



A high-precision method for manufacturing tunable solid microneedles using dicing saw and xenon difluoride-induced dry etching

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ABSTRACT

Numerous fabrication techniques have been employed to produce solid microneedles (MNs); yet precise manufacturing of MNs with adjustable features (height, aspect ratio, and array number) remains the main limitation. Developing tunable MNs holds immense promise for personalized and efficient drug delivery systems. In this study, we utilized a combination of dicing saw and XeF₂ isotropic dry etching processes to fabricate solid MNs with tunable characteristics. We herein created rectangular arrays using a dicing saw with desired geometry followed by dry etching to form MN arrays without further processing. Employing optimized parameters, the average heights of the MNs were $522 \pm 15 \mu\text{m}$, $614 \pm 42 \mu\text{m}$, and $698 \pm 22 \mu\text{m}$ for initial pattern depths of 500 μm , 600 μm , and 700 μm , respectively. Moreover, we achieved an aspect ratio as high as 3.7, a radius of curvature less than 10 μm , and a tip angle as low as 6.4° . The mechanical and surface properties of the MNs were enhanced through magnetron sputtering with titanium. An ex vivo penetration test conducted on porcine skin demonstrated the significant potential of these MNs for transdermal drug delivery in future investigations. Overall, a cost-effective production of a single solid MN patch, featuring 400 MN arrays per cm^2 , can be achieved within a remarkably short timeframe (approximately 2 h). Investigating fundamental principles, this study addresses the persistent challenge in manufacturing solid MNs with adjustable features, such as height, aspect ratio, and array number. This presents a substantial advantage over alternative fabrication techniques.

1. Introduction

Microneedle (MN) technology is an innovative tool with broad applications in transdermal drug delivery, an approach where drugs diffuse through the skin layers and join the bloodstream (Praisnitz and Langer, 2008). Herein, biomolecules can be easily and effectively administered or detected using MNs without inducing pain in the patient, providing rapid healing over the skin (Yilmaz et al., 2023). MNs – micron-sized needles typically measuring less than 1 mm – are hence extensively utilized in humans, as a note to mention that their reputation has already surpassed far beyond human use and reached out to agricultural products and foods by combining with sensing systems (Cao et al., 2022). There are different types of MNs, including solid, dissolving, and hollow versions, among which solid MN is the simplest form (Erdem et al., 2021). The typical usage of solid MNs involves opening holes on the skin surface in order to aid the absorption of drugs into the skin using "poke-and-patch" technique (Tariq et al., 2021). First and

foremost, solid MNs can be used as a template to generate dissolving MNs (Donnelly et al., 2012). by pouring polymeric solutions over the template, or their surface can be coated with a polymeric material to form coated MNs (Jiang et al., 2007), which have potential use in controlled drug delivery and biosensing applications. Hence, their fabrication will facilitate the transformation of such MN type into either coated or dissolving ones.

Geometrical aspects of MNs (i.e., height, aspect ratio, tip angle, and the radius of curvature) need to be carefully designed and mostly revisited relying on the application that takes into account these parameters for a more effective and precise treatment (Larraneta et al., 2016). For example, aspect ratio, radius of curvature, and tip angle of a MN determine stiffness and flexibility, therefore directly affecting the performance of MN-mediated drug delivery or sensing. MNs with small radius of curvature and tip angle will demand less force upon insertion into skin; however, they may be extremely prone to bending or breaking. On the contrary, MNs with higher radius and tip angle will need more

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force to be applied for a successful penetration into the skin (Gill et al., 2008). Both situations may generate discomfort and pain in the patients, hence their design parameters need to be defined, and accordingly, MNs would be fabricated (Caffarel-Salvador et al., 2021). Although state-of-the-art MNs have greatly boosted drug delivery or sensing efficacy, the paucity of cost-effective microfabrication techniques to produce MNs with desired features still needs to be resolved in unravelling its clinical fulfilment.

Various fabrication methods and a range of materials can be employed to attain the desired geometrical features of MNs (Krieger et al., 2019). As an example, 3D printing has frequently been utilized as a method for fabricating MNs (Han et al., 2020). Although 3D printing has advantages in MN fabrication, such as design flexibility, rapid prototyping, and the ability to create complex 3D structures, it faces limitations related to resolution constraints, material limitations for biocompatibility, surface roughness, and limited throughput, which need to be carefully considered when choosing this technology for specific MN applications (Ozyilmaz et al., 2021). Two-photon polymerization is another precise method for fabricating MNs with intricate designs; but it has limitations in terms of slow fabrication speed, specialized and expensive equipment requirements, and difficulties in scaling up for mass production (Faraji Rad et al., 2021). Similarly, laser micromachining (i.e., femtosecond lasers) crafts precise MNs with customization choices in a more throughput way, yet it faces restrictions such as higher setup costs and challenges in scaling for large-scale production (Trautmann et al., 2019). On the other hand, photolithography holds a central position in MN fabrication, serving as one of its fundamental pillars. While this technique boasts several merits, including remarkable precision, scalability, and design flexibility for creating MNs with high-resolution features, this technology continues to encounter challenges concerning equipment cost, material compatibility, complexity in creating 3D structures, and substrate limitations. This fabrication technique is often coupled to deep reactive ion etching (DRIE) or inductively coupled plasma reactive ion etching (ICP-RIE) systems, which are anisotropic etching processes with an etch rate much higher in the vertical direction than in the horizontal direction, leading to very high aspect ratios and smooth sidewalls (Roh et al., 2022). However, such equipment possesses very slow etching rate (Tanaka et al., 2001). It is noteworthy that SF_6 possesses a high global warming potential, making it a potent greenhouse gas; hence its use in DRIE systems is subject to regulation and environmental considerations (Rabie and Franck, 2018). Therefore, photolithography and DRIE- or ICP-free techniques that are effectively replaced with MEMS fabrication methods are essential for a more feasible MN production. Isotropic etching of silicon with xenon difluoride (XeF_2)—a powerful etchant, has been recently shown to be a cost-effective and rapid alternative to generate MNs with varying geometrical features (Eş et al., 2023). Although XeF_2 etching possesses lower operation cost and less fabrication steps, the produced MNs usually have low aspect ratio and height values when a silicon wafer is etched isotropically following photolithographic patterning and deposition processes (Eş et al., 2023). As an example, the highest height of MNs attained through this technique ranged from 300 to 350 μm , even when etching a silicon wafer with a thickness of 1000 μm . Conversely, this process can be drastically facilitated and accelerated by crafting deep microarrays using mechanical tools such as dicing saw. A dicing saw uses a high-speed spindle and a diamond blade to cut through the wafer with high precision and minimal damage to the surrounding material. The dicing saw can be programmed to cut the wafer into a variety of shapes and sizes. Overall, the combination of XeF_2 dry etching and dicing saw can be an alternative to SF_6 -assisted DRIE processes, this way, eliminating the need for sophisticated and high-cost methods dependent on photolithography, reducing the overall process time and cost.

In our work, we have presented an alternative strategy through a dicing saw technology to form microarrays with varying patterns and depths, thereby accelerating the etching process of XeF_2 to generate MNs

with a tunable aspect ratio in considerably shorter periods (≈ 2 h). With mutual combination of a dicing saw and XeF_2 isotropic etching, we were able to fabricate MNs (400 MN arrays/ cm^2) with aspect ratio and height reaching up to 3.7 and ~ 800 μm , respectively, and this was not possible to achieve employing the combination of photolithography and XeF_2 isotropic etching. The surface and morphological features of the MNs were comprehensively analyzed using 3D laser scanning and scanning electron microscope. Additionally, we have assessed penetration tests on porcine skins as a model mimicking human skin using titanium-coated MNs. The changes in displacement values upon applied static force (between 0 and 18 N) were further explored using a dynamic mechanical analyzer. We utilized Si_3N_4 thin layer as a protective layer on silicon wafer during isotropic etching process. Through the substitution of Si_3N_4 coating with epoxy, followed by its curing on the silicon wafer using a UV light source, we have achieved a reduction in cleanroom requirements for the process by eliminating the reliance on PECVD tool. Overall, the current study presents a new technique that has several advantages over photolithography-based fabrication of solid MNs (Eş et al., 2023), as well as other techniques such as laser micromachining (Trautmann et al., 2019), two-photon polymerization (Faraji Rad et al., 2021) and 3D printing (Krieger et al., 2019), making it a highly favorable option for MN fabrication. Firstly, it boasts a significantly higher throughput, allowing for the processing of more MN arrays in a shorter time frame. Additionally, it enables to produce customizable MNs in terms of geometry, height, aspect ratio, and MN array number, allowing precise tailoring for specific applications. Another notable advantage is the reduced tip angle, enhancing effectiveness and minimizing discomfort during usage. Moreover, the technique yields MNs with excellent surface properties, potentially leading to improved performance and longevity. Lastly, it is a rapid process, facilitating increased productivity and faster delivery to end-users, promoting widespread implementation of this technology.

2. Materials and methods

2.1. Materials

4-inch silicon wafers (prime grade with thicknesses of 500 and 1000 μm) were purchased from Adesis (Turkey). Isopropyl alcohol with a minimum purity of 99.5% was acquired from Isolab Laborgeräte GmbH (Eschau, Germany) and used for cleaning silicon wafers. The sputtering target for titanium coating in the magnetron sputtering system was obtained from Kurt J. Lesker (UK). Hexamethyldisilazane (HMDS) was purchased from TECHNIC (Rhode Island, USA). Epoxy-based negative photoresist (SU-8 2000) with the optical transmission above 360 nm was obtained from Kayaku Advanced Materials (Massachusetts, USA).

