

Xenon Difluoride Dry Etching for the Microfabrication of Solid Microneedles as a Potential Strategy in Transdermal Drug Delivery

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Although hypodermic needles are a “gold standard” for transdermal drug delivery (TDD), microneedle (MN)-mediated TDD denotes an unconventional approach in which drug compounds are delivered via micron-size needles. Herein, an isotropic XeF₂ dry etching process is explored to fabricate silicon-based solid MNs. A photolithographic process, including mask writing, UV exposure, and dry etching with XeF₂ is employed, and the MN fabrication is successfully customized by modifying the CAD designs, photolithographic process, and etching conditions. This study enables fabrication of a very dense MNs (up to 1452 MNs cm⁻²) with height varying between 80 and 300 μm. Geometrical features are also assessed using scanning electron microscopy (SEM) and 3D laser scanning microscope. Roughness of the MNs are improved from 0.71 to 0.35 μm after titanium and chromium coating. Mechanical failure test is conducted using dynamic mechanical analyzer to determine displacement and stress/strain values. The coated MNs are subjected to less displacement (≈15 μm) upon the applied force. COMSOL Multiphysics analysis indicates that MNs are safe to use in real-life applications with no fracture. This technique also enables the production of MNs with distinct shape and dimensions. The optimized process provides a wide range of solid MN types to be utilized for epidermis targeting.

1. Introduction

The skin—the largest organ of the body, plays a prominent role in the permeation and penetration of the drugs. This remarkable organ comprises two distinguishable layers: (i) epidermis as the outermost layer and (ii) dermis as the innermost layer.^[1] Although the structure of skin diverges considerably throughout the body's different regions, previous histometric measurements revealed that the thicknesses of epidermis and

dermis layers range from ≈75 to 275 μm, and 2100 to 5900 μm, respectively.^[2] On the other hand, skin thickness is an essential parameter to achieve transdermal drug delivery (TDD)—a decisive approach where a drug compound diffuses through the skin layers and joins circulation to achieve a therapeutic outcome.

Moreover, TDD is one of the preferred methods in drug studies, especially for the delivery of drugs that are unstable in gastrointestinal system and susceptible to the first-pass effect—a phenomenon whereby the bioavailability of an orally-administered drug is drastically reduced before reaching the bloodstream.^[3] A diverse range of active^[4] and passive^[5] TDD systems has been designed and emerged as attractive administration strategies. Active TDD approach mainly involves the use of hypodermic needles.^[6] Although the injection by hypodermic needles has been “gold standard” for TDD, microneedle (MN)-based TDD is a novel technology in which drug compounds are delivered to the bloodstream via micron-

size needles. The delivery of drugs is usually limited by the barrier effect of the top layer of the skin—stratum corneum. A drug molecule's diffusion coefficient (D) is hundreds of times smaller than the D of drugs diffusing through other layers.^[7] MNs have been, on the other hand, demonstrated to enhance drug permeability drastically by several orders of magnitude through piercing the stratum corneum.^[8] They are widely preferred due to the fact that large molecules would be administered easily without inducing pain to the patient, while offering faster healing at the injection site than hypodermic needles.^[9] This type of platform is considered one of the most popular TDD methods, and in addition, it is currently an active area of the most recent research as they have been revolutionizing the concept of TDD.

MNs are mainly divided into four sub-categories in which each MN type possesses a different role in TDD. Solid MNs are employed to pre-treat the skin surface, whereas hollow MNs contain a reservoir to introduce a drug solution through the hollow structure, usually by a pumping system. Coated MNs have their tips covered with specific biomolecules to capture biomarkers through the skin. Last, dissolving MNs are made of water-soluble materials and penetrate through pre-treated skin

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to release the drug upon dissolution.^[10,11] Among all these four categories, solid MNs are the most standard form of MNs.^[12] TDD systems using solid MNs consist of a two-step process based on the “poke-and-patch” approach.^[13] In the first step, MN microarrays are applied onto the skin to create micropores on the surface, followed by applying a transdermal drug patch containing the drug formulation. The permeation of the drug from a patch occurs by passive diffusion through the resultant pores. Therefore, semi-solid forms of drugs (e.g., gel, cream, or lotion) can be topically introduced and delivered through solid MNs.

Pondering skin types, geometrical, and mechanical configurations of MNs need to be determined. For example, while the epidermis layer in foot dorsum in women is considered the thickest ($267.4 \pm 120.6 \mu\text{m}$), whereas the skin on a woman's breasts contains the thinnest epidermis ($76.9 \pm 26.2 \mu\text{m}$). On the other hand, the thickest dermis is measured as $5888 \pm 2422.3 \mu\text{m}$ on the breast in men, and the thinnest dermis is characterized as $2115 \pm 946.4 \mu\text{m}$ in the dorsum of hand in women.^[2] Therefore, different layers of skin have a variety of thicknesses ranging from ≈ 75 to $\approx 5800 \mu\text{m}$ (including dermis and epidermis). Hence, the height of the MNs should be carefully designed and fabricated according to the thickness of the target skin layer. More detailing, main drawbacks in unlocking clinical implementation of MNs rely on the availability of low-cost and rapid manufacturing methods.^[14] As a general strategy, MNs can be fabricated using metals (e.g., stainless steel and titanium),^[15] metalloids (e.g., silicon),^[16] biodegradable polymers (polylactic acid and polyglycolic acid),^[17] and non-biodegradable polymers (e.g., polyvinyl acetate or polyetherimide).^[18] Additive manufacturing techniques such as 3D printing and two-photon polymerization processes are transformative methods in solid MN fabrication. Other manufacturing techniques include micromilling, thermal nanoimprinting, injection molding, hot embossing, and laser engraving.^[19] However, as the mainstay technique, solid MNs are fabricated using microelectromechanical systems (MEMS) fabrication methods involving deposition, patterning, and etching (dry or wet). Basically, a deposition process involves coating a silicon surface with photoresists whose thickness ranges between a few nanometers to micrometers. Patterning step involves transferring a well-designed pattern onto the deposited film. Last, the etching process (dry or wet etching) is employed to create the desired design by etching the silicon surface. As wet etching requires large amounts of hazardous wet chemicals and offers less control over the etching rate, dry etching (either isotropic or anisotropic) is the preferred method. Anisotropic etching removes material in specific directions, enabling the formation of deep cavities and flat surfaces. In contrast to anisotropic etching, isotropic etching generates concave shape at a faster etching rate.^[20] Sulfur hexafluoride (SF_6) in an inductively coupled plasma-reactive ion etching (ICP-RIE) reactor is an effective etchant used for isotropic etching; meanwhile, xenon difluoride (XeF_2), independent from ICP-RIE, can be employed for isotropic silicon etching for MN formation.^[21]

Although XeF_2 has been previously used in many applications spanning from PZT micro cantilevers to the other micromachined device designs such as thermopile radiation sensor,^[22–25] and to the best of our knowledge, there is no reported study that

demonstrates the fabrication of MNs with different geometries using XeF_2 -based dry etching process as a comprehensive optimization study. In earlier studies, the researchers investigated the selectivity of XeF_2 against silicon and its compounds,^[22] paving the way to explore this etching system as a fundamental aspect rather than fabricating geometries; yet, they did not demonstrate to produce MNs through this strategy. Moreover, another study demonstrated the fabrication of micro-scale structures using XeF_2 gas; however, these were PZT microcantilevers rather than MNs.^[23] Through this strategy, the micromachining of MEMS has been demonstrated for bulk silicon micromachining and producing pit structures within $10\text{--}50 \mu\text{m}$ in size.^[25] In addition, this approach has been expanded to wafer-level MEMS applications by investigating the kinetics of XeF_2 etching and showed a promising alternative to deep reactive ion etching (DRIE) method.^[24] Concentrating on the fabrication of MNs, DRIE has been a mostly employed method due to its highly anisotropic nature, enabling MNs with improved resolution and higher aspect ratios. Due to its anisotropic etching nature, only pillar-like structures can be formed, and further isotropic etching is required for sharpening MN array tips.^[26] For this reason, the combination of isotropic and anisotropic etching as a two-step process needs to be conducted in such a scenario. Unlike DRIE combined with anisotropic etching, dry etching using XeF_2 is an isotropic etching process in which XeF_2 molecules carve silicon at a specific rate in all directions (both lateral and vertical).^[26] Having said that, MN arrays with sharp tip can be formed as a one-step process simultaneously. In addition, comparing to the XeF_2 strategy, DRIE can be carried out only in a cleanroom facility and operated under high-vacuum condition with a turbo-molecular pump system. Gas scrubber system connected to a liquefied petroleum gas (LPG) tank is also required to eliminate hazardous gases during the operation of DRIE. On the other hand, XeF_2 etching does not need any gas scrubber or special exhaust systems, and it is operable outside of the cleanroom. Briefly, DRIE process requires cleanroom, gas scrubber, SF_6 storage, LPG tank, nitrogen gas, potassium hydroxide solution tank, compressed dry air, and so on. In contrary, XeF_2 strategy requires less number of device (only a benchtop equipment, general exhaust system, and mechanical pump) and low operational cost for the process, making it economically more viable, which reduces the total cost down to ≈ 100 times compared to DRIE.

In our work, we have revealed an isotropic XeF_2 dry etching process to fabricate silicon-based solid MNs with distinct geometries, numbers, and dimensions (length and height). We have further evaluated the performance of these MNs in penetrating both chicken and porcine skins as human skin mimicking models along with theoretical aspects behind this strategy. The way that we have demonstrated to fabricate MNs enriches the current literature and proposes an unconventional alternative to the other techniques such as DRIE. In addition, we have comprehensively assessed our findings through COMSOL Multiphysics simulation analysis, which denotes a comprehensive perspective and differentiates our study from the others in the literature. Herein, a multilayer skin model consisting of the stratum corneum, epidermis, and dermis was designed in COMSOL Multiphysics, and the efficiency of MN insertion into the skin was numerically analyzed using hyperelastic Ogden model. Such modeling analysis is also an essential perspective to support the experimental

findings, augmenting the current literature of MNs. Overall, the optimized process provides a wide range of solid MN types that would be utilized for either epidermis or dermis targeting to current transdermal drug delivery studies.

