

Hollow microneedles as a flexible dosing control solution for transdermal drug delivery

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ABSTRACT

Microneedles, small needle-like structures typically less than 1000 μm in length, are effective tools for transporting substances across biological barriers via minimally invasive pathways. Various microelectromechanical system (MEMS) processes enable the production of different types of microneedles, including solid, coated, dissolving, hydrogel, and hollow microneedles, each tailored to specific drug and fluid delivery mechanisms. Among these, hollow microneedles stand out for their ability to offer flexible dosage control adaptable to varying drug formulations, making them particularly promising for transdermal drug delivery systems. This review examines the fabrication processes of hollow microneedles, highlights the advantages of their hollow structure for medical applications, and discusses the key factors influencing their performance. Finally, it proposes directions for advancing these technologies in both industrial and research settings.

1. Introduction

For decades, intact human skin has been considered an impermeable barrier to exogenous substances [1]. However, studies conducted before the 20th century gradually revealed the multilayered structure of the skin, identifying the stratum corneum (SC) as the primary barrier [2] that shields against various physical and chemical threats, the SC poses a significant obstacle to effective transdermal drug delivery (TDD).

TDD typically occurs through one of three pathways: trans-appendageal, intracellular, or intercellular [3]. The trans-appendageal route involves drug transport via hair follicles and sweat glands. Although this route provides continuous channels for drug delivery, its effectiveness is limited because these glands account for only 0.1 % of the skin's surface area [4]. In contrast, intracellular and intercellular routes are determined by the SC's unique "bricks and mortar" structure [5]. As illustrated in Fig. 1(a), the SC is composed of keratin and lipids, forming the outermost layer of the skin with a thickness of 10–15 μm [6]. The intracellular route, suitable for hydrophilic solutes, involves drug transport through keratin-rich corneocytes. Conversely, the intercellular route facilitates drug diffusion through the lipid matrix between cells, making it more suitable for lipophilic drugs. The permeability of

substances across the SC depends on factors such as molecular weight and hydrophilic-lipophilic balance [7], necessitating careful consideration of drug formulations for successful TDD. To address these challenges, microneedles (MNs) have been developed as a minimally invasive solution to bypass the SC while efficiently delivering drugs [8].

The concept of using MNs to penetrate the SC barrier for drug administration was first introduced in 1976 [9]. However, significant research and development did not begin until the 2000s, due to limitations in MEMS fabrication technologies. As shown in Fig. 1(b), five primary types of MNs have been developed to date. Solid MNs, the earliest type, are inserted into the skin to create channels for subsequent topical drug application [10–13]. Coated MNs improve drug delivery efficiency and minimize waste as the MN shaft is coated with drugs that dissolve and are released into the body within minutes of skin penetration; the MNs are then discarded [14–17]. Dissolving MNs, typically made from biodegradable polymers encapsulating drugs [18], dissolve upon penetrating the SC, releasing the drugs and leaving no hazardous waste [19–21]. Hydrogel MNs, constructed from swellable hydrophilic crosslinked polymers, deliver drugs upon insertion and absorb interstitial fluids (ISF), and have potential diagnostic applications in addition to drug delivery [22–24]. Hollow MNs (HMNs), in contrast, feature an

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internal cavity through which drugs are delivered under pressure, functioning similarly to injections. Compared with other MN types, hollow MNs are particularly suitable for delivering high-viscosity or high-dose drugs [25,26]. Fig. 1(c) illustrates how HMNs require applicator devices to facilitate drug delivery. This design enables precise control of dosage and delivery rates, making HMNs a promising alternative to conventional injections. Their applications extend to liquid drug microinjection and minimally invasive fluid or tissue extraction [27].

This review aims to provide valuable insights into the potential advantages of HMN structures for medical applications. It begins by examining the penetration mechanisms of HMNs and discussing the geometric parameters that enhance their efficiency. Subsequently, a comprehensive review of various manufacturing processes for HMNs is presented. Furthermore, the study explores the applications of HMNs to deliver varied drug formulations, with an emphasis on the benefits of precise dosage control. By delving into the principles behind HMN fabrication and their versatile applications, this study seeks to contribute to a deeper understanding of HMN technology and support its development in both industrial and research settings.

2. Hollow microneedles

2.1. Mechanical insertion mechanism of HMNs

For effective design of HMNs, it is essential to understand their structural characteristics and skin penetration mechanisms. Structurally resembling single needles, insertion mechanism of HMNs can be evaluated by analyzing injection-like motions. Among the various factors

influencing performance, the insertion force is the most critical parameter for assessing and optimizing microneedle performance. Lower insertion forces are generally preferred as they reduce pain and ensure minimal invasiveness. As previous studies have shown [28–30], the resistance force $f_{needle}(z)$ acting on a needle during skin insertion can be expressed as follows:

$$f_{needle}(z) = f_{stiffness}(z) + f_{friction}(z) + f_{cutting}(z) \quad (1)$$

where $f_{stiffness}(z)$ represents the deformation force before the needle pierces the skin, $f_{friction}(z)$ is the frictional force caused by the interaction between the needle and skin tissue during insertion, and $f_{cutting}(z)$ is the cutting force required to penetrate the tissue. According to the nonlinear spring model proposed by Simon and Okamura [29,30], the deformation force before the needle pierces the skin can be expressed as

$$f_{stiffness} = az + bz^2 \quad (2)$$

where a and b are fitting constants derived from experimental data, and z represents the position of the needle tip. HMNs are typically designed with short lengths, keeping the needle tips within the upper skin layers. This minimizes $f_{friction}(z)$, rendering it negligible in most cases [28]. However, for longer microneedles, friction becomes significant. Reducing $f_{cutting}(z)$ is critical for efficient insertion. Decreasing the cross-sectional area of the sharp needle tip induces stress concentration during skin contact, enhancing penetration efficiency [31–33]. Consequently, shorter needles with sharper tips exhibit lower insertion resistance, minimizing patient discomfort and preventing needle breakage.