2.2. Microneedle fabrication

To fabricate solid MNs with tunable height and aspect ratio, a silicon wafer with a thickness of 1000 μm was first coated with a protective thin layer of silicon nitride (Si_3N_4) or epoxy-based negative photoresist. The desired patterns were formed on the wafer using a dicing saw tool, which was then followed by isotropic dry etching with XeF_2 . Fig. 1 displays the process involved in fabricating solid MNs.

2.2.1. Silicon nitride (Si_3N_4) deposition via plasma enhanced chemical vapor deposition (PECVD)

Initially, a 4-inch silicon wafer with the thickness of 1000 μm was diced into 1 cm^2 squares. Later on, a thin film with exceptional selectivity against XeF_2 gas was produced by depositing silicon nitride (Si_3N_4) onto the silicon wafer using plasma-enhanced chemical vapor deposition (PECVD). Si_3N_4 coating was conducted at 110 $^\circ\text{C}$ with 400 mTorr process pressure. %2 of SiH_4 in N_2 gas with a total pressure of 180 mTorr, and NH_3 with a total pressure of 45 mTorr were introduced into

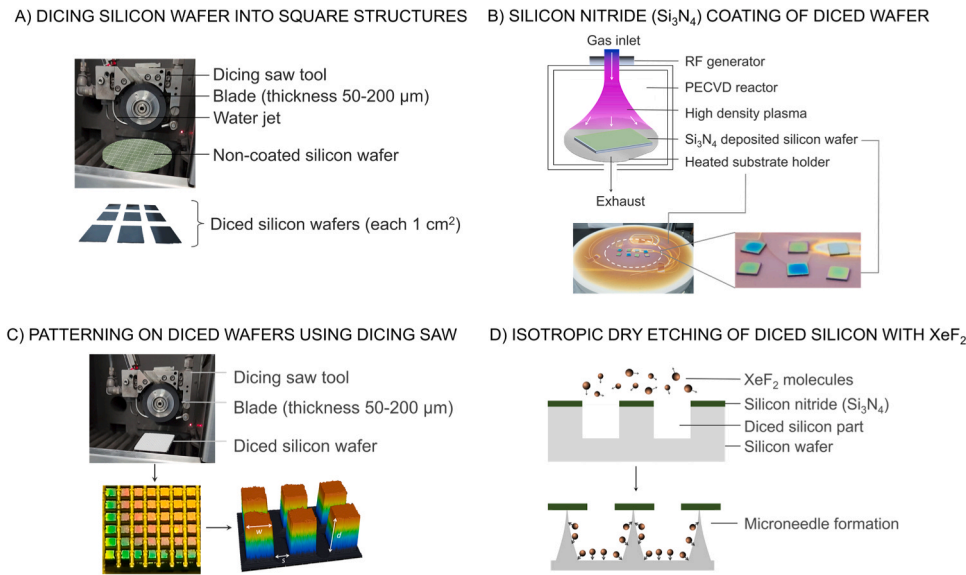


Fig. 1. Process design for MN fabrication using a combination of a dicing saw and isotropic dry etching: (A) Dicing silicon wafer into square structures (1 cm² each), (B) silicon nitride coating of diced square structures (including lateral coating), (C) patterning on diced wafers using dicing saw with varying depth and width, and (D) isotropic dry etching of diced silicon with XeF₂.

the chamber to form a Si₃N₄ thin film with a thickness of ~300 nm. Radio-frequency (RF) power was set to 100 W. After this process, the Si₃N₄-coated square pieces were removed from the reaction chamber and prepared for the mechanical patterning process in a dicing saw tool. Subsequently, the process was effectively substituted by employing epoxy coating.

2.2.2. Epoxy coating

As a separate process, silicon wafers were also coated with an epoxy material (as a replacement with Si₃N₄) to confirm whether it is effective in protecting MN tips during dry etching or not. Initially, the wafers were cleaned using an ultrasonic cleaner (Branson, Model 2510, USA), and the wafer was then coated with an epoxy material using a spin coater (WS-650MZ-23NPPB, Laurell Technologies Corp., USA). Once the coating process was completed, the epoxy was cured using a UV light source with a wavelength of 365 nm (EVG 620, EV Group, Austria) for 30 s with a UV dose of 60 mJ cm⁻². Subsequently, the wafers underwent additional processing using a dicing saw for patterning.

2.2.3. Mechanical patterning using the dicing saw process

Si₃N₄-coated or epoxy-coated silicon squares were patterned using a dicing saw equipment (DAD3220, Disco, Japan) equipped with a high-speed spindle and a thin diamond blade (with thicknesses of 100 and 200 µm). Each square was additionally attached to a double-sided tape to prevent random peeling off during the dicing process. The spindle revolution was set to 30,000 rpm. Working and tape thicknesses (dicing saw tape and double-sided tape together) were 1 mm and 0.1 mm (0.09 + 0.01 mm), respectively. Blade height values were 400, 500, and 600 µm to obtain a depth of 700, 600, and 500 µm, respectively. Y-index value was set to 0.5 mm, indicating the distance between the blade's center, generating the patterns on the surface of the silicon. Specific patterns with varying depth (blade height) and width (Y-index) were generated over the silicon wafer to accelerate XeF₂ etching efficiency. Each square was exposed to an infrared heat lamp (Philips) for 15 s to separate them from double-sided tapes easily. The defined process conditions were elaborated in Table 1.

2.2.4. Isotropic dry etching process

A XeF₂ dry etching tool (SPTS Technologies, UK) was employed to isotropically etch the diced silicon wafers to generate solid MNs. The

Table 1

Parameters for dicing saw process in generating the intended patterns on the silicon wafer.

Process parameters	Defined values
Work shape	Square
Work size	10 mm × 10 mm
Spindle revolution (rpm)	30,000
Work thickness (mm)	1
Dicing saw tape thickness (mm)	0.09
Double-sided tape thickness	0.01
Blade height (mm)	0.4, 0.5, or 0.6
Yindex (mm)	0.5
Feed speed (mm/s)	1
Blade thickness (mm)	0.2

Work shape and work size represent wafer's geometry and side length, respectively. Work thickness is total thickness of wafer, while blade height is the parameter defining the total depth of patterns opened on the wafer.

process parameters, including XeF₂ chamber pressure and silicon exposed area, were carefully calculated to determine the number of cycles required to generate solid MNs with the complete formation. The results were verified through periodic observation using a light microscope. No delay was added between each cycle, and N₂ pressure was set to zero. The equation from our prior study was employed to estimate the etch depth of the silicon wafer.

2.3. Structural analysis of microneedles

Periodic visualization of the tip formation was assessed under an optical microscope (Carl Zeiss, Heidelberg, Germany) equipped with Dino-lite digital camera. After Si₃N₄ thin layer or epoxy layer completely disappeared and once the sharp tips were formed, the dry etching process was interrupted, and the MNs were characterized. Morphological properties of the MNs were assessed with a field emission gun scanning electronic microscope (FEG-SEM) (FEI, Quanta-200, Netherlands) equipped with an EDAX system. The working distance and voltage were set to 5 mm and 5 keV, respectively. The structure of the MNs was explored using a 3D laser scanning microscope (VK-X100 and VHX-1000, Keyence, Osaka, Japan) with objective lenses of 20x and 200x. Similarly, the surface profile of the fabricated MNs was analyzed utilizing the same microscope (VK-X100). λ_s and λ_c cut-off values were

determined as 0.25 μm and 0.8 mm, respectively. JIS B 0601: 2001 (ISO 4287: 1997) standard was considered for this evaluation. λ_s is the short-wavelength cut-off, indicating the upper limit for evaluating fine surface details, set at 0.25 μm . On the other hand, λ_c is the long-wavelength cut-off, representing the lower limit for assessing overall surface variations, with a value of 0.8 mm. These cut-off values establish the range within which surface features, such as roughness, skewness, and kurtosis of silicon MNs, are systematically measured and characterized, ensuring a standardized and consistent evaluation.

2.4. Magnetron sputter coating of solid microneedles with titanium

Once solid MNs were formed, they were additionally coated ($\sim 1 \mu\text{m}$) with titanium (purity over 99.9%) to improve their roughness and tensile strength. The coating was carried out in a dual-target magnetron sputtering system (PVD-Handy, Vaksis, Turkey) using a titanium sputtering target. Process pressure was set to 7.5 mTorr. Argon plasma flow rate was 20 sccm, and the DC power source was 100 W.

2.5. Dynamic mechanical analyzer

Mechanical strength assets of solid MNs, particularly stress/strain curves and displacement values, were assessed with a dynamic mechanical analyzer (DMA Q800, TA Instruments, USA). Compression mode was selected without temperature control. The solid MNs were subjected to a static force ranging from 0 to 18 N, incrementing at a rate of 0.25 N per minute. Additionally, a preload force of 0.01 N was applied with a force track set at 125%.

2.6. Ex vivo penetration test on porcine skin

The required force to pierce the stratum corneum is impacted by the height and aspect ratio of the MNs. Therefore, the penetration efficiency of the solid MNs with varying height and aspect ratio was tested using porcine skin. The skin was purchased from a local butcher and was subjected to a rigorous sterilization process to ensure the elimination of any potential contaminants. The skin samples were first thoroughly rinsed with a sterile saline solution to remove surface debris. Subsequently, the samples were immersed in a 70% ethanol solution for 5 min, followed by a final rinse with sterile water to achieve complete sterilization. Using a scalpel, excess fats beneath the porcine skin were carefully removed. The porcine skin obtained from a pork belly was chopped into square shapes with a side length of approximately 15 mm. Each skin piece was then placed on the lower clamp of the mechanical analyzer. In the meantime, solid MN (10x10mm) was immobilized on the upper clamp with double-sided tape. A similar method as explained in the Section 2.5 (Dynamic mechanical analyzer) was employed to determine the penetration rate of the solid MNs. The pierced porcine skins were examined in further detail using a 3D laser scanning microscope.

