with a pyramidal top was created using the photolithography technique. Next, hollow MNs were created using the SU-8 polymer on the integrated PDMS mould.[36] The hollow stainless steel

MN array may be created utilising an unique fabrication technique of femto second laser micromachining, disclosed by Vinayakumar et al.[37] It is simple to manage and produce various MN forms in a single exposure device utilising laser micromachining technology, avoiding multilayer masking and patterning, exposure, and chemical etching.[3]

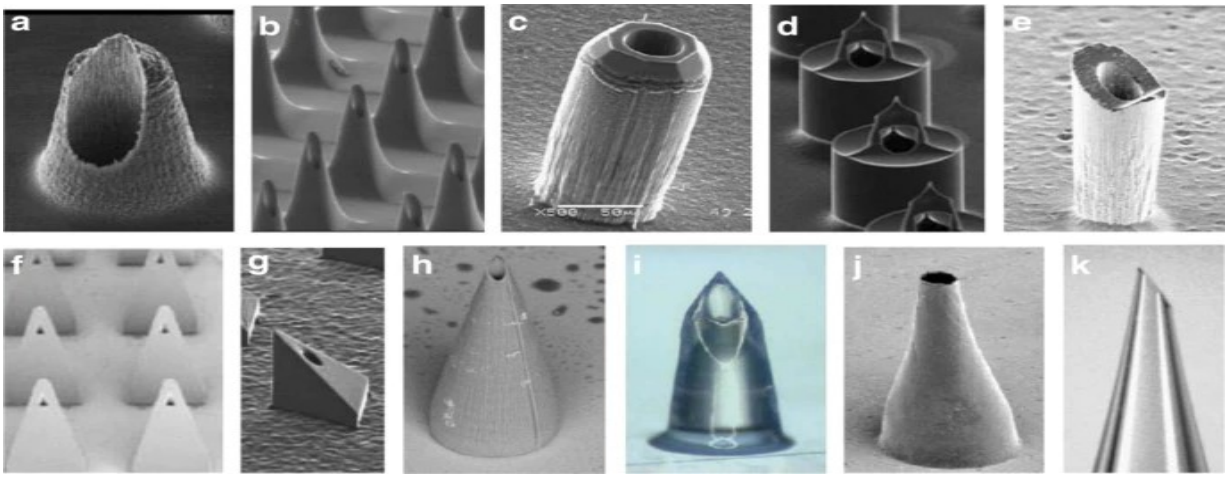


**Fig 1 Hollow MNs fabricated with silicon and polymers. Reprinted with permission from[32]**

Richa et alcreated a brand-new kind of insulin delivery system that consists of a hollow MN array, drug reservoir, and an IPMC membrane-actuated micropump.[38] Two components made up this apparatus. The reservoir with entrance to the hollow MN array was the initial component. It was made from SU-8 polymer by direct laser writing. The micropump actuator assembly made up of a Nafion membrane sandwiched between two copper electrode rings coupled to an external electrical source made up the second component.[38] The reservoir was topped with the micropump. Insulin was poured into the reservoir and then forced out through the MNs when the Nafion membrane was electrically actuated to deflect and press the liquid in the reservoir.

The main part of this device was the micropump actuation assembly. The frequency and voltage response of the membrane have been characterised in this research using a Laser Doppler Vibrometer (LDV) in great detail. The traditional membrane was restrained either circularly or squarely in a micropump. Nafion membrane with eight cuts around the circumference was changed to enhance deflections. This novel MN device produced an insulin flow rate of 44.8 L/min, which is significantly greater than the standard membrane design. The administration of insulin might be made painless by adjusting the insulin flow rate between 20 and 45 L/min by varying frequency (0.1 to 0.5 Hz) and voltage (3-6 V).[38]

The manufacturing of hollow MNs requires a complex procedure that is often difficult, time-consuming, and costly.[39] Due to its versatility, precision, and greater repeatability at the microscale, three-dimensional (3D) printing has gained more and more attention in Minnesota's manufacturing during the last five years.[40] Stereolithography (SLA), fused deposition modelling (FDM), liquid crystal displays (LCD), selective laser sintering (SLS), and digital light processing (DLP) are only a few of the 3D printing technologies now under development.[41–43] In order to

create a novel device (3DMNMEMS) for regulated insulin administration, Economidou et al. combined 3D printing technology with MN and MEMS (Fig. 2).[44] With the use of laser SLA and photopolymerization-based technologies, they initially manufactured hollow MN patches.