Due to their hollow structure, HMNs are prone to failure under axial and lateral loads [31,34]. The axial fracture force, as shown in Fig. 2(a),

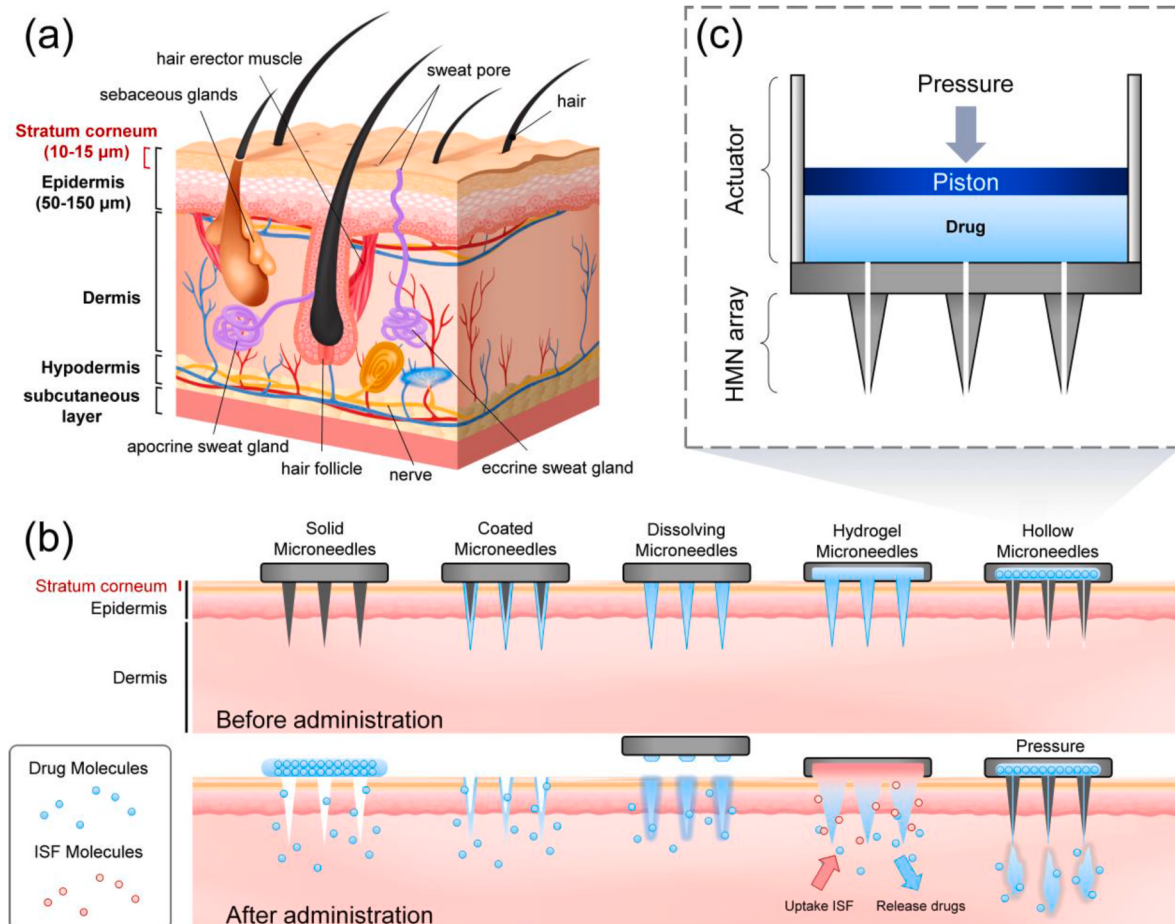


Fig. 1. (a) Skin anatomy. (b) Different types of drug delivery mechanisms using microneedles. (c) Example configuration of HMN combined with an actuator.