2.7. Statistical analysis

We statistically analyzed the data using Violin-shaped Box-Whisker plots in Prism - GraphPad to evaluate the penetration rate of the MNs into porcine skin. Student's t-test was used in Origin Pro (v.9) to confirm the statistical difference between each MN height. The data was presented as the average of three repetitions. Comparisons with $p < 0.05$ were considered significantly different. In all figures, the error bars represent the standard deviation values.

3. Results and discussion

In the present study, the combination of dicing saw and dry etching was employed as a photolithography-free approach to fabricate solid MNs with tunable features, including height, aspect ratio, and array

number. Process conditions of a dicing saw (width, depth, and array tip length) and isotropic dry etching (cycle time, chamber pressure, and etching time) were optimized to fabricate solid MNs with a sharp tip and desired length. The penetration efficiency of each solid MN was evaluated using porcine skin.

3.1. Dicing process for mechanical patterning of silicon wafer

A 4-inch silicon wafer with 1000 μm thickness was diced into 1 cm^2 square patches. A thin Si_3N_4 layer ($\sim 300 \text{ nm}$) was deposited on each patch prior to the patterning process. Si_3N_4 coating, as an etch-stop mask, was employed, because it provided excellent chemical resistance and mechanical durability during etching processes, making it ideal for protecting the underlying material (in our case, silicon) from the chemical attack of XeF_2 gas (Manginell et al., 1998). Additionally, Si_3N_4 was expected to provide a low-friction, non-stick surface that prevents unwanted adhesion of XeF_2 etchant (Sun et al., 2023). Despite the advantages of thin layer coating over silicon wafers with Si_3N_4 , it also has disadvantages, such as the requirement for specialized PECVD tools and a controlled cleanroom environment, which adds complexity and cost to the fabrication process. To address this issue, we further coated an epoxy layer over the silicon wafer to dice the wafers. After coating silicon patches with either Si_3N_4 or epoxy, microarrays with desired depth (d), width (w), and space (s) were generated using a dicing saw tool (Fig. 2A). After the dicing process, we observed slight differences between the projected and the resultant geometrical values due to the variations in blade efficiency. While we projected to have 500, 600, and 700 μm in depth (d_p), the obtained depths (d_o) were 489 ± 2 , 589 ± 3 , and $690 \pm 1 \mu\text{m}$, respectively. Differences in depth values were comparable to the intended values. Similarly, the width values (w_o) were $\sim 6\%$ less than the ones projected. The distance between each microarray (s_p) was obtained to be $\sim 180 \mu\text{m}$ ($\sim 10\%$ less than projected value). This value mainly depends on the thickness of the blade. In our process, we utilized a blade with the thickness of 200 μm . Each patch had approximately 400 microarrays after dicing process under the defined parameters. Adjusting these parameters, one can obtain MN arrays with desired properties and number. For instance, when we decreased w value from 300 to 200, the number of MN arrays per patch increased from 400 (20×20) to 625 (25×25). Similar results could be obtained by decreasing the distance (s) between each MN array. To manipulate s value, a blade with different thickness should be used. Overall, altering these parameters directly impacts the dry etching conditions, such as the etching time required to form MNs. Post-dicing results demonstrate that our system can be replaced with DRIE process as the tilt angle (θ) was 93° , which was close to a perfect microarray structure (90°).

In terms of MN array number, the dicing saw offers a significantly higher throughput over other techniques including 3D printing and two-photon polymerization, allowing for the processing of larger quantities of MNs in a shorter timeframe compared to laser machining. Rapid and efficient production of MNs facilitates increased productivity and accelerated delivery to end-users, thereby promoting widespread implementation and accessibility of this cutting-edge technology. Despite these advantages, our fabrication method has potential drawbacks to consider. A potential limitation of our method is the necessity for optimization to attain the desired MN characteristics, as variations in parameters may influence the final product. Moreover, the reliance on mechanical tools such as the dicing saw introduces the prospect of tool wear, which has the potential to impact precision over time. To address these challenges, careful consideration and fine-tuning of parameters throughout the process are imperative to mitigate drawbacks and guarantee consistent and reliable MN production.

The reproducibility of MNs in our method is a key focus. Once the dicing saw process is optimized with well-defined parameters, each batch of MNs shows consistent outcomes. Statistical analysis reveals no significant differences between batches, affirming uniformity ($n = 5$,

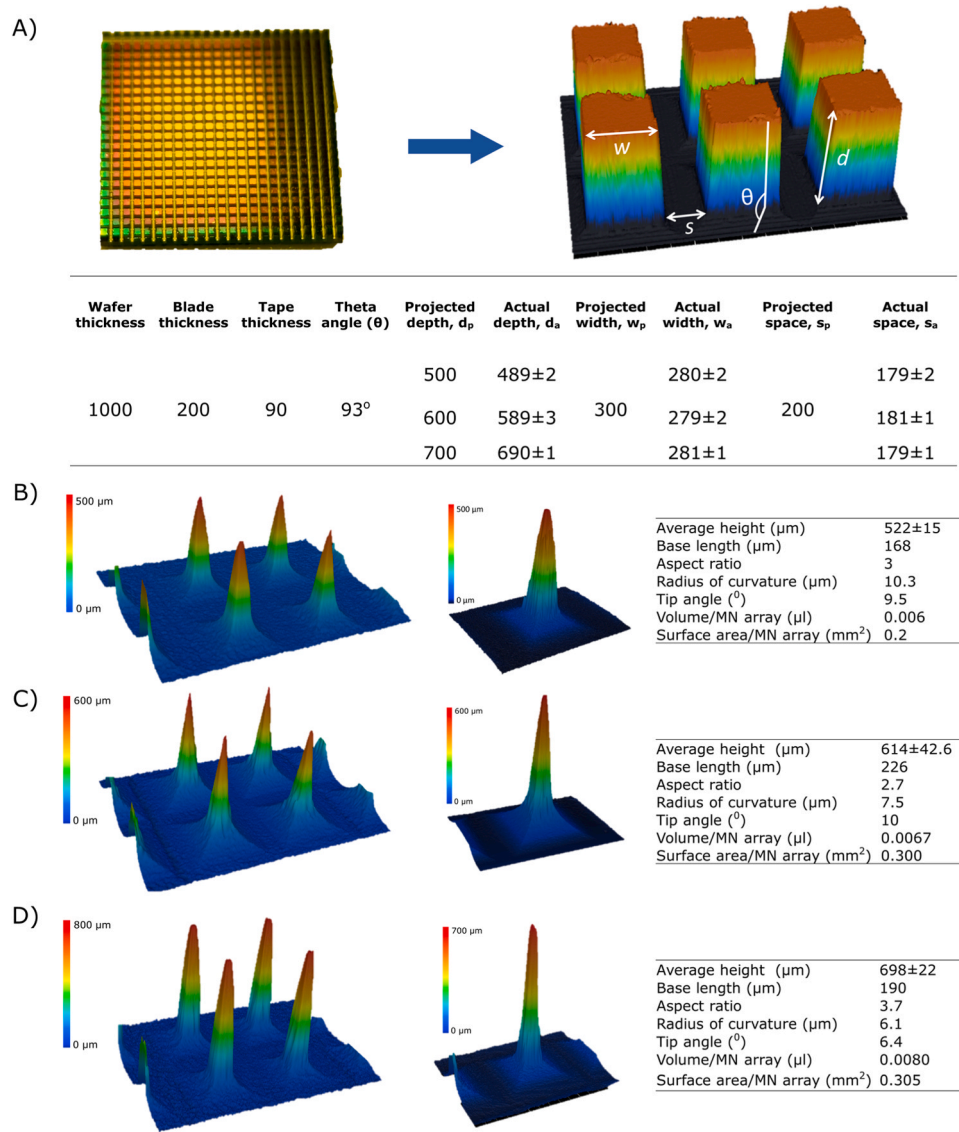


Fig. 2. (A) The parameters set to create patterns on each Si_3N_4 -coated silicon wafer. The values shown for wafer, blade, and tape thickness as well as depth, width, and space values are in μm . (B-D) 3D laser scanning microscope images of the MNs with diverse structural characteristics. The characteristics of the MNs with depth of (B) 500 μm , (C) 600 μm , and (D) 700 μm . The distance between the tips of each MN is approximately 500 μm . Average height was calculated by measuring 6×6 MN arrays (total of 36) at the center of the silicon wafer. Average height of each MN was statistically different.

$p > 0.05$). Ongoing exploration and adjustment of these parameters are essential for maintaining strict control over the variables, ensuring dependable and reproducible MN fabrication. This continuous optimization ensures that each batch of MNs adheres closely to defined specifications, reinforcing the reliability of our fabrication process.

3.2. Effect of dry etching on microneedle formation

After forming patterns with the desired features on the silicon patch, silicon samples were isotropically etched using XeF_2 ions. We have observed that the time required to form MNs with the desired features was closely associated with parameters used in dicing saw tool, which needed a different XeF_2 pressure, etching time, and cycle parameter. When we fixed XeF_2 pressure as 4 Torr and etching time as 90 s, we observed that cycle number was directly affected by depth, width, and space values as stated in Fig. 2A. In our study, we have completed optimization studies for array depth of 500, 600, and 700 μm , width of 300 μm , and distance of 200 μm . The distance between each MN array was constant as we used a dicing saw blade with a thickness of 200 μm .

Keeping the width value constant at 300 μm , we varied depth between 500, 600, and 700 μm .