2. Experimental Section

2.1. Materials

Acetone and isopropyl alcohol were purchased from Isolab Laborgeräte GmbH ($\geq 99.5\%$, Eschau, Germany), and they were used for silicon wafer cleaning. Hexamethyldisilazane (HMDS) was purchased from TECHNIC (Rhode Island, USA) and used to promote the adhesion of photoresist coating on a silicon wafer. AZ 400 K Developer was purchased from Merck Group (USA). AZ5214E photoresist was obtained from MicroChemicals GmbH (Ulm, Germany).

2.2. Microneedle Fabrication

MN arrays with different structures were fabricated by employing MEMS fabrication methods that comprise deposition and patterning steps followed by a dry etching process with XeF_2 . The structures with varying sizes and interspaces between each MN array were tested to determine the optimum geometrical features. Process design for MN fabrication is shown in **Figure 1**.

2.2.1. CAD Design of the Microneedles

The MNs with four distinct structures (conical, pyramidal, tetrahedron, and star) were first designed using Autodesk AutoCAD 2022, and then, the CAD designs were further processed in Layout Editor (Unterhaching, Germany) (Figure S1, Supporting Information). The designs were written on a square ($5'' \times 5'' \times 0.09''$) soda-lime chrome mask (Telic Company, Valencia, CA, USA) using DWL-66FS Laser Mask Writing Tool (Heidelberg Instruments, Germany). The number of MN arrays and initial area to be exposed to XeF_2 in single patch with area of 1 cm^2 can be found in Table S1, Supporting Information.

2.2.2. Photolithography Process

Four-inch silicon wafers with thicknesses of $500 \mu\text{m}$ were used during the photolithography process. Prior to the process, the wafers were placed in a glass container filled with acetone and cleaned for 5 min using ultrasonic cleaner (Branson, Model 2510, USA). The wafer was immediately washed with isopropyl alcohol and dried using compressed air. Afterward, the wafer was kept on a hot plate (Athena Technology, Mumbai, India) at 120°C for 2 min for the dehydration baking step. After cooling the dehydrated wafer, it was placed on a spin coater (Model WS-650MZ-23NPPB, Laurell Technologies Corp., PA, USA). To increase the photoresist adhesion, the wafer was

initially spin-coated with HMDS at 5000 rpms with an acceleration speed of 500 for 30 s. The wafer was left on the spin coater for 1 min to allow evaporation of solvent residues; and then, it was further spin-coated with AZ5214E photoresist at the same speed for 1 min, thereby obtaining a thickness of $\approx 1.4 \mu\text{m}$. The wafer was later placed on a hot plate at 110°C for 60 s for the soft bake step. Following that, the wafer was exposed to 60 mJ cm^{-2} UV dose using EVG 620 Contact Mask Aligner (EV Group, Austria). After the UV exposure, the wafer was left in an AZ 400 K developer solution for 60 s, and rinsed with DI water. After drying the wafer with compressed air, the patterns were verified using a Dino-Lite digital camera integrated into an optical microscope (Carl Zeiss, Heidelberg, Germany). The photolithography process was concluded after leaving the wafer on a hot plate at 120°C for 2 min for the post-exposure bake step.

2.2.3. Silicon Nitride Coating Using Plasma-Enhanced Chemical Vapor Deposition

To overcome any instability issues observed in the physisorption of photoresist on the silicon wafer during XeF_2 etching process, the photoresist masking layer was replaced with silicon nitride (Si_3N_4). Initially, a new chrome mask was produced with an inverted polarity of the previous one (photoresist-coated). Then, the photoresist process was employed using a new mask. A silicon wafer was spin-coated with AZ5214E photoresist and exposed to UV in a mask aligner (UV dose of 50 mJ cm^{-3}). Please note that only the soft bake process was employed prior to UV treatment. Later, the UV-exposed wafer was developed in the developer solution (diluted with pure water at 4:1). The developed wafer was placed in the plasma Asher (1 min, 100 W power, 40 sccm O_2 , 10 sccm Ar) to further remove the remaining photoresist and other organic residues as a removal and stripping process. Afterward, Si_3N_4 was coated on the silicon wafer using plasma-enhanced chemical vapor deposition (PECVD) in order to obtain a hard masking layer with a thickness of $\approx 300 \text{ nm}$. The coating was carried out at 150°C with a chamber process pressure of 400 mTorr using 2% Silane (v/v) in nitrogen with a gas pressure of 180 mTorr and NH_3 with a pressure of 45 mTorr at 100 W of RF power. After this process, the Si_3N_4 -coated wafer was removed from the PECVD chamber, and a lift-off process was employed by keeping the wafer in acetone to lift all the Si_3N_4 from the surface, where there were no tips of MN arrays. Then, Si_3N_4 -coated wafers were coated with AZ5214E photoresist (soft bake); and then, a flood exposure lithography was performed using flood UV exposure without any mask. This step was employed to protect the wafers from the mud release during the operation of the dicing sawing. The wafer was cut with the dicing saw, followed by an additional lift-off process in order to finally obtain clean Si_3N_4 -coated hard masks only on the surface of MN array tips.

2.2.4. Dicing Saw Process

Prior to the dry etching process, the silicon wafer was sliced into 1 cm^2 of square-shaped frames to fabricate MN patches

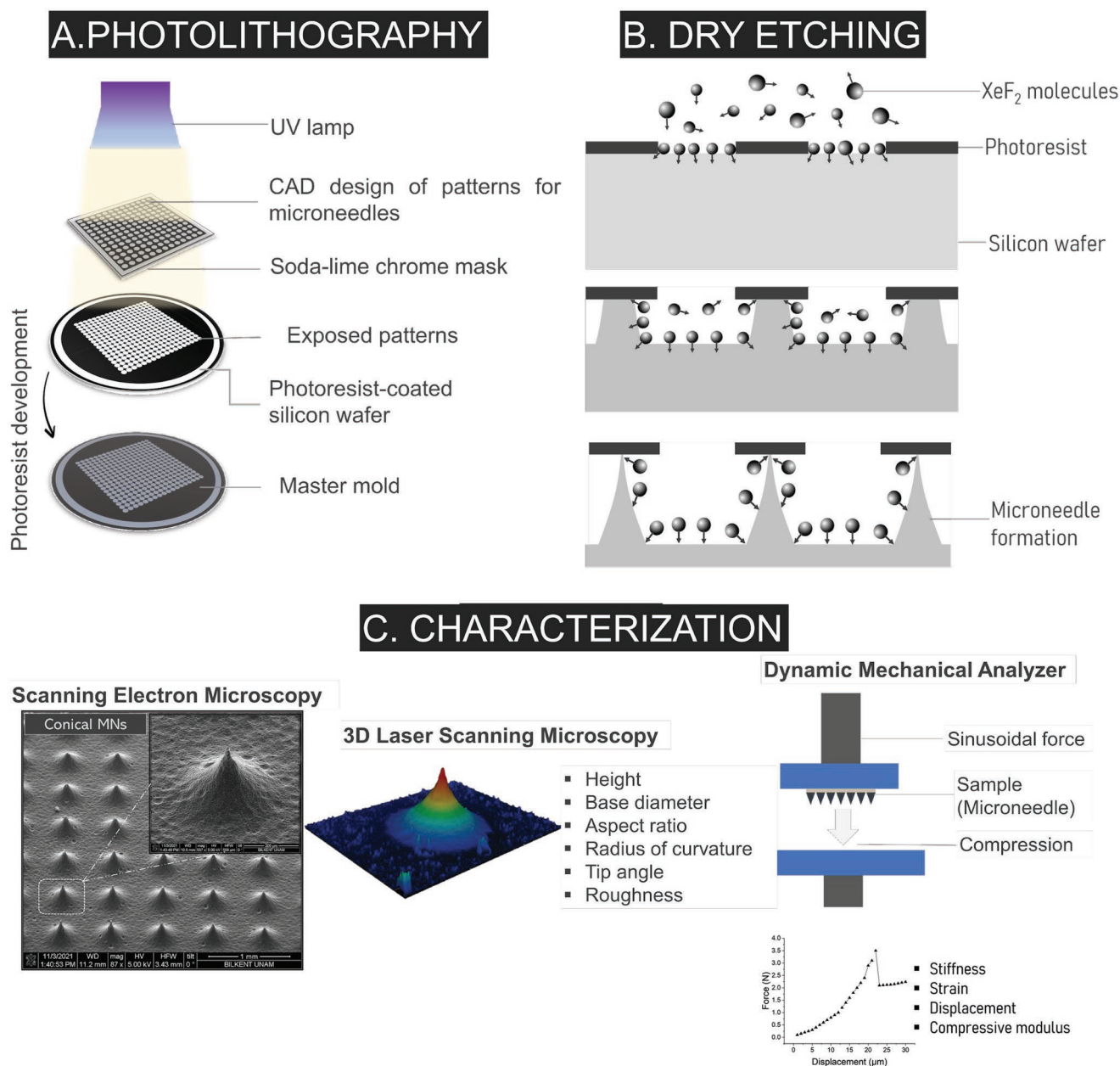


Figure 1. Process design for MN fabrication: a) photolithography, b) isotropic dry etching, and c) analyses using scanning electron microscopy, 3D laser scanning microscopy, and dynamic mechanical analyzer.

separately. An automatic dicing saw machine (DAD3220, Disco, Japan) with a high-speed spindle fitted with a thin diamond blade (the thickness of 200 μm) was utilized to dice the wafers. An infrared heat lamp (Philips) or weak UV exposure was used to peel off the double-sided tapes from the silicon wafer easily.