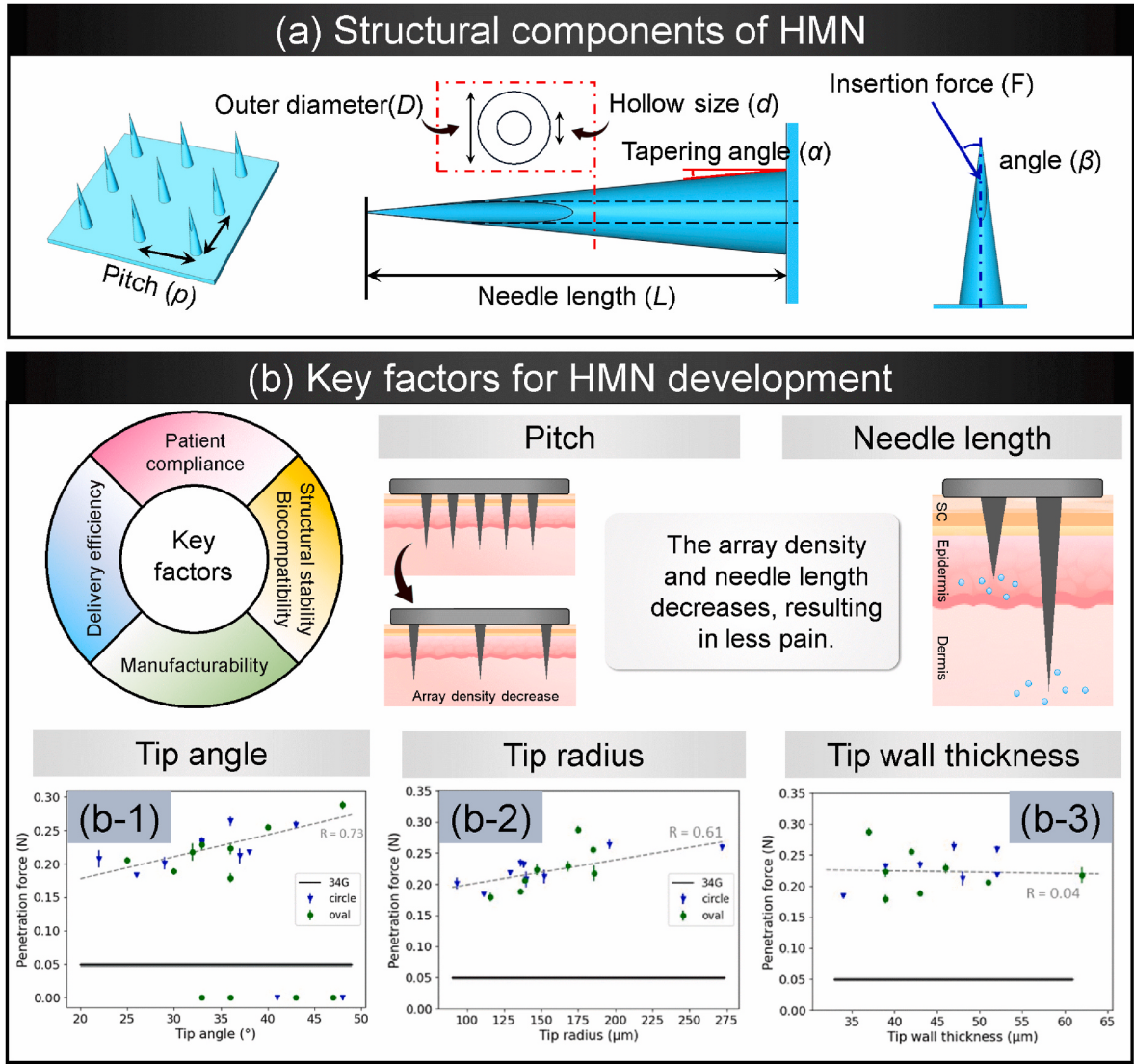


Fig. 2. (a) Structural components of HMNs. (b) Key factors for HMN development. (b-1,2,3) Reproduced with permission from Ref. [40] © 2024 Springer Nature.

can be expressed as

$$F_f = \pi D t \sigma_b \sin \alpha \quad (3)$$

where D is the outer diameter of the needle tip, $t = (D - d)/2$ represents the wall thickness, σ_b is the ultimate strength of the needle material, and α is the tapering angle of the tip. To prevent axial failure, the insertion force must remain below F_f . Although axial failure is rare in practice

owing to the high strength of HMN materials relative to human skin, bending stress from oblique forces during insertion is a critical factor.

Guojun et al. [28] theoretically predicted bending failure due to forces perpendicular to the axial direction and buckling failure under axial loads. Maximum tensile stress (σ_T) and critical buckling load (P_{cr}) for HMNs can be expressed as

$$\sigma_T = \frac{32F \sin \beta (L - z)}{\pi [(12D \tan^2 \alpha - 12d \tan^2 \alpha)(L - z)^2 + (6D^2 \tan \alpha - 6d^2 \tan \alpha)(L - z) + D^3 - d^3]} - \frac{4F \cos \beta}{\pi [(4D \tan \alpha - 4d \tan \alpha)(L - Z) + D^2 - d^2]} \quad (4)$$

$$P_{cr} = \frac{E}{80\pi L^2} \left[\frac{5\pi^4}{16} (D^4 - d^4) + \left(5\pi^2 + \frac{5}{4}\pi^4 \right) (D^3 - d^3) L \tan \alpha + \left(15\pi^2 + \frac{5}{2}\pi^4 \right) (D^2 - d^2) L^2 \tan^2 \alpha + \left(-120 + 30\pi^2 + \frac{5}{2}\pi^4 \right) (D - d) L^3 \tan^3 \alpha \right] \quad (5)$$

where β represents the angle between the insertion force (F) and the central axis of the HMN (see Fig. 2(a)), and E denotes the elastic modulus of the material. For stable insertion into the skin, tensile and shear stresses induced by bending must be carefully managed. Equations (1)–(5) highlight the importance of optimizing the geometric design of HMNs to prevent mechanical failure.

In particular, the taper angle α plays a crucial role in determining both insertion efficiency and structural stability. While a smaller α reduces insertion force by concentrating stress at the needle tip, it simultaneously weakens the needle's resistance to axial fracture and buckling. As α decreases, the axial fracture force (F_f) and critical buckling load (P_{cr}) decrease, making the needle more prone to mechanical failure. Moreover, the increase in tensile stress (σ_T) due to reduced α further elevates the risk of bending-induced fracture.