The number of cycles required to form MNs with sharp tips was 85, 95, and 125 cycles per 1 cm^2 patch for the depth of 500, 600, and 700 μm , respectively. According to the Eq. 1 (Eş et al., 2023), the cycle number is directly proportional to the silicon exposed area (A_{exposed}). There was a 48 mm^2 difference in A_{exposed} between each MN patch with the depth of 500, 600, and 700 μm ($A_{\text{exposed } 700} > A_{\text{exposed } 600} > A_{\text{exposed } 500}$). The theoretical ratio for $\frac{\text{Cycle number } 600}{\text{Cycle number } 500}$ and $\frac{\text{Cycle number } 700}{\text{Cycle number } 600}$ was approximately 1.2, which was in accordance with our experimental findings. Decreasing width of each MN array from 300 μm to 200 μm resulted in faster formation of MNs with sharp tips. This issue is associated with the basic mechanism of XeF_2 etching. Vertical etching rate is usually dominant in anisotropic etching processes. However, as observed in our experiment, XeF_2 etching rate at the MN tip is higher than etching rate at lower parts; hence, MNs with bigger projected width (for example, 300 μm) will require longer etching periods due to the larger silicon area available for horizontal etching. Similar to the width, distance between each MN array has a great impact on etching time.

Reducing this distance will eventually diminish the silicon exposed area, leading to faster formation of MNs. On top of that, the number of MN per patch will increase as more MN arrays can be formed.

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

Using the parameters shown in Fig. 2A, we have structurally analyzed the fabricated MNs after isotropic etching. 3D laser scanning microscopy confirmed that average MN height was very similar to the projected values. The average heights were 522 ± 15 , 614 ± 42 , and $698 \pm 22 \mu\text{m}$ for the projected values of 500, 600, and 700 μm , respectively (Fig. 2B-D).

On the other hand, aspect ratio is a critical parameter in MNs as it affects the performance of the MNs in several ways. Aspect ratio is the ratio of the MN height to its width, and it enables to determine MN's strength, stiffness, and flexibility (Gittard et al., 2013). Moreover, it is associated with pain sensation during insertion into the skin (Gill et al., 2008). As previously demonstrated by Caffarel-Salvador et al., 2021, a MN with higher aspect ratio will penetrate deeper into the skin; however its penetration will require more force to insert, potentially increasing pain and discomfort for the patient (Caffarel-Salvador et al., 2021). Instead, a MN with lower aspect ratio will be less painful; but it may not penetrate the skin deep enough to reach the desired region. In this study, aspect ratios were found to be 3, 2.7, and 3.7 for MNs with the depth of 500, 600, and 700 μm , respectively. Considering the fact that stratum corneum, epidermis, and dermis layers of the skin had an average thickness of 20, 100–300, and 600–3000 μm , respectively (Li et al., 2019), the fabricated MNs had enough aspect ratio to penetrate into dermis layer. The aspect ratios achieved in our study were similar to those reported in previous studies, such as 3D printing with aspect ratios ranging from 3:1 to 5:1 (Krieger et al., 2019); or two-photon polymerization with aspect ratio as high as 5:1 (Faraji Rad et al., 2021). Nonetheless, our fabrication technique demonstrated a higher throughput in terms of MN array number than these studies with faster fabrication time.

The radius of curvature and tip angle of a MN are the other vital parameters to be carefully optimized as they determine how sharp MN tips are. MNs with smaller radius and tip angle will require less force for skin penetration; yet, they may also be more fragile and prone to bending or breaking during insertion. Larger values will lead to MNs with blunter tip, which requires more force to penetrate. Such MNs will also cause discomfort and pain for the patient. Radius of curvature and tip angle were $10.3 \mu\text{m} - 9.5^\circ$ for 500 μm , $7.5 \mu\text{m}$ and 10° for 600 μm , and $6.1 \mu\text{m}$ and 6.4° for 700 μm depth, which confirmed that our MNs were highly sharp. For instance, dicing saw-assisted manufacturing technique surpasses 3D printing in this context as it is more challenging to achieve such reduced tip angles with 3D printing.

We also calculated the surface area and volume of a single MN. Volume and surface area of a single MN were $0.0060 \mu\text{L}$ and 0.2 mm^2 for 500 μm , $0.0067 \mu\text{L}$ and 0.3 mm^2 for 600 μm , and $0.0080 \mu\text{L}$ and 0.305 mm^2 for 800 μm of depth (Fig. 2B-D). Additionally, increasing MN aspect ratio resulted in a more surface area per MN as expected. Each single MN array had between 0.006 and 0.008 μL of volume capacity. These parameters are able to affect the amount of drug that is delivered into the skin. For instance, if the volume of the MN array is too low, insufficient amounts of the drug may be delivered to the desired depth in the skin. Increasing volume capacity will allow a better control over drug loading and delivery. As an example, an earlier study has reported that MNs with $0.00012 \mu\text{L}/\text{MN}$ array were considered small, while 0.00096 – $0.0032 \mu\text{L}/\text{MN}$ array and 0.00096 – $0.0032 \mu\text{L}/\text{MN}$ array were considered intermediate and large volumes, respectively (Pearson et al., 2015). Solid MNs fabricated in this study can be categorized as “very large” as the smallest volume of our MNs was twice the volume of a MN array ($0.0032 \mu\text{L}/\text{MN}$ array). Overall, our method excels in customizing

MN arrays, enabling the fabrication of patches with hundreds of MNs. This distinctive capability, combined with the precise control over surface features, accentuates the potential for increased drug loading efficiency compared to alternative techniques.

Wafer thickness is the main parameter that impacts the maximum MN height that can be achieved using dicing saw followed by dry etching. Initially, we have a silicon wafer with the thickness of 500 μm to dice it to form MNs. We later varied the space between each MN array from 100 to 200 μm while dicing a depth of 200 and 300 μm on the wafer. Per the SEM and 3D laser scanning microscope images, MNs with lower aspect ratio less than 1 were obtained (Fig. S1). The formation of MN tips during dry etching process was shown in Fig. S2. To obtain MNs with higher aspect ratio, it was required to use a silicon wafer with the thickness of 1000 μm (Fig. 3A-C). Variations observed in the MN tips illustrated in Fig. 3 result from the sequential fabrication steps involving dicing saw blade cutting and subsequent XeF_2 dry etching. The initiation of tip formation occurs during this multi-step process. It is imperative to perform periodic examinations using a light microscope to monitor the evolution of tip structures, as variations may arise due to influencing factors like fluctuations in temperature affecting the etching rate within the system during sublimation process of solid XeF_2 into the gas phase. Although there might be minor irregularities in tip diameter, their overall impact is not statistically significant. To address this, continuous monitoring of process parameters is essential to maintain consistent pressure and temperature conditions of the XeF_2 system, thereby contributing to the enhancement of uniformity in MN tips. With such a tool, besides pyramidal structures (four-sided), solid MNs with varying geometries (i.e., tetrahedron as a three-sided structure) can also be fabricated (data not shown). However, in theory, it takes a little bit longer to create structures such as tetrahedron using dicing saw as the blade must pass over the wafer more than twice (Fig. S3). This demonstrates that our proposed technique has potential to flexibly create solid MNs not only in terms of height and aspect ratio, but also geometry.

Typically, Si_3N_4 coating is carried out in a cleanroom using the sophisticated process of PECVD. Nevertheless, it is possible to substitute Si_3N_4 -coating with alternative materials to form a protective layer over silicon for XeF_2 dry etching. In this manner, we coated the surface of silicone with epoxy and cured it using a simple UV light source. Subsequently, we conducted experiments on both epoxy-coated silicon and Si_3N_4 -coated silicon wafers, and then compared the results. According to the data presented in Fig. S4, XeF_2 exhibited notable selectivity against epoxy, and there was no significant difference observed in the final MN heights between Si_3N_4 - and epoxy-coated silicon etching.

The surface properties of a MN—particularly roughness, can significantly affect its ability to penetrate the skin and deliver drugs (Zvezdin et al., 2020). Roughness is the presence of surface irregularities on the MN. In general, roughness increases the friction between the MN and the skin, causing resistance during the penetration. Roughness can also impact on the amount and rate of drug delivery (Pradeep Narayanan and Raghavan, 2017). For example, a surface with certain roughness level can potentially increase the effective surface area of a MN (Buckwalter et al., 1982); hence increasing the amount of drug that can be coated onto the MN. Higher roughness values can lead to the drug to become trapped in the surface of irregularities, negatively impacting on the amount of drug that can be delivered. Additionally, MNs with rough surface can increase the shear stress between the MN and skin (Ali and Sen, 2018), potentially leading to tissue damage. Hence, roughness can be controlled by altering etching conditions or post-processing techniques of silicon MN. The roughness mostly depends on the parameters used in etching process. The study conducted by Pandey and Pandey, 2019 demonstrated that roughness values of unpolished and polished silicon wafer were previously measured as 0.22 μm and 0.011 μm , respectively (Pandey and Pandey, 2019). Although a polished silicon wafer was used in our study, after etching process, the polished side was lifted off and with further XeF_2 bombardment, and accordingly, the