2.2.5. Dry Etching Process

A selective XeF_2 etching system (SPTS Technologies, UK) was used for the isotropic dry etching of silicon sacrificial layers on a silicon wafer in order to create MN arrays. A delay of 10 s was added between the end of etching pulse

and the beginning of the next cycle; hence, allowing the MN samples to cool before starting the next etching cycle. The process parameters such as XeF_2 pressure, etching time, and etch delay were determined depending on the designs shown in Figure S1 and Table S1, Supporting Information. In our study, XeF_2 pressure of 2 Torr and cycle duration of 60 s were used. The following equations (Equations (1) and (2)) were used to estimate the approximate etch depth on the silicon wafer and total amount of XeF_2 used for fabricating MNs:

$$\text{Etch depth } (\mu\text{m}) = (1.7 \mu\text{m}) \times \text{number of cycles} \times (\text{pressure in Torr} - 0.3) / (\text{Si exposed area in cm}^2) \quad (1)$$

$$\text{XeF}_2 \text{ used} = (4.8 \text{ mg}) \times (\text{number of cycles}) \times (\text{pressure in Torr} - 0.3) \quad (2)$$

2.3. Structural Analysis of Microneedles

Preliminary visualization was assessed using a light microscopy as electron microscopy damages photoresists structure on the tip of the MN arrays. After photoresist or Si_3N_4 structures disappeared and the tip of the MN arrays appeared, the dry etching process was finalized and morphological features of the MN arrays were visualized using scanning electron microscopy (SEM) (FEI 430 Nova NanoSEM) with a working distance of 5 mm and voltage of 5 keV. A 3D laser scanning microscope (VK-X100, Keyence, Osaka, Japan) with a lens of 20–200 $\times$ was used to analyze structural properties of the MNs. Similar microscope was used to explore surface profile such as roughness, skewness, and kurtosis of silicon MNs. JIS B 0601: 2001 (ISO 4287: 1997) standard was employed and λ_s and λ_c cut-off values of 0.25 μm and 0.8 mm were selected, respectively.

2.4. Magnetron Sputter Coating of Solid Microneedles With Titanium And Chromium

After solid MN arrays were formed, MNs were further coated ($\approx 1 \mu\text{m}$) with titanium and chromium to improve surface and tensile strength properties. The coating was conducted in Vaksis PVD Handy Twin Sputtering System (Turkey) using titanium and chromium sputtering targets (Kurt J. Lesker, UK) separately. The coating was carried out under 7.5 mTorr pressure, 20 sccm Argon Plasma, and 100-Watt DC power source.

2.5. Dynamic Mechanical Analyzer

Mechanical strength features such as stiffness, stress, strain, displacement, and compressive modulus of the MN arrays were measured using a dynamic mechanical analyzer (DMA Q800, TA Instruments, USA). Compression mode was selected and MNs were held isothermally at 25 $^\circ\text{C}$. The MNs were deformed at a constant amplitude value of 15 μm . Preload force was set to 0.01 N with a force track of 125%. The maximum force was set to 18 N with a change of 0.5 N per min.

2.6. Penetration Test on Porcine and Chicken Skin

Chicken and porcine skins were selected as biological skin models to confirm the penetration efficiency of solid MNs. The skins were purchased from a local butcher and disinfected and cleaned prior to penetration test. The porcine skin was cut in circular shape with the diameter of 15 mm; and then, immobilized on the lower clamp of the DMA while the MN patch was attached on the upper clamp using a double-side tape. Compression mode was selected and the maximum force of 18 N with a 0.25 N min^{-1} step was applied over the porcine

skin. On the other hand, the chicken skin was kept stretched on a metal surface, and MN patch was manually pressed over the skin and left for 1 min; and then, gently removed. The thickness of the stretched chicken skin was ≈ 1.5 mm. Pierced skins were further analyzed under 3D laser scanning microscope.

2.7. COMSOL Stress Analysis of Microneedles

The penetration of pyramidal MN into the skin was evaluated using COMSOL Multiphysics 5.6 Solid Mechanics module. Briefly, the geometry of manufactured MNs was saved as an STP file by the software of the laser scanning microscope (VK-X100, Keyence, Osaka, Japan). After obtaining the STP file, one MN was isolated from the rest. Isolated MN was then modified using Autodesk Fusion 360 mesh features. A face covering the tip of the MN was generated, and the remaining volume went under smoothing, remeshing, stitching, and removing operations. The final geometry was exported as an STL file and imported into COMSOL Multiphysics. The steps and final geometry are shown in Figure S2, Supporting Information.

After importing the MN into COMSOL Multiphysics, three cylinders with a radius of 0.5 mm were created to represent the skin layers that are stratum corneum, epidermis, and dermis having a thickness of 20, 80, and 1 mm, respectively.^[27] The skin layers and the imported MN are shown in Figure S3, Supporting Information. While the material for MN was chosen as silicon, the skin layers were modeled as hyperelastic Ogden material.^[28] The Ogden model parameters used during the simulations are given in Table 1. Stratum corneum and epidermis were assumed to undergo perfect plastic deformation when the stress reached 60 MPa, that is the ultimate strength for stratum corneum.^[29] The yield strength for MN silicon was chosen to be 165 MPa.^[30] The skin layers were fixed at their outer faces and at the bottom. The MN was assumed to move 0.6 mm min^{-1} in the normal direction to the skin.

To evaluate the stresses at the stratum corneum and epidermis, two studies were performed on COMSOL Multiphysics: (i) contact study between MN and stratum corneum and (ii) contact study between MN and epidermis. While defining the contact between the tip and epidermis for the latter, scaled MN tip volume was extracted from the stratum corneum and the MN tip was assumed to be in contact with the epidermis top layer. The configurations for contacts are shown in Figure S4, Supporting Information. The contact formulation was chosen to be the penalty method with a direct search, while the mapping method employed the deformed configuration.

Table 1. Ogden model parameters used to represent each layer of the skin.

Skin layers	E [MPa]	α
Stratum corneum	0.752	8.68
Epidermis	0.489	20.68
Dermis	7.33	57.89

Before running the simulations, cylinder volumes having a radius of 0.1 mm at the center of each skin layer were meshed according to the predefined extremely fine element size. The MN tip meshed with elements having a size of nearly three times bigger than the elements at the extremely fine volume. The remaining volume had extra coarse element size. The reason was to reduce the computational complexity caused by the contact problem between MN and non-linear hyperelastic Ogden model skin. The final mesh for the studies is given in Figure S4, Supporting Information. After completing mesh operations, two time-dependent studies with backward differentiation formula (BDF time stepping) were performed. The first study for the contact between the MN tip and stratum corneum was assumed to last 10 s, 5 s for the penetration, and 5 s for withdrawing the needle. The second study lasted 1 s, 0.5 s for the penetration, and 0.5 s for withdrawing the MN.

Mechanical properties of the manufactured MN were also evaluated on COMSOL Multiphysics. After importing the MN, the MN was fixed at the bottom and a force increasing from 0 to 18 N with 0.5 N min⁻¹ slope was applied to the tip in the normal direction. After meshing the MN, a time-dependent study was performed for 2160 s. The material for MN was chosen as silicon.

2.8. Statistical Analysis

All the data obtained were expressed as the mean of three replicated $\pm$ standard deviation (SD). *t*-test was used to provide the single-step multiple comparisons of values obtained for each MN array varying with the shapes, tip diameter, and interspace. Statistical analysis of the values was performed through SPSS 28 software. Comparisons with $p < 0.05$ were considered significantly meaningful. In all figures, error bars represent the SD value of the mean.

3. Results and Discussion

In the present study, an isotropic XeF₂ dry etching process was employed to fabricate silicon-based solid MNs with four different structures (conical, pyramidal, tetrahedron, and star) varying in height between 50 and 300 μ m. Process conditions such as CAD designs, photolithographic process, and etching parameters were customized for the fabrication of each MN type. The tensile strength of the MNs was further improved by chromium and titanium coatings, and the impact of coating on surface properties of MN arrays was determined.

3.1. Isotropic XeF₂ Dry Etching Process

The dry etching process was carried out for four types of MNs. The distance between initially projected photoresists (or Si₃N₄) was set to 100 and 200 μ m, and tip lengths were projected to be 200, 300, 400, and 500 μ m (hatched area in Figure S1, Supporting Information). The average height of each MN was determined by measuring different MN arrays randomly selected from both center and perimeter of the MN patch.

3.1.1. Effect of Geometry on XeF₂ Efficiency

The distance between each MN array (Figure S1, Supporting Information) was found to influence the average height of MNs at the end of dry etching process. As indicated in Equation (1), the etch depth was inversely proportional to silicon exposed area. Expectedly, 100 μ m of distance resulted in shorter MN arrays because the initial silicon area to be etched for the design containing 200 μ m distance was larger than the one with 100 μ m of distance (Table S1, Supporting Information). Depending on the designed shape, space between each MN array, and MN array tip length, the minimum and maximum numbers of MN array on each patch varied between 169 and 900 for conical and pyramidal, 266 and 1452 for tetrahedron, and 49 and 324 for star-like MNs (Table S1, Supporting Information). The number of MN per patch plays an essential role in TDD applications. For instance, solid MNs are expected to generate more holes on epidermis layer, while dissolved or hollow versions of MNs enable to introduce more volume of drugs through epidermis due to an increased number of MNs.^[31] On the other hand, increasing number of MN array may induce more pain to patients when applied.^[32,33]

The average height of MN arrays significantly increased as the projected tip length was varied from 200 to 500 μ m in each group (Figure 2a–d). The shortest MN arrays were observed in tetrahedron MNs with less than 100 μ m for each geometrical parameter, while the highest MN arrays were found in star MNs with an average height of 281 ± 19 μ m (200 μ m of space). The highest conical and pyramidal MN arrays (100 μ m space) were 195.3 ± 18.6 and 201.25 ± 65.1 μ m, respectively. According to the Equation (1), the height of MNs for each type was expected to decrease as we increased the projected tip length (from 200 to 500 μ m) since the initial area exposed to XeF₂ was higher for 200 μ m than that of 500 μ m (Table S1, Supporting Information). Overall, the height increased significantly, affirming the fact that initial projected tip length had greater impact on the formation of MNs during the dry etching process. This issue was strongly associated with the initial projected tip length (200–500 μ m), and most importantly, with the mechanism of XeF₂ etching system. During isotropic etching, XeF₂ has been shown to possess more etching rate at the MN tip than etching rate at lower parts. Considering this fact, MNs with larger projected tip dimensions, for instance 500 μ m (Figure S1, Supporting Information), need to be etched for longer periods of time by XeF₂ molecules because there is more area available for etching until the tip becomes sharper. In the meantime, XeF₂ molecules will continue to etch the MN arrays vertically, and in this way, they will increase the height of the MNs. On the other hand, when we etch a MN array with smaller projected tip length, for example 200 μ m (Figure S1, Supporting Information), the area to sharpen the MN tip is smaller. Hence, there is less time available for vertical etching, resulting in a smaller height. Overall, the height increases significantly, affirming the fact that initial projected tip length has greater impact on the formation of MNs during the dry etching process. We here simplified this process as an illustration in Figure S5, Supporting Information.