An MEMS-like diaphragmatic micropump was then linked to the hollow MN patch. A single dose of 0.5 IU insulin was completely identified in the receptor in 1 hour, according to an in vitro release assay. The in vivo investigation using diabetic animal models showed that the release profile of the insulin administered by 3DMNMEMS was identical to that of the SC injection. The 3DMNMEMS group showed a more moderate decrease in plasma insulin concentration at 6 hours after treatment (16.1 IU/mL) compared with SC injection (9 IU/mL at 6 hours after treatment), indicating a more sustained insulin action.[44] The relative pharmacological availability (RPA) of 3DMNMEMS was 105.14% compared with SC injection.

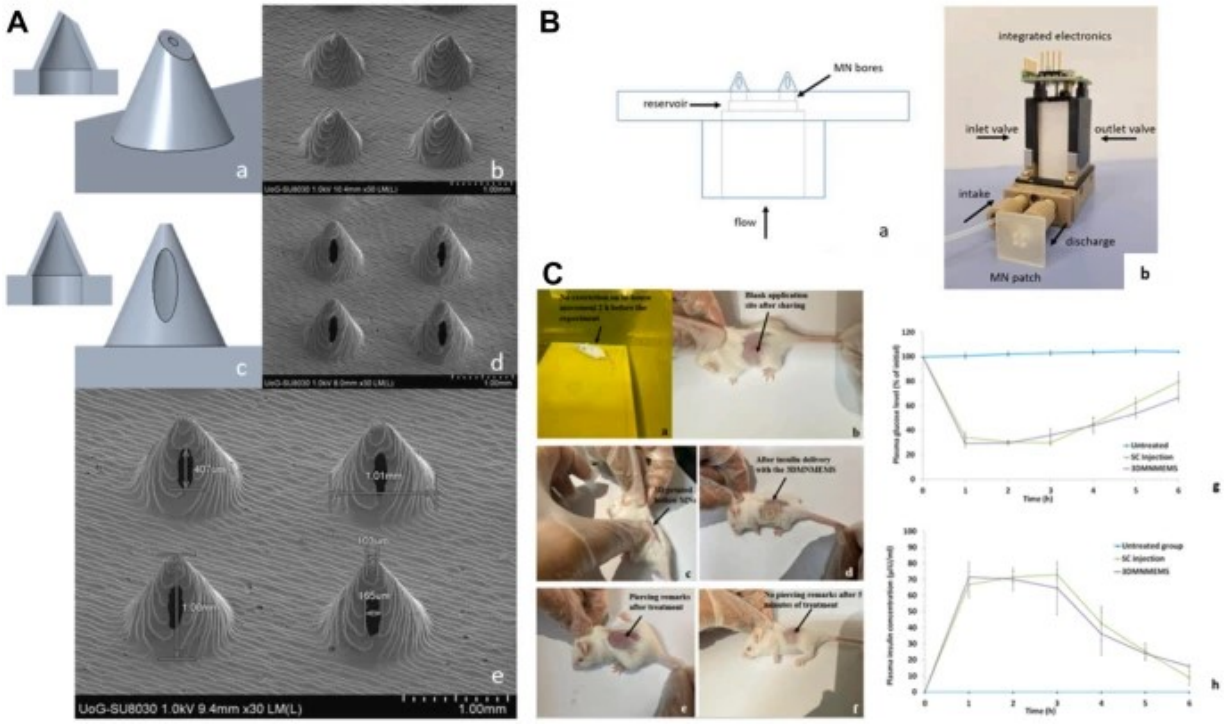


**Fig. 2 3D printed hollow MN microelectromechanical system (3DMNMEMS). A Hollow MN fabricated by 3D printing. B 3DMNMEMS configuration. C Hypoglycemic effect of 3DMNMEMS in diabetic mouse. Reproduced with permission from[44]**