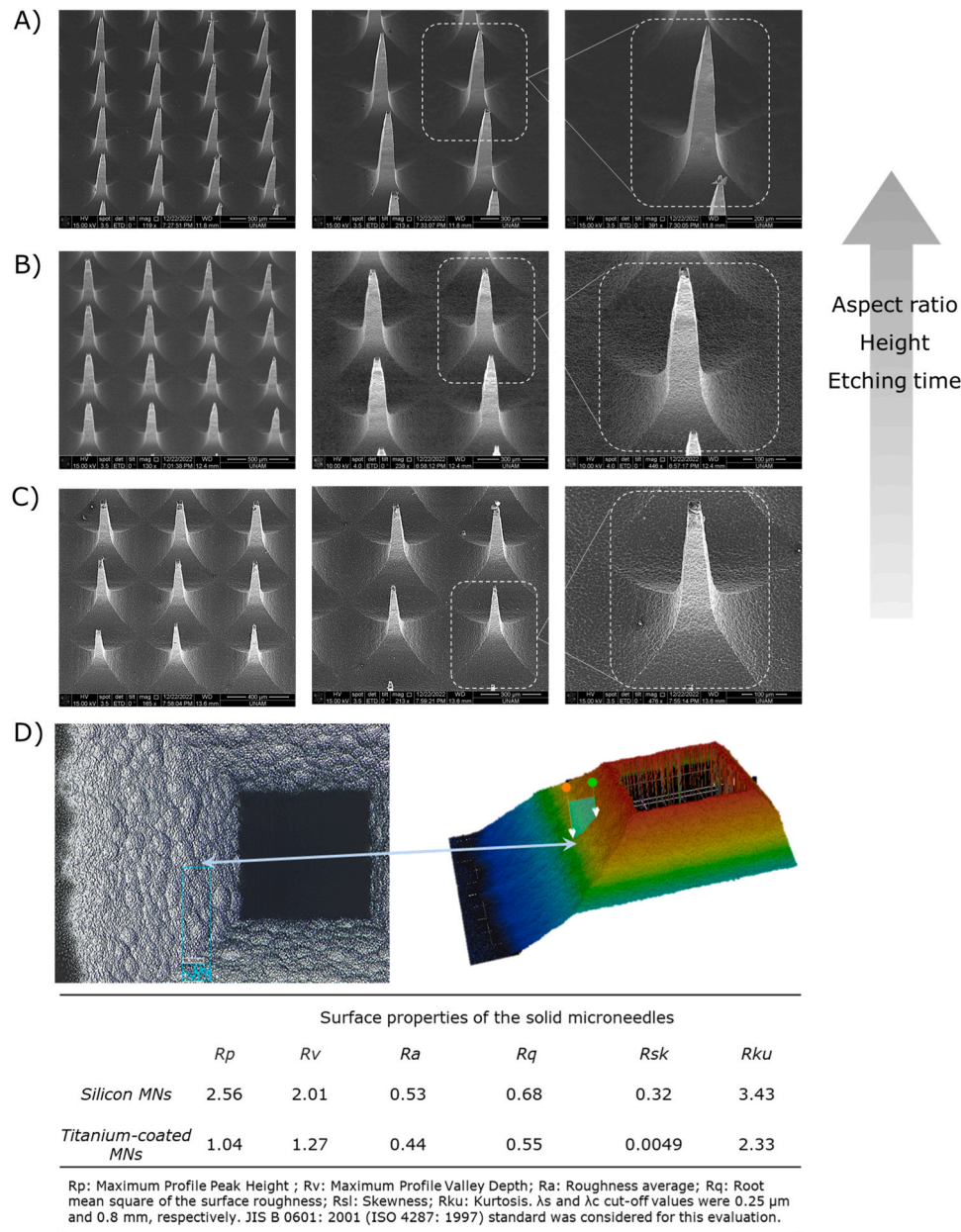


Fig. 3. Scanning electron microscope images of the fabricated MNs with the depth of (A) 700, (B) 600, and (C) 500 μm . The arrow represents higher values in aspect ratio, height, and etching time. (D) Surface properties of the silicon and titanium-coated solid MNs after dry etching process using XeF_2 .

roughness was expected to increase. Herein, the roughness of MNs was 0.53 μm at the end of dry etching process (Fig. 3D). The roughness caused by XeF_2 molecules also depends on the temperature of the etching system as XeF_2 is naturally in solid phase, and XeF_2 molecules are generated upon sublimation. Variations in temperature may result in different molecule size, which directly influences the etching efficiency.

Table 2
The difference between two mask layers used in MN fabrication.

Protective layer	Si_3N_4	Epoxy-based negative photoresist (SU-8 2000)
Coating technique	PECVD	Spin coating or drop casting
Process time of coating	1 h	15 min
Required equipment	PECVD, Dicing saw	UV source, Dicing saw
Surface roughness	0.53 μm	0.71 μm

The choice of protective layer material, whether PECVD Si_3N_4 or epoxy, does not significantly impact the final surface roughness of the MNs (Table 2). The XeF_2 dry etching process, coupled with the properties of silicon, primarily determines the surface characteristics. As both PECVD Si_3N_4 and epoxy serve as inert protective layers during the etching process, we expect similar surface properties in the finished product. Therefore, any variations in surface characteristics between these protective layer materials are anticipated to be minimal, with the overarching influence on the final surface features attributed to the XeF_2 etching and the intrinsic nature of silicon. Another determinant influencing surface quality could be the additional coating of the silicon MNs with another material to improve the quality of the surface properties. Therefore, we have also coated MNs with a thin film of titanium to improve surface properties. Titanium-coated MNs had a roughness of 0.44 μm (a decrease of 20%). Improvement in roughness upon titanium coating has been previously reported in the literature (Eş et al., 2023).

Our proposed method, employing a dicing saw followed by isotropic

etching, offers distinct advantages over a wide range of techniques. As an example, unlike photolithography, which involves complex mask alignment and multiple processing steps, our method facilitates the fabrication process, reducing both time and resource requirements. Compared to the previous study involving photolithography and isotropic etching (Eş et al., 2023), our method using the same 1000 μm thick silicon wafer achieved better outcomes. We achieved MNs with higher height values (up to 700 μm) compared to the previous study (~ 300 μm in height), enhancing their effectiveness. While maintaining the same number of MN arrays per patch, our process proved faster by eliminating complex steps like mask writing (mask design, writing, and developing steps) (several hours to days depending on the mask complexity), photoresist coating, and UV processing (roughly 3 h). This method not only accelerated MN production, but also reduced resource requirements (photoresists, mask aligner, UV aligner, yellow room, spin coater etc.), highlighting the efficiency of our approach. On the other hand, DRIE, coupled with photolithography, can yield MNs with high aspect ratios (up to 25) and minimal tip diameters as shown in a previous study (Roh et al., 2022). The versatility of this technique allows for easy adjustment of the MN array number (625 MN mm^{-2}) by manipulating the mask. However, it has been reported that the DRIE process is notably slow (Xu et al., 2017), impacting overall fabrication speed and efficiency, and also, photolithography step is required prior to etching step. Stereolithography, as an additive technique, offers a cost-effective approach for producing MNs with high aspect ratios (up to 5) (Krieger et al., 2019). However, customization is necessary based on the resin material used, and printing and post-processing steps, including washing, curing, and polishing, are required and can be time-consuming (roughly 4–5 h for printing and 1–2 h for post-processing) (Ngo et al., 2018). Despite the affordability, low-cost 3D printers typically have limitations in throughput, with studies commonly demonstrating MN patches with a low number of arrays (i.e., 5×5 arrays) (Wu et al., 2021). Two/multi-photon polymerization, as another additive approach, offers the advantage of producing MNs with extremely fine surfaces, small features, and desirable shapes (Rad et al., 2021). However, the associated equipment can be costly, with prices reaching up to 1 million USD. Moreover, the process is highly time-consuming (sometimes over 24 h) and limited to specific resins, which may restrict its versatility and accessibility (Ligon et al., 2017). Laser processing stands out for its potential high throughput and ability to fabricate MNs with desired aspect ratios using a variety of materials such as metals, ceramics or plastics including acrylic or polycarbonate. However, it comes with

challenges, such as surface property dependency on the laser beam spot size, making precise control of surface roughness challenging. It has been shown that each MN array varied in size on the same patch (Tu and Chung, 2016). Additionally, laser processing is recognized for its potential cost-effectiveness (as low as 1000 USD) and often eliminates the need for post-processing. However, achieving enhanced surface properties often demands the use of specialized equipment such as nano-second, UV or femtosecond lasers (Trautmann et al., 2019). Yet, these tools are quite expensive (over 200,000 USD) and take more time for processing (several hours), affecting efficiency and cost-effectiveness. In summary, our technique, despite some drawbacks, proves to be an effective tool in MN fabrication, particularly in terms of high-throughput production. Table 3 demonstrates the comparative study between our study and other reported techniques on MN fabrication.

3.3. Mechanical strength analysis

The mechanical strength of solid MNs is a critical factor in determining their effectiveness and longevity. This feature is determined by several factors, including their height, aspect ratio, shape, and material properties. Additionally, MN's strength can be characterized by its bending stiffness—a measure of how much force is required to bend the MN tips. We have further coated silicon MNs with pure titanium to improve their tensile strength, hardness, as well as corrosion resistance. Titanium was expected to be close to 100% (wt%) in the energy dispersive X-ray (EDAX) analysis; however, the recipe we used for titanium coating resulted in $\approx 83\%$ (wt%) coating efficiency (Fig. 4A). The total number of MN arrays was 400 per patch. The total force was distributed to 400 MN arrays to determine the static force applied over a single MN. Each MN was subjected to constant static force varied from 0 to 18 N. Displacement value is the difference between the height of a MN array before and after compression. According to the findings obtained from DMA, MNs showed different bending resistance. Silicon MNs with the height of 500, 600, and 700 μm showed displacement values of approximately 40, 30, and 35 μm , respectively (Fig. 4B). The height of silicon MNs did not affect the displacement. On the other hand, titanium-coated MNs had a displacement of 30, 20, and 60 μm for the MNs of 500, 600, and 700 μm height. Comparing the MNs with 500 μm height, titanium-coated MNs were more resistant against bending while the titanium-coated MNs with 700 μm height exhibited less bending resistance (≈ 20 μm more displacement). Among all tested MNs, silicon and titanium-coated MNs with 600 μm of height demonstrated the most

Table 3
Comparison of our technique with the other techniques in MN fabrication efficiency.