Although isotropic dry etching with XeF₂ for MN fabrication has not been reported, a number of isotropic etching

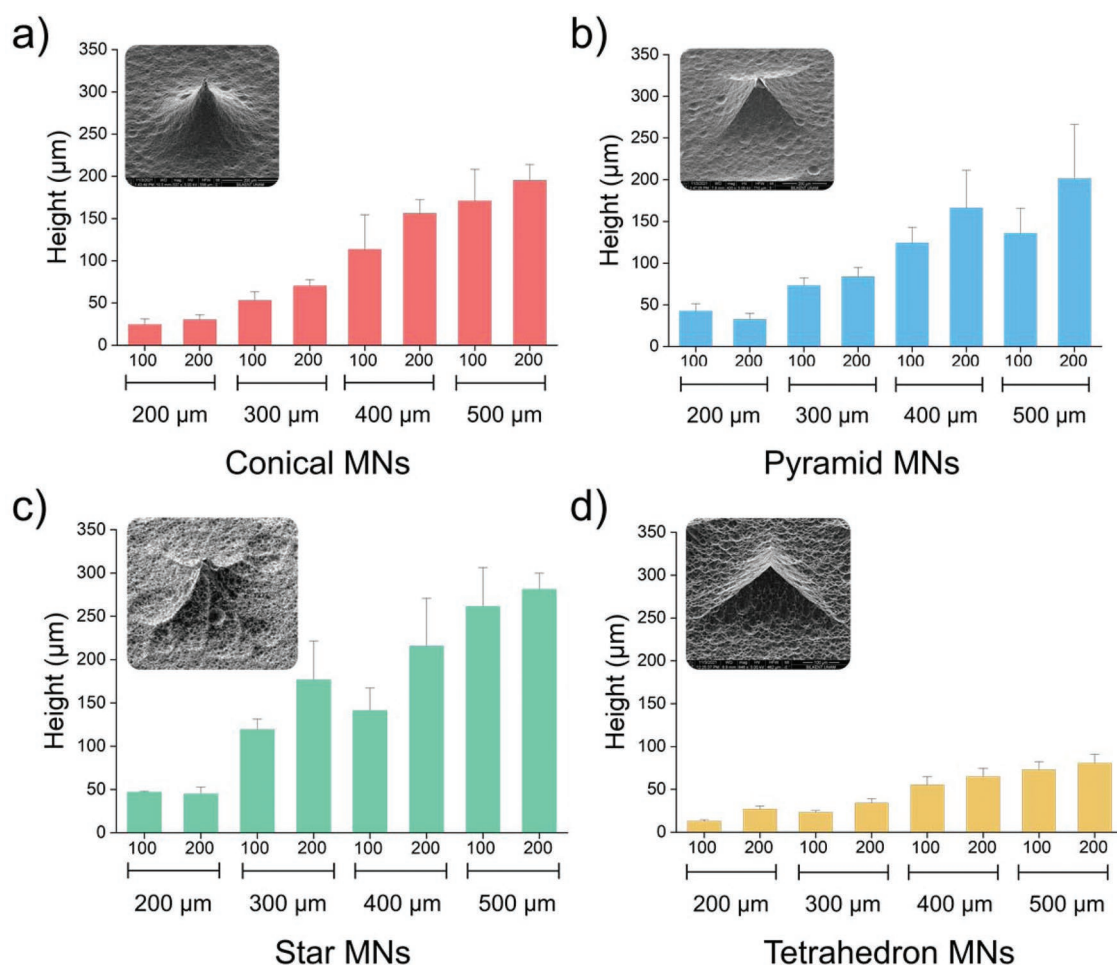


Figure 2. The average height of the arrays for a) conical, b) pyramidal, c) star, and d) tetrahedron MNs. The values (200, 300, 400, and 500 μm) on the x-axis indicate the diameter of the photoresist at the beginning of the process while the other values (100 and 200 μm) on the x-axis are the distance between each MN array.

processes have been conducted for such productions. However, ion etching is usually employed in combination with anisotropic process to obtain MN array with higher aspect ratio. Isotropic inductively coupled plasma etching using SF_6 , for instance, was shown to be effective in creating MN arrays.^[34] If not optimized efficiently, isotropic etching alone may result in shorter MN arrays. Employing isotropic etching with SF_6 alone resulted in a MN array with a maximum height of ≈ 120 μm. When it was combined with anisotropic etching (both dry and wet), higher aspect ratio was obtained.^[35] Similar finding was also observed when dry etching with SF_6 was combined with reactive ion etching process.^[36] In our study, isotropic etching was used alone and successfully resulted in fabrication of MNs by altering the process configuration.

3.1.2. Effect of XeF_2 on MN Geometry

Unlike anisotropic etching, dry etching using XeF_2 molecules is an isotropic etching process in which XeF_2 molecules carve silicon at the same rate in all directions (both lateral and vertical).^[26] Having said that, one of the disadvantages observed

during etching process is the fact that MN arrays at the perimeter of the wafer were found to be shorter than the MN arrays in the center (Figure S6, Supporting Information). The highest MN arrays in the center of each conical, pyramidal, star, and tetrahedron patch were reported to be 220, 260, 300, and 95 μm, respectively. On the other hand, these values were 142, 102, 262, and 71 μm for the MN arrays at the perimeter of the patch for conical, pyramidal, star, and tetrahedron, respectively. This issue was possible due to the fact that there is a region at the perimeter (including corners), which is exposed to XeF_2 in an irregular manner, and also, due to loading effect in the etching system (Figure S1, Supporting Information). The loading effect could be faced relying on the sample size and the amount of exposed silicon.^[37] Hence, once XeF_2 gas was released into the reaction chamber, it started off its etching activity more robustly toward the MN arrays at the perimeter, prompting the formation of early arrays and consequent fall of photoresists. In different reports, similar height distributions on a silicon wafer were obtained after isotropic etching (wet or dry) following DRIE process.^[38] This study, on the other hand, has benefitted from this difference and intentionally attempted to increase the difference in achieving out-of-plane MN structures

with various heights up to 1779 μm of maximum difference between the center and perimeter of the wafer. Another recent study has also observed a significant difference in hollow MN height after employing the same etching technique.^[26] This height distribution from perimeter to center can be a drawback as each MN array is expected to be the same in height for a more uniform MN patch to reduce variation for an effective TDD system.

In our study, we coated the sides of silicon wafer with Si_3N_4 as a material inert to XeF_2 ; however, XeF_2 molecules lifted this layer after a number of dry etching cycles, leaving the sides unprotective and exposed to XeF_2 robust action. Once the diced wafers were in the chamber, XeF_2 gas started off the etching process from all sides of the wafer. Inevitably, there might have been extremely small gaps between the surface of the chamber and bottom of the wafer, where XeF_2 gas attempted to penetrate and to etch the bottom of the wafer, diminishing it in its thickness faster than expected. In our experiments, we observed the diced wafers were thinning out quickly, limiting the maximum height to be achieved. Moreover, the MN patch would become exceedingly fragile to be applicable on the skin. Hence, the bottom and side of the silicon wafer were additionally coated with a material that is chemically inert to XeF_2 . In our experiment, we further coated the bottom and lateral sides of the diced wafer with photoresist and/or Si_3N_4 separately before a dry etching process and successfully eliminated this issue.

3.1.3. Silicon Nitride Coating

We initially carried out MN fabrication using only photoresist-coated silicon wafer. However, during dry etching process, we observed that air flow of XeF_2 could move the objects placed in the chamber. During the periodic visualization under the light microscope to confirm MN tip formation, we observed air flow in the chamber knocked some of the photoresist layer on the top of MN tip (Figure S7, Supporting Information). Once the photoresist layer fell or was partially deformed, it may have caused irregularities in dry etching process during the MN formation. To prevent early fall of photoresist layer, we coated the silicon wafer surface with Si_3N_4 . We observed a more stable layer after depositing it on the wafer using plasma-enhanced chemical vapor; hence, preventing the early fall of the layer that protects the MN tip. We have conducted further analyses using Si_3N_4 -coated wafers.

3.2. Structural Analysis of MNs

Once photoresist or Si_3N_4 structures completely disappeared from the MN tip, the dry etching process was interrupted, and morphological and structural features of the MN arrays were visualized using the SEM and a 3D laser scanning microscope, respectively. Base diameter, height, aspect ratio, radius of curvature, and tip angles were calculated for each MN type considering the diameter of the photoresist (or Si_3N_4) at the beginning of the etching process as 500 μm and the distance between each MN array as 200 μm . (Figure 3). The base diameter of MNs was projected to be 500 μm and due to the

excess etching time, the base diameter obtained at the end of the process was smaller than 400 μm .