A number of hollow MN devices, including the MicronJet® (Nanopass Technologies), MicronJet600® (Nanopass Technologies), and the Microstructured Transdermal System® (3 MTM), are now on the market and some are being tested in clinical settings. Without further formulation research, hollow MNs can administer injectable formulations that have already been developed. As a result, to administer biological medications like insulin and vaccines, the majority of clinical studies nowadays use hollow MN devices that are readily accessible on the market.[28] An efficient substitute for conventional insulin injections is intradermal infusion of insulin using

hollow MNs. It is pain-resistant and dramatically reduces local and regional skin irritability.Numerous academic investigations and clinical trials have shown that intradermal insulin infusion has better PK/PD characteristics, a quicker time to achieve the maximum blood concentration (Cmax), a quicker start of action, and a higher bioavailability than conventional subcutaneous insulin injection.[45]

There are still certain areas where hollow MNs can grow. Due to the dermal tissue's density, when hollow MNs are put into the skin, the bore in the needle tip can quickly get blocked, which can impact drug delivery.[46] The design of the hollow MNs' tips is crucial since bigger tip apertures need more insertion effort, which might break the needle, but smaller tip openings are simpler to stop.[47] Additionally, the squeezed skin tissue may increase liquid flow resistance.[46,48] This may be avoided by using the MN tip's side-open hole design.[49,50]

The earliest silicon MNs created by Griss et al. were hollow out-of-wafer-plane devices with orifices in the shaft rather than the tip.[51] This hollow MN array demonstrated low liquid flow resistance, a sizable contact area between fluid and skin tissue, and reduced clogging potential. Hollow MNs are also prone to breaking due to the empty void and the fragile materials employed. The breaking force and insertion force of hollow MNs should be increased in order to achieve safe skin implantation. To prevent needle breakage, geometry is crucial in determining the insertion force. First, Davis et al. empirically evaluated and theoretically studied the breaking force and insertion force of MNs into the skin.[52]

Additionally, although less painful than the subcutaneous approach, insulin administration through hollow MNs is nonetheless uncomfortable. If MNs are intended to function on the dermis and have no access to blood arteries or nerve fibres, then theoretically they should be painless.[53,54] Micro-syringes and hollow MNs both use similar delivery systems. The administration discomfort for hollow MNs can be influenced by the infusion volume and liquid formulation flow rate in addition to needle shape.[55,56,57] Gupta et al. discovered that higher pressure applied and MN retraction both enhanced discomfort, however that lower flow rate and concurrent hyaluronidase treatment would lessen pain.[58]

### 3.2 Dissolving MNs

Due to their evident benefits, including as easy preparation, high drug loading, and one-step administration, dissolving MNs have recently drawn increasing amounts of interest. They are also often utilised to administer insulin in literature study. Insulin is incorporated into a water-soluble or biodegradable polymer matrix using dissolving MNs, and insulin is released when the inserted MNs dissolve or degrade. The versatility of drug loading is one advantage of dissolving MNs. Depending on the MN array, only certain needle layers or the needle tip can contain drugs.[59] Additionally, by modifying drug loading, drug distribution, and the polymer matrix's dissolving profile, quantitative and controlled drug release may be obtained.[60,61] Additionally, preserving the action of insulin to some extent is made possible by the solid-state storage of dissolving MNs. The need for rigorous cold chain storage during transit is decreased by the fact that insulin encapsulated

in MNs made with dextrin may be kept at 40 °C for 1 month without significantly impairing insulin action.[62]

The majority of water-dissolvable polysaccharides are utilised to create dissolving MNs , such as hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), hyaluronic acid (HA), dextran, sodium alginate, amylopectin, and sodium chondroitin sulphate.[63-65] Additionally, gelatin, poly—glutamic acid (-PGA), polyvinyl pyrrolidone (PVP), poly(vinylpyrrolidone-co-methacrylic acid) (PVP-MAA), polyvinyl pyrrolidone-cyclodextrin (PVP-CD), and polyvinyl pyrrolidone-polyvinyl alcohol (PVP-PVA) are some polymers having biodegrable.[66-68]