To mitigate the increase in tensile stress and enhance mechanical stability, several key design parameters must be optimized. Increasing the needle wall thickness by enlarging the outer diameter (D) or reducing the inner diameter (d) helps distribute stress more effectively and prevents structural failure. Adjusting the taper angle (α) to avoid excessive sharpness minimizes localized stress accumulation while maintaining efficient penetration. Additionally, reducing the needle length (L) lowers bending moments, thereby decreasing tensile stress. Selecting materials with a higher elastic modulus (E) further enhances rigidity and prevents excessive deformation under applied loads. By carefully balancing these factors, HMNs can be designed to achieve both efficient skin penetration and long-term structural integrity.

2.2. Key design considerations for HMNs

The primary objectives in developing HMNs are to safely penetrate the skin, minimize pain, improve patient compliance, and efficiently deliver drugs. Achieving these goals requires careful consideration of both structural safety—such as preventing needle breakage during insertion—and functional factors, including high drug delivery efficiency, painless application, and a minimally invasive design. Central to HMN design is the optimization of structural parameters such as pitch, length, tip angle, tip radius, and tip wall thickness.

Fig. 2(b) illustrates the interplay between key HMN design factors and structural characteristics. Pitch, which determines the needle array density, is a crucial parameter in HMN design. Unlike single needles, HMNs are typically arranged in arrays, allowing for flexible adjustments in the number of drug delivery channels. Generally, a smaller pitch increases the number of drug delivery channels per unit area, thereby enhancing drug delivery efficiency. However, when microneedles are excessively dense, the skin experiences distributed pressure, preventing individual needles from generating sufficient insertion force—known as the ‘bed-of-nails’ effect [35]. In this case, the insertion depth is reduced, and the applied force is spread across the entire array, leading to skin deformation rather than effective penetration.

Olatunji et al. [36] demonstrated through theoretical analysis that when the spacing between needle tips exceeds 150 μm , the insertion force decreases. While increasing the array density enhances drug delivery efficiency, it also raises insertion force, potentially reducing patient compliance. Gill et al. [37] reported that a tenfold increase in microneedle count doubled the associated pain. Jahan et al. [35] for successful microneedle penetration, the pitch should be at least 8–10 times the needle diameter to prevent excessive skin deformation. Therefore, optimizing the pitch is essential to balance microneedle insertion efficiency and drug delivery performance, ensuring effective penetration while minimizing unnecessary skin resistance.

Needle length is a critical design parameter that directly influences the depth of drug delivery. The SC, the outermost layer of the skin, is approximately 15 μm thick in a dry state and can swell to about 48 μm when fully hydrated [38]. To effectively penetrate this barrier and reach

the target site, HMNs must have a minimum length of 50 μm . However, studies have shown that the actual penetration depth of microneedles is often lower than their nominal length due to skin elasticity, deformation upon contact, and variations in insertion force.

Longer microneedles do not always result in deeper penetration. As the needle length increases, the skin's mechanical resistance and flexibility may cause microneedles to bend or fail to fully insert, limiting their effectiveness. Consequently, optimizing microneedle length is essential to balance penetration efficiency with patient comfort and drug delivery performance.

Additionally, increasing microneedle length can lead to higher pain perception and potential adverse effects. Needles exceeding 1450 μm have been associated with post-insertion bleeding [37], making them less suitable for minimally invasive applications. Therefore, HMNs are typically designed to remain within the limits for intradermal (ID) injections, ensuring effective drug administration while minimizing discomfort.

Despite their shorter lengths, HMNs have demonstrated high efficiency in drug delivery. A study involving 24 healthy adults found that ID injection of adalimumab using HMNs resulted in faster absorption and higher bioavailability than subcutaneous (SC) injection [39]. These findings highlight that HMNs, even at reduced insertion depths, can facilitate effective drug delivery and therapeutic outcomes, underscoring the need for precise length optimization in HMN design.

Vanwersch et al. [40] analyzed the effects of geometric characteristics such as tip angle, tip radius, and wall thickness on penetration efficiency. Their study revealed that smaller tip angles and radii reduced the insertion force, while variations in wall thickness alone had negligible impact. However, a lower product of the tip angle, tip radius, and wall thickness significantly reduced the insertion force, emphasizing the importance of minimizing the needle-skin contact area to facilitate easier penetration.

Finally, discrepancies between theoretically predicted and experimentally observed penetration forces warrant further investigation [41]. Additionally, it is crucial to assess whether current manufacturing techniques adequately account for the interrelationships among these structural factors [42].

2.3. Applicators for hollow microneedles

HMNs are designed to be compatible with applicators that enable precise and controlled drug delivery. Unlike solid microneedles, which rely on passive diffusion or dissolution, HMNs require external pressure mechanisms to actively drive fluids through their hollow channels. Various applicators have been developed to optimize fluid injection efficiency and delivery precision, including syringe-based manual systems, microfluidic or micropump-assisted devices [43,44], pneumatic actuators [45], pre-vacuum actuator [46,47], and ultrasonic vibration injection [48]. While different applicator mechanisms can be selectively applied for drug delivery, several critical challenges must be addressed to ensure safety, efficacy, and practicality in clinical and self-administration applications.