Although obtaining MNs with higher aspect ratio is a desired property due to facile penetration into the skin, MNs at higher aspect ratio would potentially face early deformations upon an applied force. In our study, aspect ratio was determined differently as the MN arrays possess concave geometry. According to our COMSOL simulation, we fixed the MN height to 125 μm . The reason to consider this height was that this MN height was sufficient to penetrate into epidermis according to the COMSOL simulation. Hence, we defined two different aspect ratios and tip angles of a single MN array. For instance, in case of conical MN array, the aspect ratio of entire MN array was 0.6 (Figure 3a); however, due to concave geometry, the aspect ratio was calculated to be ≈ 2 . Likewise, for pyramidal (Figure 3b) and star MNs (Figure 3c), the aspect ratio increased from ≈ 0.70 to 2 and from 0.6 to 1.2, respectively. As the tetrahedron structure did not pose a concave structure (Figure 3d), there was only one aspect ratio (0.2). Radius of curvature and tip angle provided information regarding the penetration ability of MN arrays. Smaller radius of curvature and tip angle denote sharper MN tip, which may significantly facilitate the penetration ability of MNs upon application on skin. Radius of curvature for conical, pyramidal, star, and tetrahedron MNs were 5.6, 13.1, 13.7, and 10.5 μm , respectively. In case of tip angle, it was continuously decreasing in a non-linear manner from the base to the tip of a MN array. Hence, we also defined two tip angles (θ_1 and θ_2) for each MN array except tetrahedron structures. The θ_1 values obtained for conical, pyramidal, and star MNs were 24.8°, 14.2°, and 21.05°, while the θ_2 values were 43.7°, 36.3°, and 39.3°, respectively.

During the MN formation, an early interruption of dry etching process was found to result in larger radius values. This might have occurred because the tip formation was not completed and when we used pressured air gently on the silicon wafer, all the photoresist or Si_3N_4 residue were blown away; hence, a tip with higher radius of curvature was obtained. In such a case, in order to address this challenge, silicon wafer would be periodically visualized under the light microscope for confirming a perfect tip formation.

Although we optimized the process conditions for a silicon wafer with the thickness of 500 μm , we have additionally fabricated a silicon wafer with 1000 μm of thickness to confirm whether MN arrays could be produced in longer height. After processing a silicon wafer with such a thickness, we obtained pyramid MN arrays ($\approx 330 \mu\text{m}$) slightly higher (27% increment) than when we used a 500 μm wafer to fabricate pyramid MNs ($\approx 260 \mu\text{m}$) (Figure 2). The radius of curvature and tip angle of each MN array were $\approx 10.4 \mu\text{m}$ and 20°, respectively. The SEM and 3D laser microscope images of these MNs are presented in Figure S8, Supporting Information.

Although, in our optimization studies, we observed the star geometry provided around 300 μm of tip height, fabricating this geometry was not uniform and provided irregular structures. On the other hand, pyramid geometry had lower tip angle and higher aspect ratio compared to star-shape MNs; hence, we continued to produce this geometry for further studies. After the structural analysis of each MNs, we proceeded our surface profile and mechanical strength tests using pyramidal

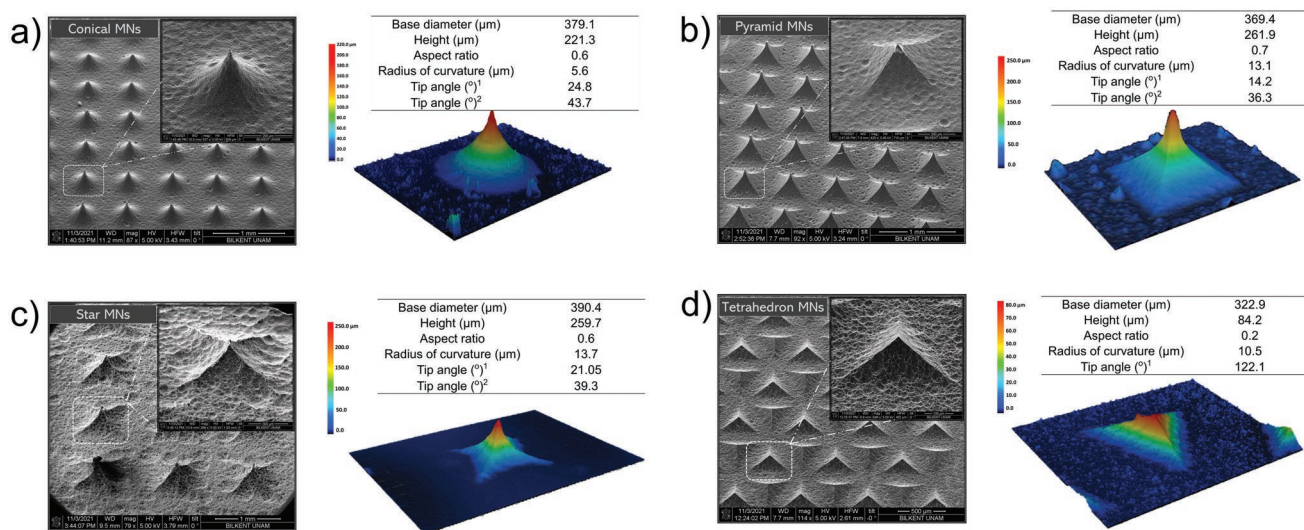


Figure 3. Structural analyses of a) conical, b) pyramidal, c) star, and d) tetrahedron MNs assessed by scanning electron microscopy (SEM, on the left) and 3D laser scanning microscope (on the right). The dashed (white) lines in (a,b,c,d) represent the zoomed MN structure. The scale bars of larger SEM images in (a,b,c) indicate 1 mm while the scale bar in (d) indicates 500 μm . The scale bars of smaller images in (a,b) state 200 μm , while the ones in (c,d) indicate 300 and 100 μm , respectively. Tip angle¹ and aspect ratio¹ were calculated based on total height and base diameter, while tip angle² and aspect ratio² were calculated using the height of 125 μm and its respective base diameter. In this process, the diameter of the photoresist at the beginning of the etching process was 500 μm , while the distance between each MN array was 200 μm .

shapes obtained with the following conditions: 500 μm of initial photoresist diameter and 200 μm of distance between each MN array. This is because pyramidal MNs have showed more uniformity on each side of patch with arrays possessing small tip diameter, which is considered a great advantage for skin pre-treatment.

3.3. Tensile Strength Analysis of MNs

Coating materials with metals such as titanium and chromium was shown to increase overall tensile strength, hardness, and corrosion resistance.^[39] Accordingly, after solid MN arrays were formed using dry etching, pyramidal MNs were further coated ($\approx 1 \mu\text{m}$) with titanium and chromium to improve tensile strength upon penetration into the target tissue. According to the energy dispersive X-ray results, (EDAX), MN surface was successfully coated with titanium and chromium, which could be visually observed in SEM images (Figure 4). According to the EDAX quantification results, chromium coated on the surface of silicon wafer was found to be 93.25% (wt), which may be due to possible contaminations (metal residues from the previous coating processes) in reaction chamber or target used for the coating.

After confirming the coating, mechanical strength features such as displacement (μm), strain (%), stress (mPa), stiffness ($\text{N } \mu\text{m}^{-1}$), and relaxation modulus (mPa) of the MN arrays were measured using a DMA. The number of MN arrays in one patch of the analyzed sample was 169 (Table S1, Supporting Information; pyramidal, 500 μm of initial photoresist diameter and 200 μm of distance between each MN array). In order to determine the force applied over a single MN, the overall force was distributed to 169 MN arrays.

Pyramidal MNs were subjected to constant force (from 0 to 18 N) with a ramp force of 0.5 N per min and the resultant displacement and strain (%) were measured. Displacement of MNs can be defined as the distance between initial and final position of MN tips upon compression. As shown in Figure 5, non-coated (silicon) MNs presented a displacement value of $\approx 35 \mu\text{m}$. This value was significantly reduced in MNs coated with titanium and chromium, being ≈ 14 and $\approx 12 \mu\text{m}$, respectively. This demonstrated that titanium and chromium coating may increase the resistance of MN tips against bending or breaking upon insertion into the skin. As the strain is a measure of deformation representing the displacement, similar curve was obtained (Figure 5). In a previous study, a displacement value of $\approx 32 \mu\text{m}$ was measured upon application of 3 N on the silicon MNs.^[40] In our experiments, silicon MNs had a displacement slightly larger than 10 μm at the same compression force. The height, base diameter, aspect ratio, tip diameter, and tip angle of MN arrays are also vital parameters to assess tensile strength.^[41] For example, MNs fabricated with acrylate-based polymer with the aspect ratio of 3:1, 2.5:1, and 2:1 presented displacement values of 182, 169, and 42 μm at 0.2 N force, respectively, and this confirms the fact that coating the MN surface is vital to improve tensile strength.^[42]

MNs with the elevated hardness properties can withstand higher load values without presenting elastic deformation. A rigid MN with less stiffness will eventually break when the exerted load exceeds MN's tensile strength. Materials made of Si coated with either titanium and chromium usually do not change their forms. When the exerted force exceeds its strength, MN tips tend to break, entirely losing its original shape. As it can be seen in Figure 5, stiffness value under force of 18 N was found to be $0.5 \text{ N } \mu\text{m}^{-1}$, while these values were 1.25 and $1.5 \text{ N } \mu\text{m}^{-1}$ for titanium and chromium coating, respectively. Material type greatly impacts the stiffness. For instance,