Different micro-molding techniques, including casting, hot embossing, and injection moulding, can be used to create dissolving MNs. In the micro-molding process, a laser, an ion, or a template flip is used to first build an MN array mould with a tapered MN structure. The mould is subsequently filled with the polymer solution. The most common methods used to fill polymer into mould tips are centrifugation or vacuum. The MN array is obtained (Fig. 3), which is followed by curing and de-molding.[69] Although this approach can increase manufacturing scale, it still has significant drawbacks. This manufacturing procedure entails a number of labor-intensive phases, including the creation of moulds, the preparation of the master batch, and the plasticization of thermoplastic polymers. Additionally, as polymer must be plasticized beyond its glass transition temperature , this approach may not be appropriate for insulin, which is heat-sensitive.[70] Researchers have thoroughly investigated water-soluble polymers, such as HA[71] , -PGA, mixtures of starch and gelatin[72] , and mixtures of fish gelatin and sucrose[73], in the fabrication of heat-sensitive drugs loaded dissolving MNs in order to avoid the high temperature required for polymer dissolution in the micro-molding method.

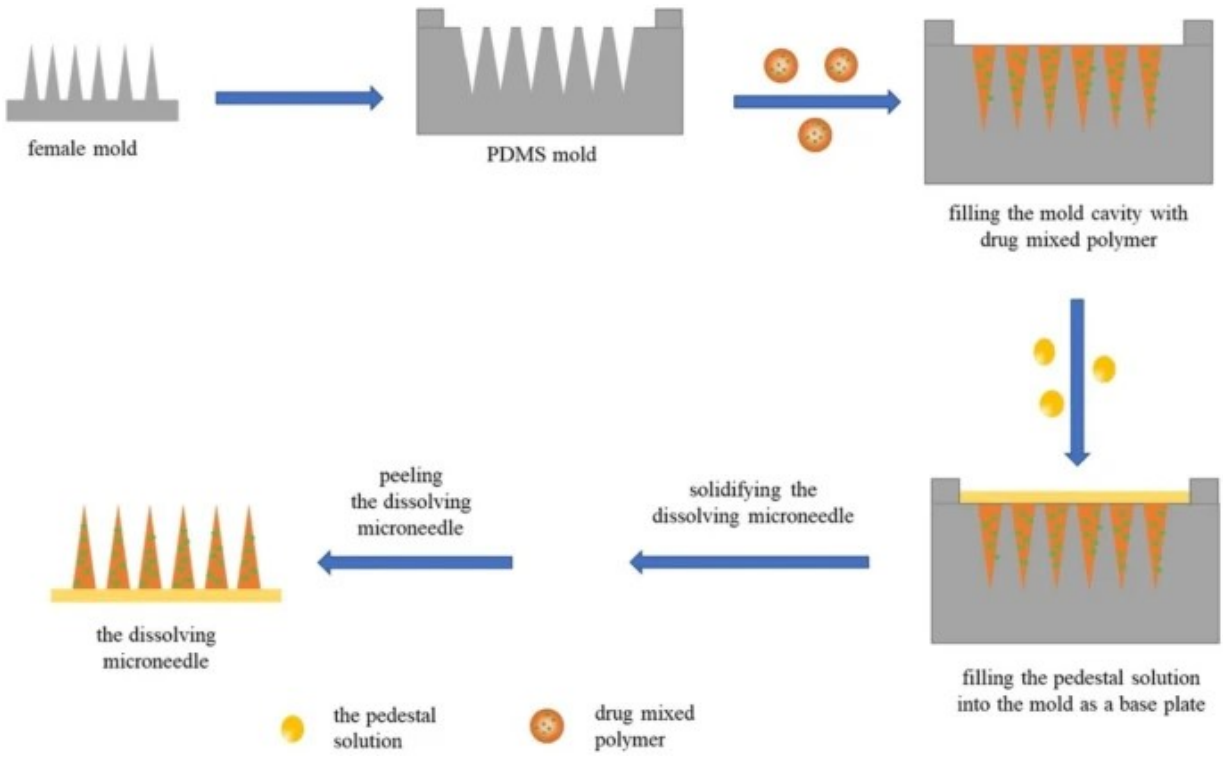


**Fig. 3 Steps of micro-molding method. Reprinted with permission from[69].**

To overcome the temperature difficulties of the melting process in micro-molding techniques, certain novel manufacturing techniques have been developed. Dissolving MNs have been produced using N-vinylpyrrolidone, the PVP monomer that can be polymerized at room temperature by UV irradiation. By employing this technique, organic solvents can be avoided. While polymerization will need more than 30 minutes of UV exposure, this may result in drug deterioration. To reduce the length of UV exposure, Kathuria et al. combined thermal and photopolymerization.[74] As a model component, hyaluronic acid (HA, 15 kD) was selected. Pre-polymerization of N-vinylpyrrolidone solution involved heating it for two minutes at 90 °C before allowing it to cool to room temperature.