One of the most crucial considerations in HMN applicator design is sterilization and reusability. Unlike conventional microneedles, which are disposable after a single use, applicators are often designed for multiple uses, requiring proper sterilization strategies to prevent cross-contamination. Existing sterilization methods for medical devices, including steam autoclaving, ethylene oxide treatment, and UV or hydrogen peroxide treatment, have been explored for microfluidic systems [49–52]. However, ensuring compatibility between these sterilization techniques and HMN applicators, which may also serve as drug reservoirs, remains a challenge. Pre-filled HMN systems introduce additional complexity, as maintaining sterility throughout the drug delivery process is critical. To address this, appropriate sterilization techniques must be selected based on the target drug, and solutions such as disposable sterilized cartridges or self-sterilizing surfaces should be

integrated to enhance usability while minimizing contamination risks.

Ensuring precise dosage and flow rate control is a critical aspect of HMN applicator development. Unlike conventional injections, which primarily rely on manual force for fluid delivery, HMN applicators must regulate drug infusion rates to optimize therapeutic efficacy while minimizing tissue damage [44]. A key challenge is controlling fluid transport direction according to the intended application. In drug delivery, the backflow of biological fluids such as blood or interstitial fluid can compromise drug purity, obstruct fluid flow, and increase the risk of infection [53]. To prevent this, applicators can integrate backflow prevention mechanisms, such as check valves, to block biological fluid ingress and maintain a stable, controlled flow.

Long-term drug stability is also an important consideration. The open structure of HMNs increases the risk of drug exposure to the external environment, leading to evaporation or contamination. To counter this, Roxhed et al. [54] proposed membrane-sealed HMNs, where thin films are ruptured through various mechanisms, such as drug delivery pressure, electrochemical reactions, or skin insertion. If these membranes are biocompatible, similar approaches could significantly enhance the long-term stability of drugs in HMN systems.

Economic feasibility and large-scale manufacturability must also be addressed to transition HMN applicators from experimental prototypes to commercially viable products. The complexity of microfabrication processes, high material costs, and stringent regulatory requirements present significant challenges for mass production. To improve cost-efficiency, advanced manufacturing techniques such as 3D printing and modular design integration have been explored. Standardizing

applicator components and simplifying assembly processes can further reduce production costs while maintaining performance reliability. For an optimal HMN system, an integrated design approach that aligns both the applicator and HMN structure is essential.

3. Manufacturing of HMNs

The geometric features of HMNs play a critical role in determining their applications and performance characteristics, making the selection of an appropriate manufacturing method essential. Common HMN fabrication techniques include 3D printing, lithography, etching, and laser processing. Each method offers distinct advantages and limitations depending on geometric constraints, precision requirements, and specific applications, enabling the production of microneedles with diverse sizes and structures. This section provides an overview of the primary manufacturing methods for HMNs, highlighting their unique features, strengths, and weaknesses.

3.1. 3D printing

3D printing is a versatile method for fabricating HMNs that involves layering and curing materials to create diverse designs (Table 1). This approach includes techniques such as material extrusion, photopolymerization, and material jetting, each with unique advantages and limitations that affect its suitability for various applications [55].

Material extrusion, as exemplified by fused deposition modeling (FDM) printers, involves melting thermoplastic filaments and depositing

Table 1
Characteristics of various 3D printing processes for HMN manufacturing.

ISO Categories	Type	Parameter (μm)	HMN Materials	Pros	Cons	Ref.
Material Extrusion	FDM	Shape: pyramid Heights: 800-3000 Hollow diameter: 200-500	Biocompatible resin	Cheap, accessible, Compatible with various materials	Lack of surface quality, limited printing speed, low strength	[56]
Vat Photopolymerization	SLA	Shapes: cone, pyramid, syringe Needle length: 710-1150 Hollow diameter: 100-600	Biocompatible resin, Biocompatible Class I resin (Dental SG), Photo-curable resins, High Temperature resin (RS-F2-HTAM-02), Medical-grade (USP-VI) photopolymer	Smooth surface quality, wide range of resolutions	High material costs, slow printing speed	[58–63]
	LCD	Shapes: syringe, pyramid, screw, triangular pyramid Heights: 650-1100 Hollow diameter: 25-1300	ABS, Biocompatible resin, Clear microfluidic resin (v7.0a)	Fast printing	Resolution limited by pixel size, short lifespan, low precision	[66–68]
	DLP	Shapes: pyramid, hexagonal horn, syringe Heights: 550-1200 Hollow diameter: 30-220	Nonconductive resin, Biocompatible class I resin (Dental SG), Methacrylated PCL (PCLMA), Clear microfluidic resin (v7.0a)	High resolution, superior precision, faster printing compared to the SLA method	Expensive equipment cost, occurrence of the staircasing effect	[64, 69–72]
	TPP (=2 PP)	Shape: syringe Heights: 200-435 Hollow diameter: 35-120	IP-S photoresist (Nanoscribe GmbH)	Extremely precise microstructure fabrication, suitable for complex structures	Expensive equipment, extremely slow printing speed	[74–77]
	PuSL	Shape: cone Heights: 1000 Hollow diameter: 250	Biocompatible light-curing resin	Micro-level high resolution implementation	Complex structures (digital mask, projection lens), potential for degradation	[80]
Material Jetting	MJM	Shape: triangular pyramid Heights: 3000-4200 Hollow diameter: 1260	Alginate gel	High precision, smooth surface quality	Expensive equipment, long printing time, limited strength	[82]
Unclassified	–	Shapes: syringe, triangular pyramid, 4-pronged cone, cone Heights: 500-1200 Hollow diameter: 22.2–300	Acrylate-based photopolymer, Transparent photosensitive resin, Photo-curable resins, Polyimide (PI)	–	–	[83–86]

them layer-by-layer (See in Fig. 3(a)). Materials like acrylonitrile butadiene styrene (ABS), polylactic acid (PLA), and thermoplastic polyurethane (TPU) are suitable materials for this cost-effective method. For instance, pyramid-shaped HMNs with heights of 0.8–3 mm and hollow diameters of 200–500 μm have been fabricated using biocompatible resins, with hollow channels formed through NaOH etching [56]. However, material extrusion is limited by lower resolution and slower

speeds due to the stepwise deposition process.