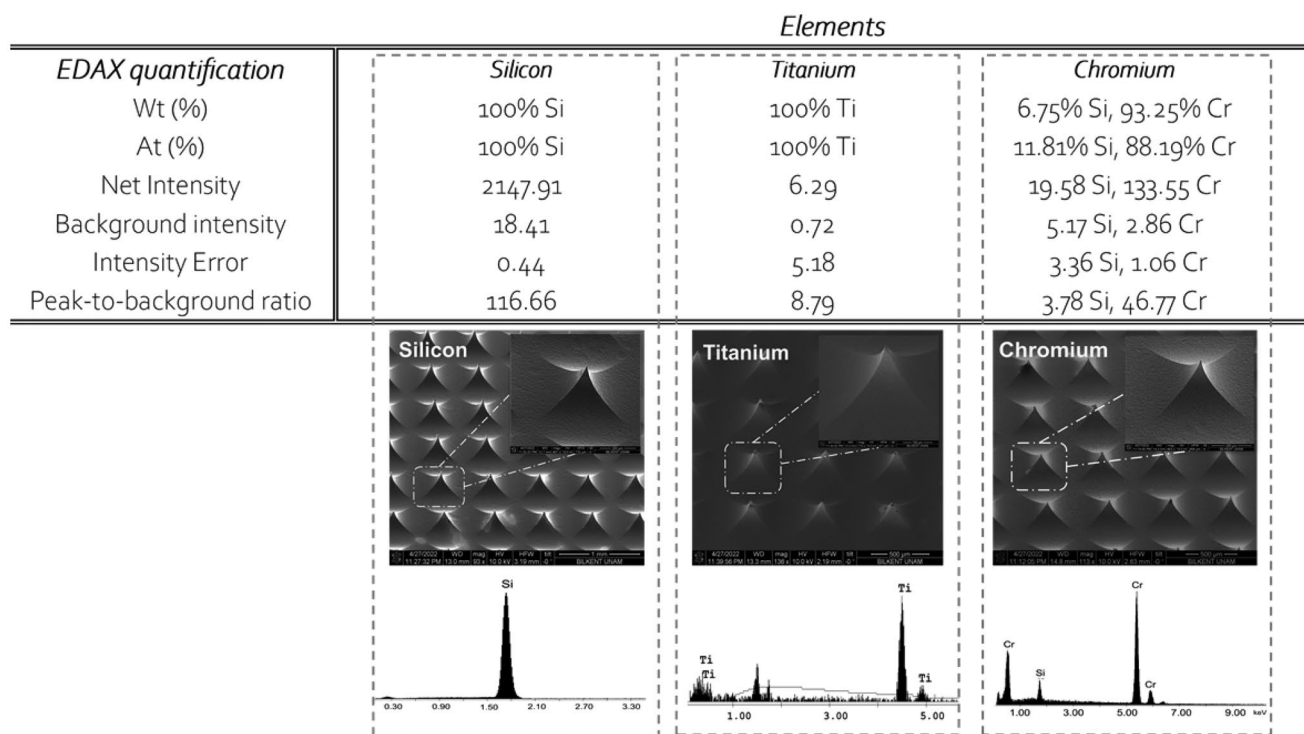


Figure 4. Scanning electron microscopy images and energy dispersive X-ray analysis of non-coated (silicon), titanium-coated, and chromium-coated pyramidal MNs. Wt (%) and At (%) represent weight and atomic percent, respectively.

MNs made of acrylate-based polymer exhibited a stiffness of $\approx 75 \text{ N } \mu\text{m}^{-1}$, which drastically increased from 1.6 to $76 \text{ N } \mu\text{m}^{-1}$ when the aspect ratio decreased from 3:1 to 2:1 (while keeping the same base diameter).

3.4. Surface Profile Analysis

Surface properties of MNs play a pivotal role in determining how they will interact with the skin. These properties become even more critical when MN is employed to deliver drugs or used as a biosensing platform because roughness may interfere with the interaction between the trio of MN arrays, selected biomolecule (i.e., coated drugs), and skin, resulting in better adsorption and/or release of biomolecules.^[43] Solid MNs were shown to have different impact on the skin depending on their roughness and waviness properties after the treatment.^[44] Moreover, solid MNs can be further exploited as a template to fabricate polymeric MNs. Achieving low roughness is additionally vital for further demolding process as it reduces the resistance in demolding.^[45] Hence, certain surface features of MNs should be explored to predict the outcome of the TDD.

Moreover, roughness is determined by measuring small-scale variations in the height of MN surface. The applied etching process using XeF_2 was found to provoke honeycomb-like irregularities with relatively small distances on silicon surface as observed in the SEM images. Hypothetically, the roughness of the MNs was expected to improve after coating with titanium and chromium. We hence coated the MNs with two different metals and determined their sur-

face properties before and after the coating. As shown in **Table 2**, non-coated pyramidal MNs had a roughness value of $0.71 \text{ } \mu\text{m}$. This value decreased to 0.45 and $0.37 \text{ } \mu\text{m}$ after coating with titanium and chromium, respectively. Similarly, conical MNs possessed a roughness value of 0.58 and after coating with titanium and chromium, this value was obtained to be 0.47 and $0.35 \text{ } \mu\text{m}$, respectively. A decrease in roughness value was previously observed after titanium coating on polished side of silicon wafer (from 0.06 to $0.04 \text{ } \mu\text{m}$).^[46]

The fabrication techniques and processed material have great impact on the surface properties of produced MNs. Hence, the initial roughness value of the material to be processed is vital and is directly associated with the final roughness value. Generally, a silicon wafer possesses two distinct sides: polished and unpolished. Polished and unpolished sides were previously reported to have roughness values of 0.44 and $369.8 \pm 105.9 \text{ nm}$, respectively.^[47] During the dry etching process, the roughness of the polished side will increase as XeF_2 gas starts to etch the surface. In this case, starting the etching process either on the polished or unpolished side will not impact the final roughness value of MNs. Having stated that, it is expected to have a roughness value over 369.8 nm after the dry etching process as it slightly increases this value. To improve surface roughness, there will be some additional steps such as wet etching.^[48]

3.5. Penetration Test on Chicken and Porcine Skins

The solid MNs produced in this study were also tested in biological skin models (chicken and porcine) to confirm their pen-

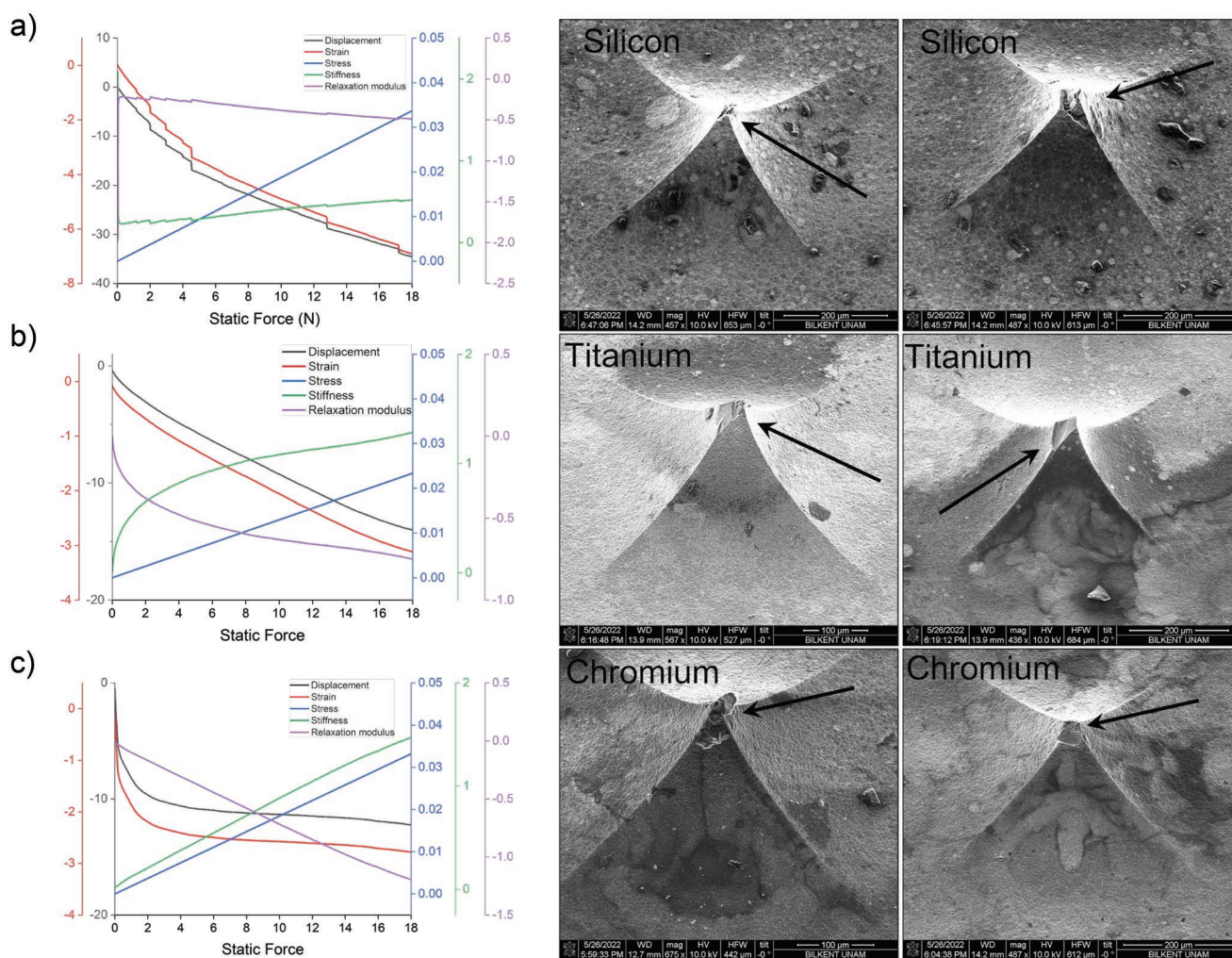


Figure 5. Mechanical failure test of a) silicon, b) titanium, and c) chromium-coated MNs. The graphics on the left demonstrate the changes in displacement (μm), strain (%), stress (mPA), stiffness (N μm), and relaxation modulus (mPA) with static force constantly increasing from 0 to 18 N with a ramp force of 0.5 N min^{-1} . The SEM images on the right show the deformation on the tip of MN array upon force application.

etration efficiencies. Initially, we used chicken skin to mimic human skin because we were able to reach it easily, and there are some published reports testing MNs on chicken skin that demonstrate electrolyte sensing,^[49] potassium detection,^[50] electrode design,^[51] wound healing,^[52] and so on. The fabricated

pyramidal MNs was tested on chicken skin without further titanium or chromium coating. After 1 min of manual pressing on chicken skin, the MNs were removed and the pierced skin was further analyzed under 3D laser scanning microscope (Figure S9, Supporting Information). As shown in Figure S9,

Table 2. Roughness properties of the silicon surface of the MN patch with and without coating.

Coating material	Geometrical structure	R_a [μm] ^{a)}	R_z [μm] ^{b)}	R_q [μm] ^{c)}
Non-coated (silicon wafer)	Pyramidal	0.71	4.671	0.888
	Conical	0.58	3.567	0.712
Titanium-coated MNs	Pyramidal	0.45	2.366	0.541
	Conical	0.47	2.537	0.583
Chromium-coated MNs	Pyramidal	0.37	1.677	0.450
	Conical	0.35	1.757	0.415

^{a)} R_a is referred to as the arithmetic mean roughness; ^{b)} R_q is referred to as the root-mean-square roughness; ^{c)} R_z is the average value of the absolute values of the heights of five highest profile peaks and the depths of five deepest valleys within the evaluation length.