The N-vinylpyrrolidone solution was then mixed with HA, pipetted onto the PDMS mould, and exposed to UV light for 8 minutes. Pre-polymerization shortened UV exposure duration and slowed HA breakdown.[74] This procedure reduced the amount of time needed for preparation and helped increase production. When using the micro-molding technique, the polymer solution is filled into the needle by centrifugation or vacuuming, which results in subpar MN tip production and impossibility to remove MNs from the mould.[75] McGrath et al [employed atomized spraying as opposed to centrifugation or vacuuming using a two-fluid external mixing nozzle to fill the solution of MNs materials into PDMS mould.[76] The filled moulds could be dried at room temperature after spraying. They created dissolving MNs using this spray technique using a variety of sugars, such as trehalose, fructose, and raffinose, as well as polymeric ingredients, such as PVA, PVP, CMC, HPMC, and sodium alginate. This enhanced micro-molding technique is

advantageous for medications that are sensitive to high temperature or viscosity since it enables continuous manufacture under benign processing conditions.

Currently, researchers are looking into more safe ways to create dissolving MNs. A brand-new droplet-born air blowing (DAB) technique was shown by Kim et al. to create dissolving MNs.[77] The basic structure of MNs was first created using this technique (Fig. 4), which involved dispensing drug-free biopolymer droplets (CMC, 90 kDa) to a flat surface before pouring droplets carrying pharmaceuticals over the base structure. The upper plate was then rotated upward after moving downward to meet the drug droplets and elongate them to create the tip of MNs. To remove the water and solidify the MNs, air blowing was used.

With a temperature range of 4 to 25 °C, DAB offers a quick and gentle way for fabricating MN that can be finished in just ten minutes. The diabetes mouse with its head shaved received the 6 9 MN array carrying 0.07 IU of insulin. After 60 minutes, there was a significant drop in blood glucose levels, which rebounded after 120 minutes. Comparing insulin-loaded MNs to subcutaneous injection, similar results were obtained in terms of bioavailability (96.6 2.4%), and hypoglycemia profile. In order to encapsulate lysozyme, which was temperature-sensitive, Shayan et al. also created dissolving MNs using the DAB technique.[78] The stabiliser, trehalose, was introduced. The findings demonstrated that after MNs were created, lysozyme activity was kept at a high level of 99.8% 3.8%.This demonstrated that the lysozyme activity was not significantly affected by air blow drying. Additionally, the lysozyme activity was kept constant after 12 weeks of storage at 99.8 3.8% at 4 °C and 96.6 3.0% at 25 °C. These experiments show that encasing heat-sensitive biomolecules in MNs using DAB may be a promising technique.