Photopolymerization methods, including stereolithography (SLA), liquid crystal display (LCD), digital light processing (DLP), two-photon polymerization (TPP), and projection microstereolithography (P μ SL) use photocurable resins to achieve higher precision (Fig. 3(b)) [57]. SLA employs a UV laser to selectively cure resin, producing smooth micro-needles with cone or pyramidal structures with heights of 710–1150 μm

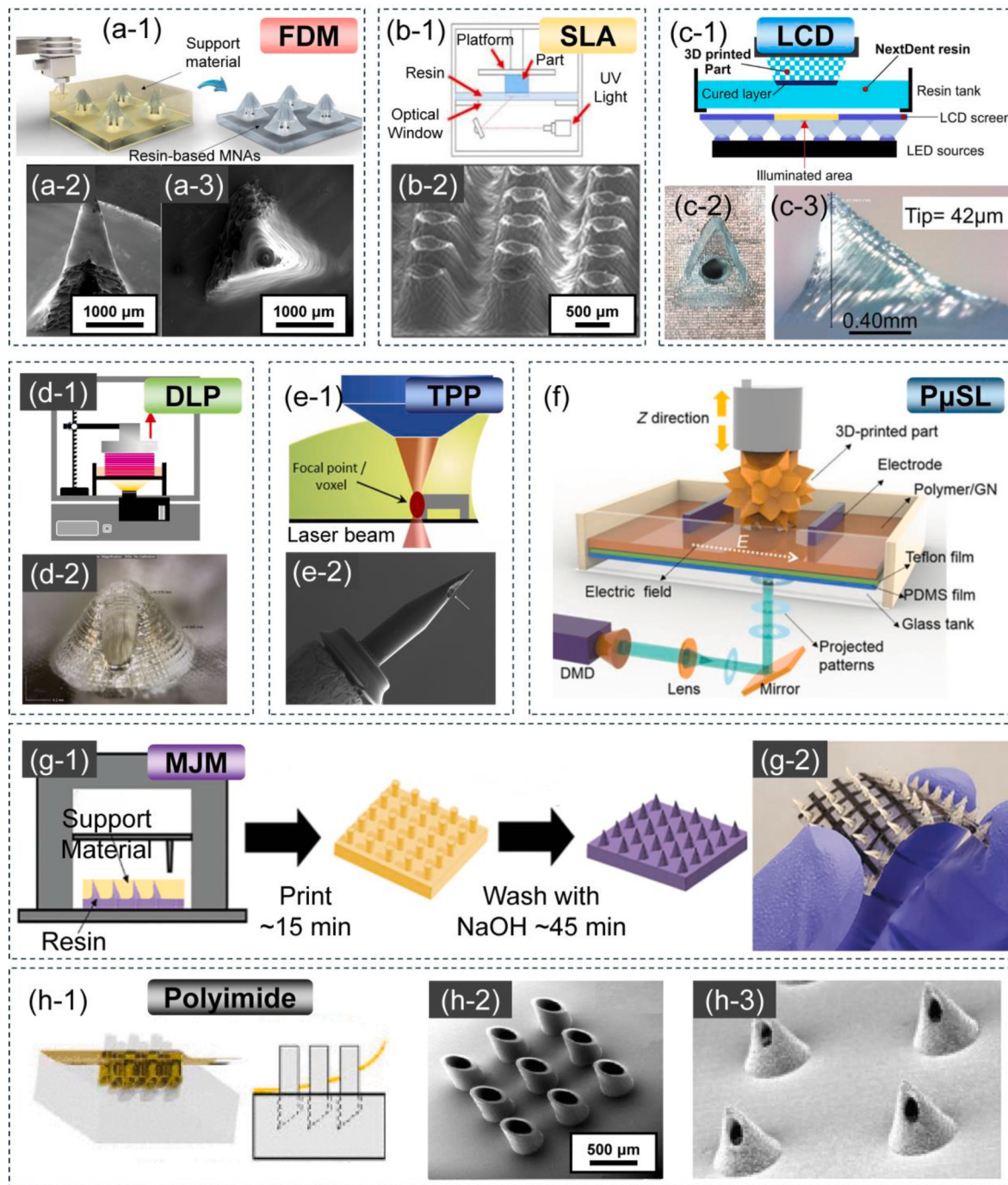


Fig. 3. Different 3D printing processes for HMN fabrication. (a) FDM printing and resulting HMN examples: Reproduced with permission from Ref. [56], © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) SLA printing and resulting HMN examples: Reproduced with permission from Ref. [58], © 2019 AIP Publishing. (c) LCD printing and resulting HMN examples: Reproduced with permission from Ref. [67], © 2021 Elsevier B.V. (d) DLP printing and resulting HMN examples: (d-2) Reproduced with permission from Ref. [69], © 2023 American Chemical Society. (e) TPP printing and resulting HMN examples: (e-1) Reproduced with permission from Ref. [73], © 2023 Elsevier B.V., (e-2) Reproduced with permission from Ref. [76], © 2021 American Chemical Society. (f) P μ SL printing: Reproduced with permission from Ref. [78], © 2020 MDPI, Basel, Switzerland. (g) MJM printing and resulting HMN examples: Reproduced with permission from Ref. [82], © 2021 Wiley-VCH GmbH. (h) Polyimide printing and resulting HMN examples: (h-1,2) Reproduced with permission from Ref. [86], © 2021 IEEE; (h-3) Reproduced with permission from Ref. [85], © 2024 Elsevier B.V.