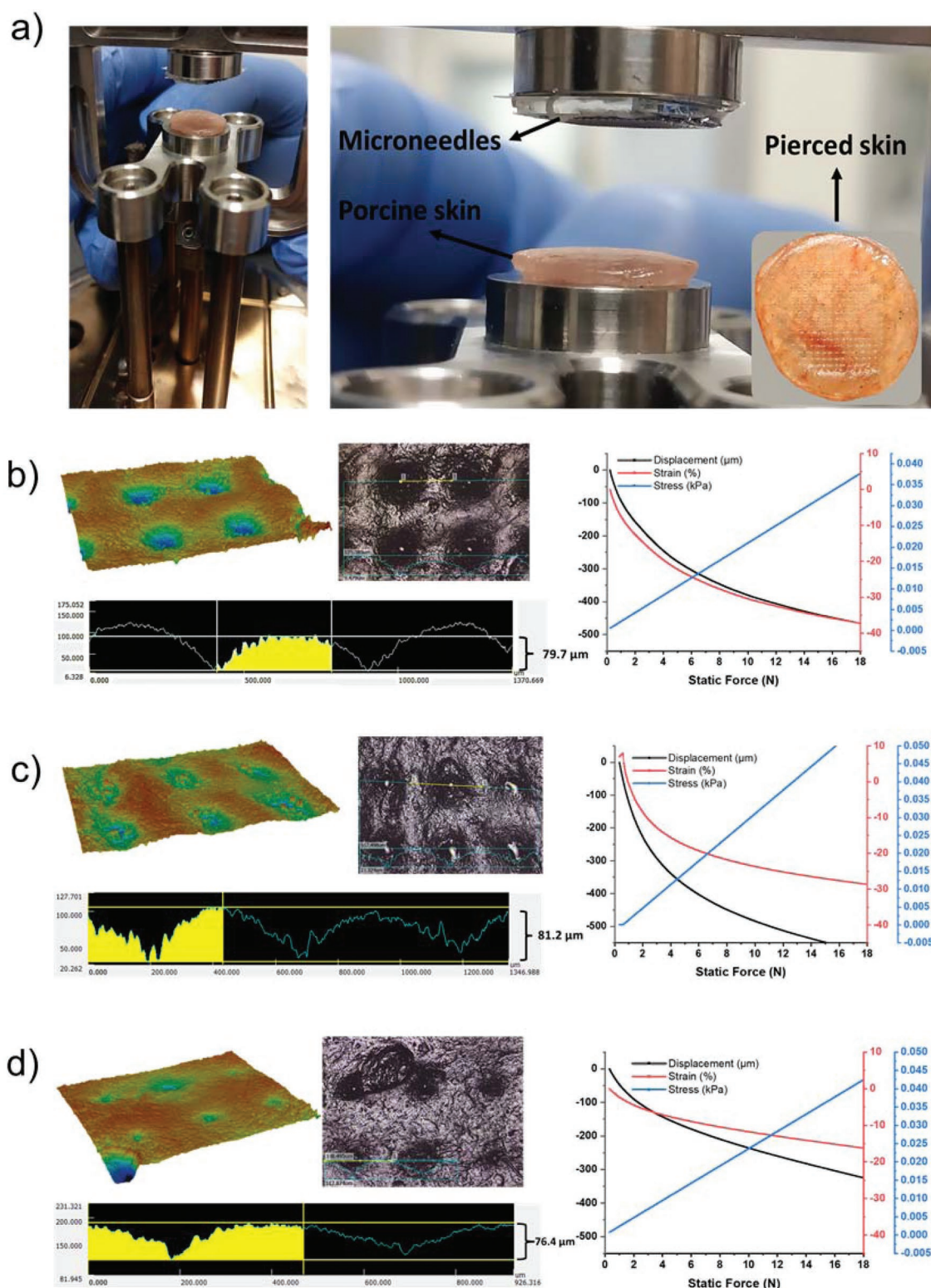


Figure 6. The penetration study of non-coated, titanium-coated, and chromium-coated MNs on porcine skin using dynamic mechanical analyzer. a) The setup represents how MNs were applied over porcine skin using dynamic mechanical analyzer. The image on the bottom right corner shows porcine skin after piercing with non-coated MNs. Penetration test results of b) non-coated, c) titanium-coated, and d) chromium-coated pyramidal MNs on porcine skin. The images on the left (b,c,d) are from 3D laser scanning microscope analysis showing topographical structure of skin and maximum penetration depth of the MN. The images on the right are the results obtained from dynamic mechanical analyzer after piercing the skin with MNs. The maximum force of 18 N (0.25 N min^{-1}) was applied on the skin during 72 min.

Supporting Information, the penetration depth of MNs on chicken skin was between 50 and 75 μm . Considering the fact that our MNs had a height of $\approx 250\text{ }\mu\text{m}$, $\approx 20\text{--}30\%$ of the MN tip penetrated into the skin. This finding can be attributed to the mechanical feature of chicken skin. The chicken skin possesses a thin epidermis and a thick dermis separated with a basal membrane. The external layer of the epidermis consists of corneocytes—a group of highly keratinized cells organized in sheets.^[53] The penetration through a more resistant outer layer can be additionally difficult due to its composition. Moreover, this layer has certain flexibility, which the MN tip cannot properly pierce through.

On the other hand, there are several reports emphasizing the similarities of porcine skin and human skin as a more precise mimicking model.^[54] Likewise, we evaluated the penetration analysis with porcine skin as another biological model. Initially, non-coated MNs were applied on the porcine skin using the DMA (Figure 6). According to the 3D laser scanning microscope, the maximum penetration depth of MNs was $\approx 79.7\text{ }\mu\text{m}$.

Mechanical analysis demonstrated that the MNs were not broken or deformed after the penetration into the porcine skin. We also tested titanium and chromium-coated MNs for their penetration capabilities into the porcine skin, and the maximum penetration depths were ≈ 81.2 and $\approx 76.5\text{ }\mu\text{m}$, respectively. Similar to the non-coated MNs, no deformations were observed in these cases. Considering that the tested MNs had a height of $\approx 250\text{ }\mu\text{m}$, the MNs were able to achieve a penetration rate of $\approx 31\%$ to $\approx 33\%$. Similar findings were obtained using polymeric MNs with the height of $\approx 650\text{ }\mu\text{m}$ inserted on pig skin and the depth of the pierced skin was found to be $\approx 150\text{ }\mu\text{m}$.^[55] Another insertion test on cadaver porcine skin was performed using hollow polymeric MNs with the height of 700 μm . The approximate penetration depth on skin was $\approx 350\text{ }\mu\text{m}$.^[56] Similarly, polymeric MNs with the height of 600 μm could penetrate only $\approx 70\text{ }\mu\text{m}$ into the cadaver porcine skin.^[57] Overall, compared to our penetration efficiency using porcine skin ($\approx 31\text{--}33\%$), these studies state a success of penetration ratio between 12% and 50%.

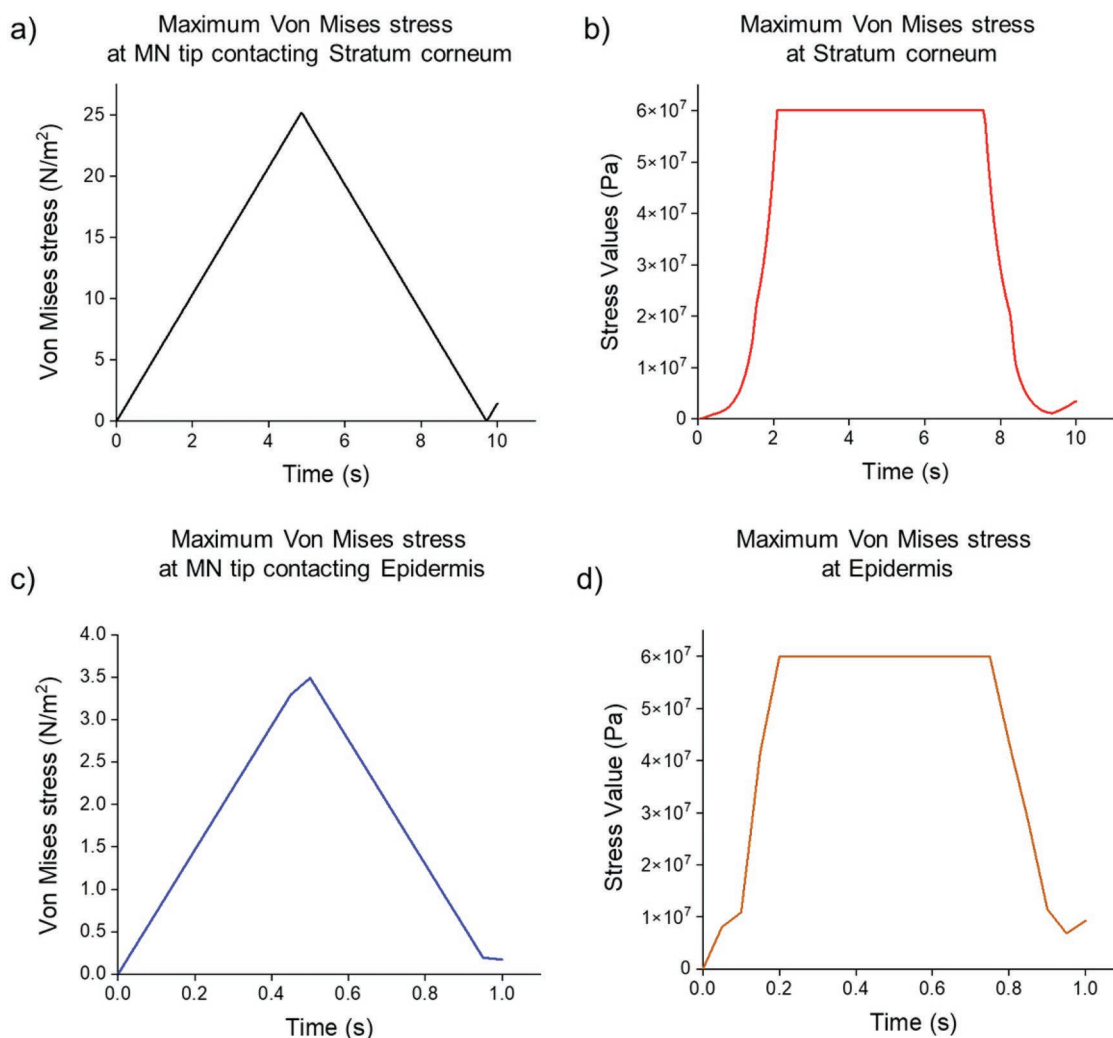


Figure 7. Maximum von Mises stress values for a) MN and b) stratum corneum for the contact study between the MN tip and stratum corneum, and maximum von Mises stress values for c) MN and d) epidermis for the contact study between the MN tip and epidermis.