Fabrication Method	Material	Microneedle Features	Advantages	Drawbacks	Reference
Photolithography followed by isotropic dry etching	Silicon	Max height < 300 μm , Aspect ratio < 1, $5 \mu\text{m}$ < Radius of curvature < 15 μm	Precision, High aspect ratios	Complex mask alignment, Multiple processing steps (mask writing, mask alignment, photoresist spin-coating, etc.)	(Eş et al., 2023)
Photolithography followed by DRIE	Silicon	High aspect ratios (up to 25), High MN density (625 MNs mm^{-2}), MN height < 200 μm	Versatile, adjustable MN array number	Slower process, Complex processing steps	(Roh et al., 2022)
Stereolithography	Resins	Aspect ratio up to 5, $20 \mu\text{m}$ < Radius of curvature < 40 μm , $200 \mu\text{m}$ < MN height < 3000 μm , Low density (25 MN per patch)	Customizable, Very low cost	Time-consuming post-processing, Requirement of customized material and 3D printer, Rough surface	(Krieger et al., 2019)
Two-photon polymerization	Photosensitive resin	Low MN density (9 MN per patch), MN height up to 1000 μm , Aspect ratio < 4.	Extremely fine surfaces, Very tiny features with high-resolution	Costly equipment, Time-consuming, Limited material variety	(Rad et al., 2021)
Laser processing	PMMA	$645 < \text{MN height} < 1185 \mu\text{m}$, Aspect ratio < 3	Versatile material use, Potential cost-effectiveness	Surface property dependency, Variations in size	(Tu and Chung, 2016)
Femtosecond laser	PMMA	Low MN density (25 MN per patch)	High precision, Fine details, Allowing complex structures	Equipment cost, Time-consuming	(Trautmann et al., 2019)
Dicing saw followed by isotropic dry etching	Silicon	MN height up to 700 μm , Aspect ratio up to 4	Streamlined process, Reduced time and resources Adjustable MN feature	Optimization of dicing saw parameters, Possibly blade can be broken if used by non-experienced user.	This study

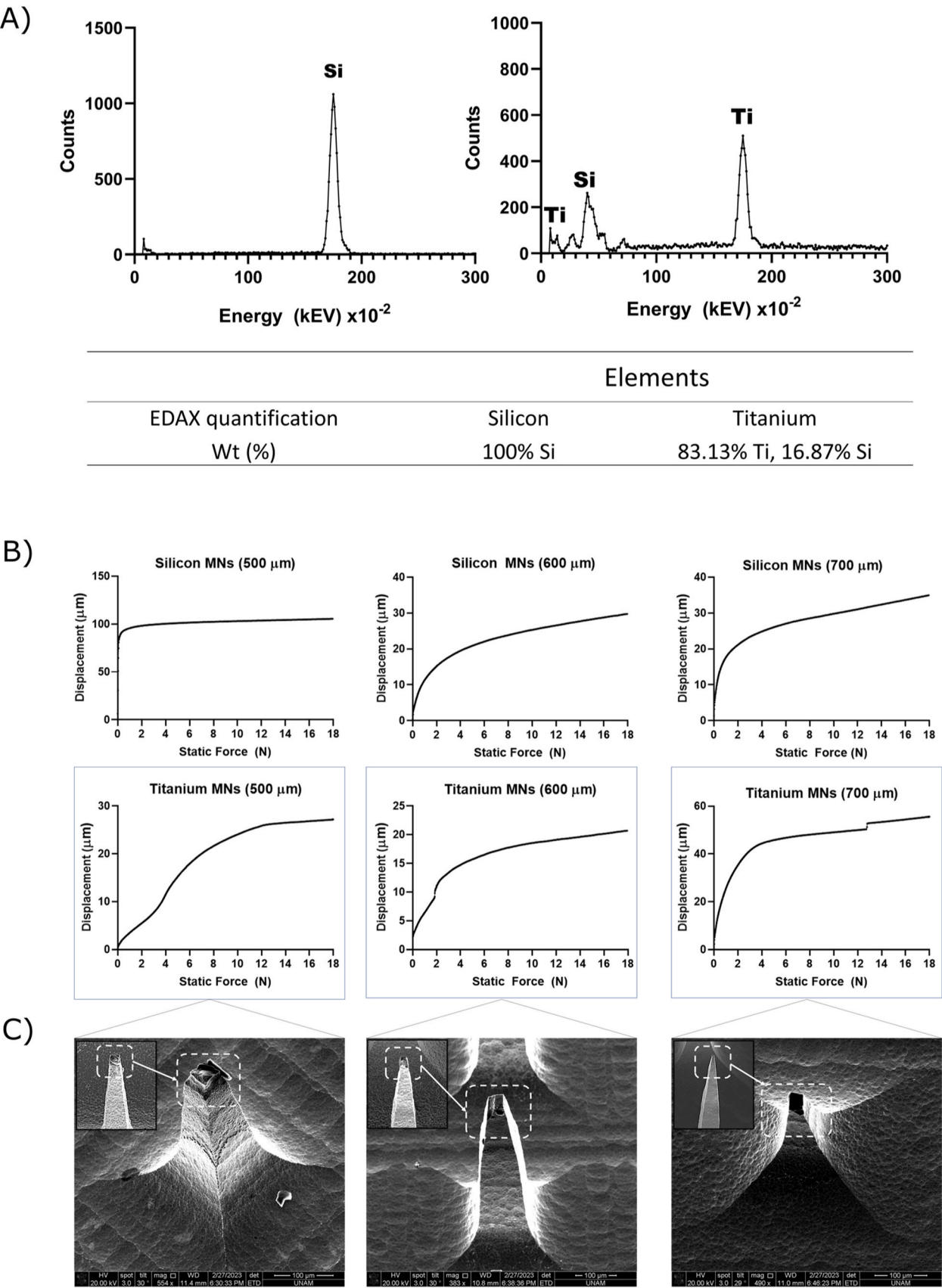


Fig. 4. (A) EDAX data for silicon and titanium-coated MNs. (B) The change in displacement of MN tips (silicon and titanium-coated MNs) against static force up to 18 N. (C) The SEM images of the MN tips after DMA process. The inset SEM images on the top left corner display the MN tips before the mechanical compression analysis.

mechanical strength against the bending. This height can be a critical value, above which MNs become sensitive to the force due to the high aspect ratios. The SEM images before and after dynamic mechanical analyzer were shown in Fig. 4C.

3.4. Ex vivo penetration test on porcine skin

The penetration efficiency of silicon and titanium-coated solid MNs was tested *ex vivo* using porcine skin, which was selected due to its structural and mechanical similarity with human skin (Summerfield et al., 2015). The insertion of solid MNs into the porcine skin was performed using a DMA to control the applied force. Per the findings as shown in Fig. 5 and Fig. S5, the penetration depth of each MN type was between 100 and 200 μm . For silicon MNs, the effect of MN height over skin penetration was not found to be statistically significant ($n = 6$, $p > 0.05$). Similar findings were obtained with titanium-coated MNs. Interestingly, titanium-coated MNs with 700 μm height could penetrate less than the other MNs. For all MN types, overall penetration depth was between 20% and 30%. This is probably attributed to the structural characteristics of porcine skin. Previous studies also confirmed our findings as they indicated a successful penetration rate between 12% and 50% (Jiang and Lillehoj, 2020).

While our fabrication method presents notable advantages, concerns regarding potential itching or other side effects upon administration should be taken into consideration. To address this point, a skin-friendly polymer coating can be applied onto the MNs, and this coating enhances biocompatibility, reducing the risk of irritation and creating a smoother,

more skin-friendly surface. Moreover, these fabricated MNs can serve as templates for soft lithography, enabling the production of polymeric MNs with enhanced skin friendliness and biocompatibility. This approach enhances the versatility of our method, allowing for MN designs that prioritize patient comfort and minimize potential adverse reactions. Additionally, upon administration, potential side effects of MNs may include redness, swelling or mild irritation (Bal et al., 2008). To eliminate these consequences, additional strategies beyond polymer coating can be implemented. Incorporating anti-inflammatory agents or utilizing biocompatible materials with minimal reactivity can help minimize adverse reactions (Lin et al., 2023).