and hollow diameters of 100–600 μm [58–63]. However, its layer-by-layer curing is associated with slower printing speeds.

LCD and DLP technologies improve SLA by curing entire layers simultaneously (Fig. 3c and d). LCD printing, which uses screen-based UV exposure, offers faster speeds but is constrained by pixel resolution and requires frequent maintenance due to backlight degradation [57]. Conversely, DLP utilizes digital projectors and micromirror technology, providing superior resolution and faster production times, though at higher costs [64,65]. LCD-fabricated HMNs have syringe, pyramid, and screw designs with heights of 650–1100 μm and hollow diameters of 25–1300 μm [66–68]. DLP-fabricated HMNs feature geometries such as hexagonal horns, with heights of 550–1200 μm and hollow diameters of 30–220 μm (Fig. 3(d)) [64,69–72].

TPP can be used to achieve nanoscale precision using dual-laser photons [73] (Fig. 3(e)). This enables the creation of complex syringe-like HMNs with heights of 200–435 μm and hollow diameters of 35–120 μm [74–77]. Despite its exceptional resolution, TPP is limited by slow speeds and high equipment costs. Similarly, P μ SL [78] employs micro-projection to achieve ultra-high resolution, facilitating fabrication of cone-shaped HMNs with heights of 1 mm and hollow diameters of 250 μm (see Fig. 3(f)) [79,80]. However, prolonged use can degrade resolution due to heat effects.

Material jetting, which is akin to inkjet printing, deposits liquid material and cures it layer by layer with UV light (Fig. 3(g)). This method produces smooth surfaces and detailed features but suffers from slow production speeds and high equipment costs [81]. Microneedles produced through material jetting include triangular pyramids with heights of 3–4.2 mm and hollow diameters of 1.26 mm [82].

Hybrid techniques and emerging materials, such as polyimides, have expanded HMN fabrication possibilities (Fig. 3(h)). These methods enable production of syringe-like and multi-pronged microneedles with enhanced biocompatibility, boasting heights of 0.5–1.2 mm and hollow diameters of 22.2–300 μm [83–86].

By leveraging the unique advantages of these 3D printing techniques, researchers can tailor HMN design and functionality to meet specific application requirements. However, challenges such as production speed, resolution constraints, and cost efficiency must be addressed to facilitate broader clinical and industrial adoption.

3.2. Laser techniques

Laser technology has been extensively utilized to fabricate HMNs through methods such as laser micromachining, writing, drilling, and cutting (Table 2). These techniques leverage different laser wavelengths and energy levels to perform specific manufacturing processes. They are applicable for the direct formation of HMN structures, mold fabrication followed by molding with biocompatible materials (e.g., PDMS), or the direct creation of hollow structures through laser drilling [87,88].

As shown in Fig. 4(a), laser micromachining uses precision laser milling at the micrometer scale to produce intricate patterns and structures [89]. This method minimizes thermal damage and is compatible with various materials. However, it is relatively slow and costly due to its complex processing requirements. HMNs fabricated using this technique have cone and pyramid shapes with heights of 250–1000 μm and hollow diameters of 40–100 μm . Infrared lasers are often employed to create tapered holes, which are subsequently refined using electroplating or milling [88,90,91].

As shown in Fig. 4(b), laser writing involves focusing a laser beam on a photosensitive material to fabricate structures without physical contact, similar to two-photon polymerization (TPP) [92]. This method is advantageous for creating intricate patterns but is constrained by the availability of photosensitive materials and the complexity of multi-layered structures. HMNs produced via laser writing have cone, cylinder, syringe, or pyramid shapes, with heights ranging from 100 to 2000 μm and hollow diameters from 15 to 200 μm [87,92–97].

As shown in Fig. 4(c), laser drilling employs high-energy laser pulses

to create small holes with precise control over diameter and depth [98]. This technique is well-suited for fabricating hollow structures but can suffer from heat-induced damage and surface uniformity issues if not optimized [98]. Combined with electroplating or milling, laser drilling has been used to produce cone-, syringe-, and pyramid-shaped HMNs with heights ranging from 50 to 1700 μm and hollow diameters of 50–1054 μm [99–104].

As shown in Fig. 4(d), laser cutting utilizes a high-power laser beam for rapid and precise material removal [105]. This non-contact method enables high-speed, wear-free cutting but is less effective for thicker materials and reflective surfaces. Laser cutting is used to fabricate HMNs with heights of 720–2000 μm in cone, syringe, and pyramid shapes, with hollow diameters ranging from 20 to 50 μm [106–110].