3.6. COMSOL Stress Analysis of MNs

The stress to which the skin and the manufactured pyramidal MN were exposed during the penetration evaluated by COMSOL Multiphysics simulations. In the simulations, the geometry of manufactured MN was used to capture more realistic results. The skin layers were chosen as hyperelastic Ogden models. The main reason behind using hyperelastic model for the skin was that the data obtained from indentation experiments fit better hyperelastic models compared to a linear model.^[28] The contact between the tip of the MN and skin layers was defined. The contact tip had a height of 125 μm . The reason for choosing this height was that stratum corneum and epidermis had a total height of 100 μm , and the contact between MN and these layers was desired to be examined.

Examining the penetration of the MN into stratum corneum and epidermis, it was observed that produced stresses at the MN tip displayed a linear trend, and did not exceed the yield strength of silicon. The maximum stress values at the MN tip were nearly 24 and 3.4 Pa for the stratum corneum and epidermis, respectively. These values were smaller compared to the yield strength of silicon. The MN tip could not undergo plastic and permanent deformation during the penetration. It indicated that the manufactured MNs were safe to use in real-life applications with no deformation and fracture.

The stresses at the stratum corneum and epidermis exceeded the chosen ultimate strength of 60 MPa during

penetration as shown in Figure 7. While penetrating the stratum corneum, the ultimate strength was obtained after nearly 2 s. For the epidermis, it took ≈ 0.2 s. These results demonstrated that the manufactured MN was able to deform the stratum corneum and epidermis. In other words, the manufactured MN tip could generate enough stress to pass the barriers of stratum corneum and reach epidermis or dermis to release the drug.^[58] Stresses at the contact surfaces were captured during different time steps, and they were found to be localized at small regions (Figure 8). It was hence concluded that the design of the MNs was effective such that it deformed limited regions during the penetration. Further, the maximum volumetric strain values were found for stratum corneum and epidermis, and the stress–strain curves were given in Figure S10, Supporting Information. Stratum corneum presented Ogden-model behavior as expected.

The last study performed on COMSOL Multiphysics was to evaluate the mechanical properties of the non-coated MNs by applying similar boundary conditions to the mechanical failure test experiments. Applying a continuous force from 0 to 18 N for 2160 s, a maximum of 31 μm displacement on non-coated MN tips was obtained. This was in accordance with the displacement value ($\approx 31 \mu\text{m}$) determined using the DMA (Figure 5). The relationship between force and displacement of non-coated MNs was found to be linear as obtained from experimental and simulation studies. The displacement results for this analysis are presented in Figure S11, Supporting Information.

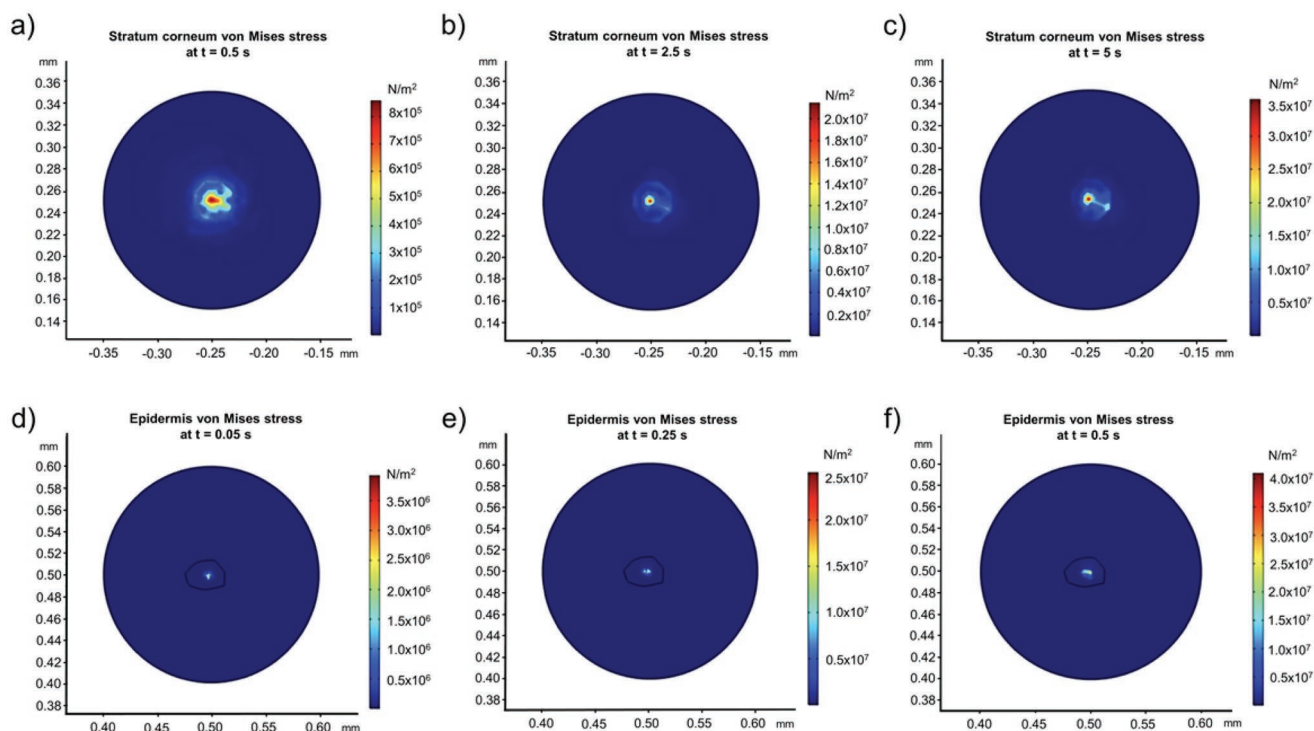


Figure 8. Maximum von Mises stress at stratum corneum contact surface for the contact study between MN tip and stratum corneum at a) $t = 0.5$ s, b) $t = 2.5$ s, c) 5 s and maximum von Mises stress at epidermis contact surface for the contact study between the MN tip and epidermis at d) $t = 0.05$ s, e) $t = 0.25$ s, and f) 0.5 s.

4. Conclusion

In the present study, we have demonstrated an isotropic dry etching process using XeF_2 to fabricate silicon-based solid MNs as a potential strategy in transdermal drug delivery. The photolithography and etching processes as well as CAD designs were optimized to customize the fabrication of MNs with desired geometry. The proposed study enabled us to achieve a very dense MNs in a single array (up to 1452 MNs cm^{-2}). In addition, the final MN shapes were easily controlled by modifying the photomask design. On the other hand, instability issues observed in the physisorption of photoresist on the silicon wafer due to the XeF_2 gas flow in the chamber were overcome by replacing photoresist with Si_3N_4 . Through this way, XeF_2 gas could be used more efficiently for a faster MN tip formation. Magnetron sputter coating of solid MNs with titanium and chromium improved their mechanical strength and surface properties such as roughness. Last, penetration ability of the MNs was evaluated on chicken and porcine skins as biological model to determine the highest depth achieved upon insertion.

Process optimization is especially essential in such micro-fabrication methods as high-cost materials are usually used especially during the photolithography process. A single 4" wafer has an average cost of \$40.00 and can be diced into ≈ 65 squares (\$0.6 per patch), each having an area of 1 cm^2 . Our study demonstrated that ten diced silicon wafers could be etched at the same time using XeF_2 pressure of 4 Torr in 500 cycles. According to the Equation (2), the amount of XeF_2 used during 1000 cycles for the simultaneous formation of 10 MN patches was ≈ 8 mg, which was equivalent to 50 mg to form 65 MN patches (1.3 mg per patch). The price of XeF_2 (solid form) in 2022 was estimated to be \$25 per gram. Ignoring the cost of a 5" mask, which can be repeatedly used for wafer design, the total cost for the fabrication of a single patch containing MN arrays with the properties given in Table S1, Supporting Information, was \$0.6325 (\$0.6 for wafer and \$0.0325 for XeF_2). Moreover, once any challenges such as early interruption of dry etching process were faced, there would be additional costs to be considered. For instance, periodic visualization of MN structures under the light microscope would help confirm the tip formation with designated geometry and dimensions, which is a standard procedure that would not significantly increase the total cost after all optimizations were completed for large manufacturing. Taken all together, the technique described here has enabled the fabrication of MNs with customizable shapes, array numbers and dimensions (length, height, and aspect ratio) and would be utilized for either epidermis and dermis targeting in pharmaceutical and cosmetic applications. Furthermore, the presented method demonstrates an advantage over the anisotropic etching process for being a one-step process with less operational and equipment cost.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceived the project and the main conceptual ideas: I.E. and F.I. *Conceived the microfabrication studies:* I.E. and A.K. *Performed mechanical and morphological analyses of microneedles:* I.E. *Performed simulation analysis:* M.B.G. *Contributed to the design of the simulation studies:* I.E., M.B.G., and F.I. All authors discussed the results and commented on the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

COMSOL stress analysis, dry etching, microfabrication, solid microneedles, transdermal delivery, xenon difluoride

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