Furthermore, optimizing the MN design, such as reducing the needle length or adjusting the insertion depth, can contribute to a more comfortable and less irritating experience from the perspective of physical parameters. In expanding on the mechanical properties of the fabricated MNs, it is essential to explore key parameters that significantly influence their performance during skin penetration. Factors such as flexibility, strength, and sharpness play pivotal roles in determining the efficacy of MNs in successfully penetrating the skin for drug delivery. The flexibility of the MNs is crucial as it enables them to adapt to the contours of the skin, ensuring optimal contact and penetration. Simultaneously, adequate strength is imperative to withstand the forces exerted during insertion without compromising structural integrity. Sharpness is another critical aspect, influencing the ease with which the MNs traverse the skin layers. A delicate balance between these mechanical characteristics is necessary to achieve efficient skin penetration, ensuring that the MNs effectively deliver drugs to the targeted

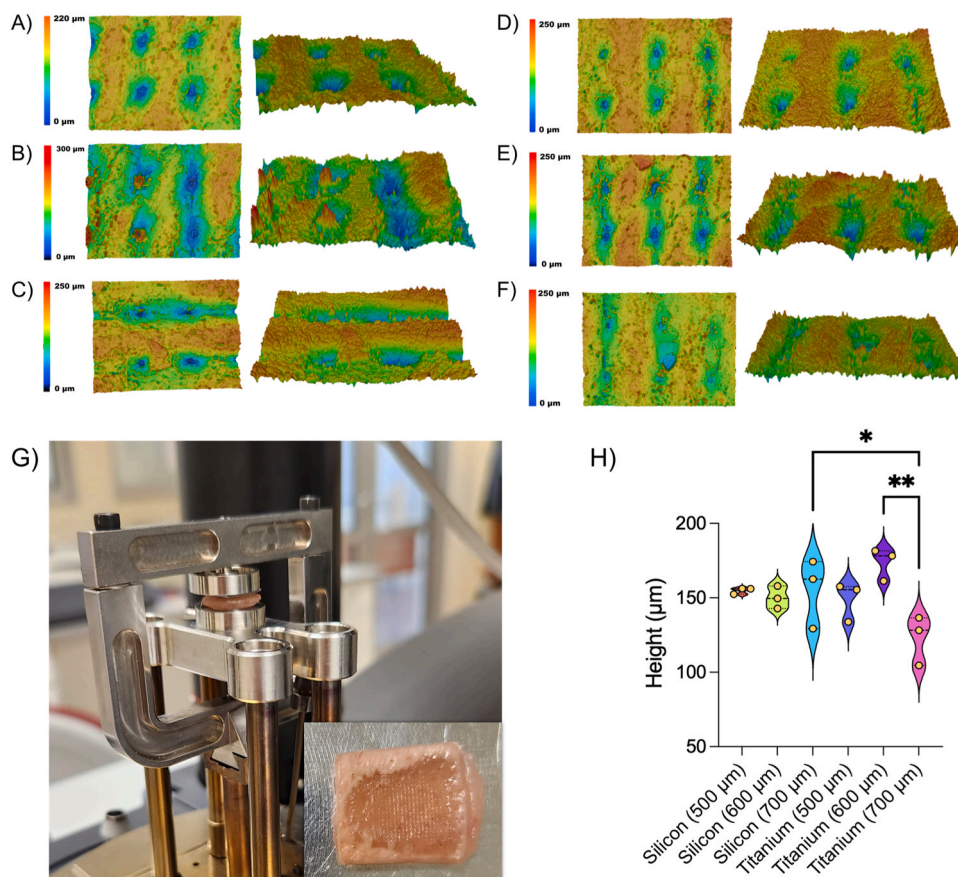


Fig. 5. The penetration study of silicon and titanium-coated solid MNs into the porcine skin. The heat-map acquired from 3D laser scanning microscopy showing topographical structure of porcine skin after insertion of silicon MNs with the depth of (A) 400 μm , (B) 500 μm , (C) 600 μm , and titanium-coated MNs with the depth of (D) 400 μm , (E) 500 μm , and (F) 600 μm . (G) DMA setup showing compression of solid MNs over porcine skin. (H) The average penetration depth of each MNs into porcine skin. The MNs were inserted into porcine skin using dynamic mechanical analyzer with a maximum force of 18 N applied during 36 min. Asterisk shows statistical difference between each group.

tissue or bloodstream. Our production method is designed to achieve a delicate balance in these mechanical characteristics, compensating for each requirement and ensuring efficient skin penetration, ultimately facilitating effective drug delivery to the targeted tissue or bloodstream. Rigorous testing and comprehensive pre-clinical studies are also crucial to ensure the safety and efficacy of MN-based drug delivery systems, allowing for refinement of design and materials to minimize any potential side effects.

Typically, solid MNs are employed as molds in the production of polymeric MNs, aiding in drug delivery by creating micro-channels in the skin. However, the inert properties of silicon MNs might potentially hinder direct drug loading onto their tips, and this can be a major hurdle of solid MNs in general. Overcoming the challenges of drug loading onto silicon MNs is crucial for optimizing their drug delivery capabilities. Despite this limitation, these silicon MNs offer adaptability. They can undergo surface modifications or coatings, expanding their functionality beyond drug delivery alone. Through surface chemistry or coatings, integrating smart materials onto the tips of solid MN would be an alternative strategy to employ these MNs in drug delivery systems while applying an external stimulus (e.g., changing temperature or pH) to release the drug (Zaid Alkilani et al., 2015). In addition to drug delivery, solid MNs can find some applications as promising biosensing tools since they can be customized for diverse applications in this field (Keirouz et al., 2023). Leveraging tunable surface properties, silicon MNs hold potential in biosensing beyond their conventional roles in drug delivery (Windmiller et al., 2011). Simultaneously, exploring their multifunctional aspects in biosensing applications represents an exciting direction for advancing their utility in biomedical technology.

4. Conclusion

MNs have recently garnered immense impact on health science and medical applications due to their potential that offers a painless and minimally invasive solution for drug delivery or sensing applications (Erdem et al., 2021). Our study presents a new method, combining the dicing saw and isotropic dry etching processes in order to manufacture solid MNs with adjustable arrangements (height and aspect ratio). With the defined parameters, we were able to achieve MNs with aspect ratio as high as 3.7, and a radius of curvature and tip angle of $10\text{ }\mu\text{m}$ and 6.4° , respectively. *Ex vivo* penetration tests on porcine skin demonstrated the MNs would hold great promise for transdermal drug delivery or biosensing in future studies.

MN fabrication methods have been extensively explored to manufacture MNs with different materials and geometrical features. For instance, photolithography is a part of these processes and demands the use of equipment such as mask writer and mask aligner, chemicals including photoresist and organic solvents (e.g., acetone and isopropyl alcohol), as well as chrome masks for patterning process. Compared to our previous work involving photolithography fabrication of solid MNs, the current study stands out as an advantageous technique in terms of several factors. For example, the total number of MN array produced on a patch with an area of 1 cm^2 increased from 200 to 400 MNs/ cm^2 . We could easily tune the MN array number by simply using a blade with a different thickness. In terms of cycle time, we had a decrease from 100 cycles with 120 s etching time to ≈ 80 cycles with 90 s etching time (1 h less etching), indicating that less XeF_2 gas was used to produce a single MN patch. Additionally, the maximum MN height achieved in the current study was ≈ 2.2 times higher (from ≈ 320 to $\approx 700\text{ }\mu\text{m}$). Moreover, by coating the surface of silicon wafer with epoxy instead of Si_3N_4 , we discarded the dependence on PECVD tool, which also requires cleanroom facility. Overall, we could fabricate 400 MN arrays using only 1 cm^2 of silicon wafer ($\approx \$0.5\text{--}0.75/\text{cm}^2$) and $0.5\text{--}1\text{ mg}$ of XeF_2 material ($2.5\text{ cents per cm}^2$ as the price of XeF_2 is $\$25.00/\text{gr}$).

With the technology exhibited in this work, (i) we minimize the need for photolithography and (ii) enable to minimize the workload in a cleanroom facility for fabricating solid MNs with adjustable geometry in

(iii) rapid (2 h) and (iv) cost-effective manners. The MN manufacturing technique in this study demonstrates (v) high reliability and reproducibility. This consistency was statistically validated with a sample size of 5 ($n = 5$), showing a p-value greater than 0.05 ($p > 0.05$), affirming the technique's robustness and ability to consistently yield comparable results (same MN height, aspect ratio, roughness, etc.). To take such a production method to the larger scale, a 11.8-inch silicon wafer (300 mm) can be mechanically patterned using a dicing saw in a single run and the wafers can be further etched in a larger scale XeF_2 etcher. Moreover, the cost can be further reduced as the dicing saw can process cheaper materials. (vi) This way, ≈ 688 MN patches (each having an area of 1 cm^2 and 400 MN array/patch) can be fabricated in a single batch. Our MN fabrication method not only outperforms techniques like photolithography, 3D printing, laser machining (including CO_2 , UV, and nano/femtosecond lasers), and two-photon polymerization in terms of several aspects, but also provides a more versatile and rapid solution for precise transdermal drug delivery or biosensing applications. In our study, we utilized a silicon wafer in conjunction with a dicing saw for the MN fabrication. It is noteworthy that dicing saw tools are versatile and can process a variety of materials, offering adaptability through the use of different-sized and shaped dicing saw blades, resulting in the formation of MNs without further processing with dry etching. This versatility widens the scope of potential applications beyond silicon, demonstrating the flexibility of our method in accommodating diverse materials and geometries for MN production. We anticipate that these advantages contribute to the uniqueness and significance of our work, making it a valuable addition to the field of MN technology.

CRediT authorship contribution statement

Eş İsmail: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **İnci Fatih:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition. **Kafadenk Abdullah:** Writing – review & editing, Writing – original draft, Methodology, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jmatprotec.2023.118268](https://doi.org/10.1016/j.jmatprotec.2023.118268).