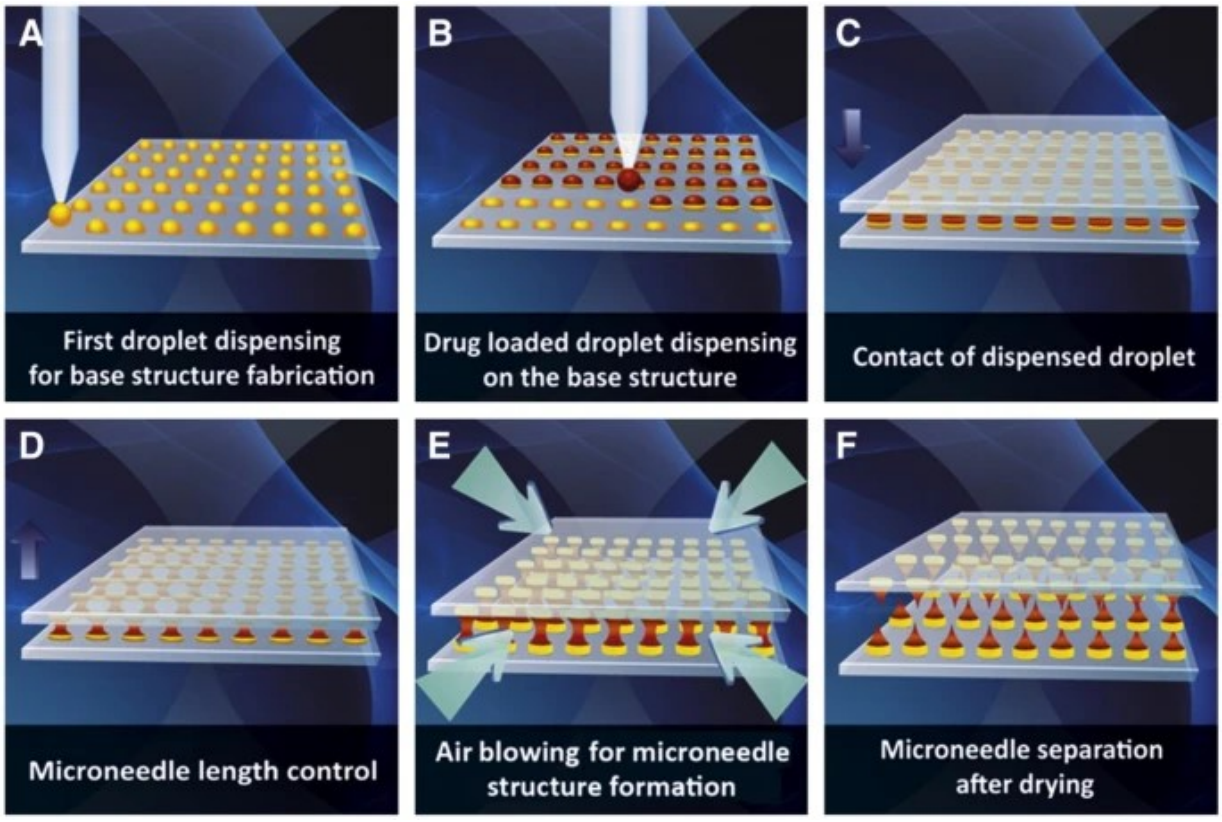


**Fig. 4 Schematic illustration of droplet-born air blowing (DAB) method. Reprinted with permission from**[77].

Mechanical strength is one of the most crucial factors in dissolving MNs since it is necessary for proper skin implantation. When compared to insoluble materials like silicon and metals, MNs constructed of water-soluble polymers typically have lower mechanical strength.[79,80] After drug encapsulation, MNs' mechanical strength may become further lessened.[81,82] The fracture strength of polymer MNs was experimentally examined during skin insertion by Park et al. They discovered that the fracture strength of MNs rose with increasing material elastic modulus and needle base diameter, but decreased with increasing MNs length.[83] When the material's elastic modulus was less than 1 GPa for the MNs they were studying, the MNs would buckle before puncturing the skin. These findings offer exceptional guidance for choosing MNs materials, particularly for choosing polymer materials. The hardness and toughness of MNs made from a single material are often not as good as those made from numerous materials with various physical characteristics. To increase the mechanical strength, Yu et al. created HA and 3-aminophenylboronic acid-modified alginate insulin-dispersing MNs. Insulin that was encapsulated might be released in the deep skin, according to an in vitro penetration test. RPA and relative bioavailability (RBA) were both shown in in vivo investigations to be above 90%.[84] Before, it had been demonstrated that CaCO3 enclosed in a polymer matrix improved mechanical strength.[85] Liu et al. produced a dissolving MNs patch with PVP after encapsulating insulin in CaCO3 microparticles.[86] Due to its pH-sensitive design, the MN patch demonstrated great mechanical strength and delayed insulin release.