References

- Ali, D., Sen, S., 2018. Computational fluid dynamics study of the effects of surface roughness on permeability and fluid flow-induced wall shear stress in scaffolds. *Ann. Biomed. Eng.* 46, 2023–2035.
- Bal, S.M., Caussin, J., Pavel, S., Bouwstra, J.A., 2008. In vivo assessment of safety of microneedle arrays in human skin. *Eur. J. Pharm. Sci.* 35, 193–202.
- Buckwalter, C.Q., Pederson, L.R., McVay, G.L., 1982. The effects of surface area to solution volume ratio and surface roughness on glass leaching. *J. Non Cryst. Solids* 49, 397–412.
- Caffarel-Salvador, E., Kim, S., Soares, V., Tian, R.Y., Stern, S.R., Minahan, D., Yona, R., Lu, X., Zakaria, F.R., Collins, J., 2021. A microneedle platform for buccal macromolecule delivery. *Sci. Adv.* 7, eabe2620.
- Cao, Y., Koh, S.S., Han, Y., Tan, J.J., Kim, D., Chua, N., Urano, D., Marelli, B., 2022. Drug delivery in plants using silk microneedles. *Adv. Mater.*, 2205794 <https://doi.org/10.1002/adma.202205794>.
- Donnelly, R.F., Singh, T.R.R., Garland, M.J., Migalska, K., Majithiya, R., McCrudden, C. M., Kole, P.L., Mahmood, T.M.T., McCarthy, H.O., Woolfson, A.D., 2012. Hydrogel-forming microneedle arrays for enhanced transdermal drug delivery. *Adv. Funct. Mater.* 22, 4879–4890.
- Erdem, Ö., Eş, I., Akceoglu, G.A., Saylan, Y., Inci, F., 2021. Recent advances in microneedle-based sensors for sampling, diagnosis and monitoring of chronic diseases. *Biosensors* 11. <https://doi.org/10.3390/bios11090296>.
- Eş, I., Kafadenk, A., Gormus, M.B., Inci, F., 2023. Xenon difluoride dry etching for the microfabrication of solid microneedles as a potential strategy in transdermal drug delivery. *Small*, 2206510.
- Faraji Rad, Z., Prewett, P.D., Davies, G.J., 2021. High-resolution two-photon polymerization: The most versatile technique for the fabrication of microneedle arrays. *Microsyst. Nanoeng.* 7, 71.
- Gill, H.S., Denson, D.D., Burris, B.A., Prausnitz, M.R., 2008. Effect of microneedle design on pain in human subjects. *Clin. J. Pain.* 24, 585.
- Gittard, S.D., Chen, B., Xu, H., Ovsianikov, A., Chichkov, B.N., Monteiro-Riviere, N.A., Narayan, R.J., 2013. The effects of geometry on skin penetration and failure of polymer microneedles. *J. Adhes. Sci. Technol.* 27, 227–243.
- Han, D., Morde, R.S., Mariani, S., La Mattina, A.A., Vignali, E., Yang, C., Barillaro, G., Lee, H., 2020. 4D printing of a bioinspired microneedle array with backward-facing barbs for enhanced tissue adhesion. *Adv. Funct. Mater.* 30, 1909197.
- Jiang, J., Gill, H.S., Ghate, D., McCarey, B.E., Patel, S.R., Edelhauser, H.F., Prausnitz, M. R., 2007. Coated microneedles for drug delivery to the eye. *Invest. Ophthalmol. Vis. Sci.* 48, 4038–4043.
- Jiang, X., Lillehoj, P.B., 2020. Microneedle-based skin patch for blood-free rapid diagnostic testing. *Microsyst. Nanoeng.* 6 (1), 11.
- Keirouz, A., Mustafa, Y.L., Turner, J.G., Lay, E., Jungwirth, U., Marken, F., Leese, H.S., 2023. Conductive polymer-coated 3D printed microneedles: biocompatible platforms for minimally invasive biosensing interfaces. *Small* 19, 2206301.
- Krieger, K.J., Bertollo, N., Dangol, M., Sheridan, J.T., Lowery, M.M., O'Cearbhaill, E.D., 2019. Simple and customizable method for fabrication of high-aspect ratio microneedle molds using low-cost 3D printing. *Microsyst. Nanoeng.* 5 (1), 14.
- Larraneta, E., Lutton, R.E.M., Woolfson, A.D., Donnelly, R.F., 2016. Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development. *Mater. Sci. Eng. R. Rep.* 104, 1–32.
- Li, Y., Zhang, H., Yang, R., Tazrin, F., Zhu, C., Kaddoura, M., Blondeel, E.J.M., Cui, B., 2019. In-plane silicon microneedles with open capillary microfluidic networks by deep reactive ion etching and sacrificial layer based sharpening. *Sens. Actuators A Phys.* 292, 149–157.
- Ligon, S.C., Liska, R., Stampfl, J., Gurr, M., Mülhaupt, R., 2017. Polymers for 3D printing and customized additive manufacturing. *Chem. Rev.* 117, 10212–10290.
- Lin, Y., Chen, Y., Deng, R., Qin, H., Li, N., Qin, Y., Chen, H., Wei, Y., Wang, Z., Sun, Q., 2023. Delivery of neutrophil membrane encapsulated non-steroidal anti-inflammatory drugs by degradable biopolymer microneedle patch for rheumatoid arthritis therapy. *Nano Today* 49, 101791.
- Manginell, R.P., Frye-Mason, G.C., Schubert, W.K., Shul, R.J., Willison, C.G., 1998. Microfabrication of membrane-based devices by deep-reactive ion etching (DRIE) of silicon. Sandia National Lab.(SNL-NM), Albuquerque, NM (United States).
- Ngo, T.D., Kashani, A., Imbalzano, G., Nguyen, K.T.Q., Hui, D., 2018. Additive manufacturing (3D printing): a review of materials, methods, applications and challenges. *Compos. Part B Eng.* 143, 172–196.
- Ozyilmaz, E.D., Turan, A., Comoglu, T., 2021. An overview on the advantages and limitations of 3D printing of microneedles. *Pharm. Dev. Technol.* 26, 923–933.
- Pandey, K., Pandey, P.M., 2019. An integrated application of chemo-ultrasonic approach for improving surface finish of Si (100) using double disk magnetic abrasive finishing. *Int. J. Adv. Manuf. Technol.* 103, 3871–3886.
- Pearson, F.E., O'Mahony, C., Moore, A.C., Hill, A.V.S., 2015. Induction of CD8+ T cell responses and protective efficacy following microneedle-mediated delivery of a live adenovirus-vectored malaria vaccine. *Vaccine* 33, 3248–3255.
- Pradeep Narayanan, S., Raghavan, S., 2017. Solid silicon microneedles for drug delivery applications. *Int. J. Adv. Manuf. Technol.* 93, 407–422.
- Prausnitz, M.R., Langer, R., 2008. Transdermal drug delivery. *Nat. Biotechnol.* 26, 1261–1268.
- Rabie, M., Franck, C.M., 2018. Assessment of eco-friendly gases for electrical insulation to replace the most potent industrial greenhouse gas SF6. *Environ. Sci. Technol.* 52, 369–380.
- Rad, Z.F., Prewett, P.D., Davies, G.J., 2021. Rapid prototyping and customizable microneedle design: ultra-sharp microneedle fabrication using two-photon polymerization and low-cost micromolding techniques. *Manuf. Lett.* 30, 39–43.
- Roh, H., Yoon, Y.J., Park, J.S., Kang, D.-H., Kwak, S.M., Lee, B.C., Im, M., 2022. Fabrication of high-density out-of-plane microneedle arrays with various heights and diverse cross-sectional shapes. *Nano-Micro Lett.* 14 (1), 19.
- Summerfield, A., Meurens, F., Ricklin, M.E., 2015. The immunology of the porcine skin and its value as a model for human skin. *Mol. Immunol.* 66, 14–21.
- Sun, J., Chen, Z., Zhou, S., Sun, Yijun, Liu, Z., Chen, C., Liu, Y., Sun, Ying, Wang, M., Xie, S., 2023. Vertical sidewall of silicon nitride mask and smooth surface of etched-silicon simultaneously obtained using CHF3/O2 inductively coupled plasma. *Vacuum* 207, 111650.
- Tanaka, S., Rajanna, K., Abe, T., Esashi, M., 2001. Deep reactive ion etching of silicon carbide. *J. Vac. Sci. Technol. B Microelectron. Nanom. Struct. Process. Meas. Phenom.* 19, 2173–2176.
- Tariq, N., Ashraf, M.W., Tayyaba, S., 2021. A review on solid microneedles for biomedical applications. *J. Pharm. Innov.* 1–20.
- Trautmann, A., Roth, G.-L., Nujiqi, B., Walther, T., Hellmann, R., 2019. Towards a versatile point-of-care system combining femtosecond laser generated microfluidic channels and direct laser written microneedle arrays. *Microsyst. Nanoeng.* 5, 6 <https://doi.org/10.1038/s41378-019-0046-5>.
- Tu, K.T., Chung, C.K., 2016. Rapid prototyping of biodegradable microneedle arrays by integrating CO2 laser processing and polymer molding. *J. Micromech. Microeng.* 26, 65015.
- Windmiller, J.R., Valdés-Ramírez, G., Zhou, N., Zhou, M., Miller, P.R., Jin, C., Brozik, S. M., Polsky, R., Katz, E., Narayan, R., Wang, J., 2011. Bicomponent microneedle array biosensor for minimally-invasive glutamate monitoring. *Electroanalysis* 23, 2302–2309. <https://doi.org/10.1002/elan.201100361>.
- Wu, L., Park, J., Kamaki, Y., Kim, B., 2021. Optimization of the fused deposition modeling-based fabrication process for polylactic acid microneedles. *Microsyst. Nanoeng.* 7, 58 <https://doi.org/10.1038/s41378-021-00284-9>.
- Xu, T., Tao, Z., Li, Hanqing, Tan, X., Li, Haiwang, 2017. Effects of deep reactive ion etching parameters on etching rate and surface morphology in extremely deep silicon etch process with high aspect ratio. *Adv. Mech. Eng.* 9, 1687814017738152.
- Yilmaz, E.G., Ece, E., Erdem, Ö., Eş, I., Inci, F., 2023. A sustainable solution to skin diseases: ecofriendly transdermal patches. *Pharmaceutics* 15, 579.
- Zaid Alkilani, A., McCrudden, M.T.C., Donnelly, R.F., 2015. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. *Pharmaceutics* 7, 438–470.
- Zvezdin, V., Kasatkina, T., Kasatkin, I., Gavrilova, M., Kazakova, O., 2020. Microneedle patch based on dissolving, detachable microneedle technology for improved skin quality of the periorbital region. Part 2: clinical Evaluation. *Int. J. Cosmet. Sci.* 42, 429–435.