The needle body may not fully penetrate the skin due to skin flexibility, wasting the medication. To address this problem, Chen et al. created an MN array with a PVA/PVP supporting structure to increase mechanical strength and counteract the effects of skin deformation during the MN insertion process.[67] The poly-glutamic acid needle tip of the MN array was loaded with insulin. The supporting structure and needle tip of the MN array could disintegrate in 4 minutes after being inserted into the skin, and the needle tip then quickly released insulin.In diabetic rats, there was no noticeable difference in the insulin profile between the first and second dose, demonstrating the great degree of repeatability and accuracy in the insulin delivery provided by the MN patch. On diabetic rats, the dissolving MN patch had a hypoglycemic effect similar to subcutaneous injection.

For diabetics, dissolving MNs can provide a long-lasting and constant glucose level, which is desirable for long-acting insulin. But several difficulties still need to be taken into account. The first is the issue with safety. Polymer deposition in the skin following a single dosage might not be a concern. However, it is not negligible for medications like insulin that must be used over an extended period of time. Theoretically, prolonged exposure to MNs that dissolve might lead to polymer deposition and buildup in skin tissue, which would then cause an immunological response and accumulate in the liver or potentially the entire body.[30] Potential consequences of polymer deposition in the skin are not currently well understoodAdditionally, the study period was brief, and the current safety assessment is primarily based on animal testing. In the McCrudden et al. investigation, a dissolving MN route with an area of 0.49 cm2 was created to distribute sodium ibuprofen.[87] Per 1 cm2 MN patch size, 5–10 mg of polymer were deposited in rat skin. A patch measuring 10 cm2 would be required when the effective dose in rats was translated to humans, which indicated that 50–100 mg of polymer would deposit in the skin. There were no issues raised during the author's studies of the polymers' biocompatibility in cells and MNs tolerance in rats.The long-term safety of these two investigations was unknown because they only lasted 24 hours in cells and one administration in rats. Vicente-Perez et al. investigated the efficacy of hydrogel and dissolving MNs for repeated applications.[88] Hydrogel MNs made of Polyethylene glycol (PEG, Mw = 10,000 Da) were applied twice daily for three weeks and dissolving MNs made of methyl-vinyl ether-co-maleic acid (PMVE/MA, Mw = 1,500,000 Da and PVP, Mw = 58,000 Da) were applied once daily for five weeks. Studies conducted in vivo on hairless mice revealed no observable changes in the appearance and barrier function of skin over the duration of the experiment.In addition, there were no statistically significant changes in the levels of the biomarkers C-reactive protein, immunoglobulin G, interleukin-1, and tumour necrosis factor.[88] Regulatory authorities may require further information about the amount of polymer left in the skin, the rate and pathway of clearance, and the long-term safety when examining the translation of this type of MNs into the clinic.

*4. Conclusion*

When compared to standard SC insulin injection, MN technology offers significant advantages in terms of pain reduction from repeated injections and ease of administration, which can help diabetes patients who are afraid of needles live better lives.[89] A simple two-layer method is used

to create a gelatin/CMC MN patch, which is a perfect substitute for regular insulin injection. It offers a simple, handy solution that is effective in regulating blood sugar in diabetic mice. After being released from MNs, insulin still has pharmacological action and significantly lowers blood sugar levels in diabetic mice. These combined findings imply that dissolving gelatin/CMC MNs are potentially effective transdermal delivery systems for a variety of biomolecules.[90]

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