3.3. Lithography

Various lithography techniques are employed to fabricate microstructures, including X-ray, ultraviolet (UV), drawing, and centrifugal lithography (Table 3). These methods differ in their light sources, process characteristics, and the type and size of structures they produce. Lithography-based fabrication approaches can be broadly categorized into techniques that rely solely on lithography and those that combine lithography with additional processes, such as etching or deposition. This section focuses on techniques where lithography is the primary fabrication method.

X-ray lithography uses short-wavelength X-rays to produce highly precise microstructures smaller than those created by traditional photolithography methods [111]. As shown in Fig. 5(a), X-rays pass through a photomask, altering the properties of a photosensitive material [112]. This enables the fabrication of deep, intricate structures with high resolution. However, the technique requires expensive equipment, poses radiation exposure risks, and involves long exposure times. X-ray lithography has been used to produce cone, pyramid, and triangular pyramid structures with heights ranging from 350 to 1500 μm and hollow diameters of up to 1084 μm [112–116]. In some instances, composite structures are created using multiple lithography steps.

As shown in Fig. 5(b), UV lithography utilizes photolithographic techniques with UV light to transfer patterns onto photosensitive materials [117]. UV light passing through a photomask causes chemical changes in the resist. The resolution is determined by the wavelength of the UV source, with i-line UV lithography commonly applied in HMN production [118]. By adjusting the incident angle of the UV light, the taper angle of the needles can be controlled, and this method can be combined with laser drilling to form hollow structures [95,99]. UV lithography offers high production efficiency and cost-effectiveness but is limited by a resolution of approximately 12 μm and restrictions on structure height due to the type of photosensitive material used [95]. This technique is used to fabricate cone, syringe, and pyramid structures with heights ranging from 400 to 1540 μm and hollow diameters from 2 to 150 μm [117–125].

Drawing lithography involves the crosslinking of photosensitive polymers, typically based on epoxy resin, using a femtosecond laser to create structures [126]. As shown in Fig. 5(c), this technique allows freeform patterning without a photomask and enables the fabrication of structures with varying thicknesses. While it provides high precision, it requires specialized equipment and has low production rates. Drawing lithography has been used to produce syringe-shaped HMNs with heights up to 2000 μm and hollow diameters of 50 μm [96,126].

Centrifugal lithography involves spinning a photoresist onto a glass wafer and using a mold to form long conical structures (see Fig. 5(d)) [127]. The fabricated structures are subsequently laser-cut and electroplated to form hollow microneedles [128–130]. This technique is advantageous for its simplicity and suitability for producing symmetrical structures, enabling mass production. However, it is limited to materials like SU-8 due to its viscosity, and achieving smaller diameters or taller structures remains challenging. Centrifugal lithography has been

Table 2
Characteristics of various laser-based processes for HMN manufacturing.

Method	Parameter (μm)	HMN Materials	Pros	Cons	Ref.
Laser Micromachining	Shapes: cone, pyramid Heights: 250–1000 Hollow diameter: 40–100	Nickel, Polyetheretherketone (PEEK), Stainless steel	High precision, minimal thermal damage, applicable to various materials	High cost, slow processing speed, complex process	[88,90,91]
Laser Writing	Shapes: cone, cylinder, syringe, pyramid Heights: 100–2000	Polymethyl Methacrylate (PMMA), Negative PR (SU-8, IP-S), polymer precursor (E-shell 300), UV sensitive hybrid material (US-S4)	Precise pattern formation, non-contact, high-speed processing capability	Limitations in processing multi-layer structures, material selection, precision limitations	[87, 92–97]
Laser Drilling	Hollow diameter: 15–200 Shapes: cone, syringe, pyramid Heights: 50–1700 Hollow diameter: 50–1054	Stainless steel, polyethylene terephthalate (Mylar), polycarbonate (PC), polymethyl methacrylate (PMMA), polymer	High-speed processing, micro hole creation capability, adjustable for various depths	Thermal damage, uniformity issues, uneven roughness	[99–104]
Laser Cutting	Shapes: cone, syringe, pyramid Heights: 720–2000 Hollow diameter: 20–50	Negative PR (SU-8), Nickel, Hyaluronic acid	Fast cutting, precise cutting capability	Thermal damage, limited to thick/reflective materials	[106–110]

used to create cone and syringe structures with heights ranging from 460 to 8000 μm and hollow diameters of 30–233 μm [127–130].

Diffraction lithography can also be used to control structure size by adjusting the intensity of UV light. As shown in Fig. 5(e), this method has been applied to fabricate cone and syringe structures with heights ranging from 800 to 900 μm and hollow diameters of up to 1550 μm [131–134].

3.4. Etching-based fabrication of HMNs

The fabrication of HMNs using etching processes can be broadly categorized into dry and wet etching, with many studies combining both methods (Table 4). Since etching typically targets the entire surface, a masking step using lithography is essential to define etched and non-etched regions, allowing for precise structure formation.

Among the dry etching methods, reactive ion etching (RIE) employs radicals and ions to chemically and physically etch surfaces (see Fig. 6 (a)) [135]. Common reactive gases include SF₆, CF₄, and O₂, with process parameters such as RF power, gas composition, chamber pressure, and etching time adjusted to fabricate diverse HMN structures [135]. RIE offers high precision and enables anisotropic etching. However, it requires expensive equipment, involves lengthy processing times, and carries a risk of surface damage. RIE has been used to etch silicon, silicon oxide, pyrex, and photoresists, yielding cone-shaped structures with heights of 42–1000 μm and hollow diameters of 1–150 μm [136–140]. Cylindrical structures within these dimensions have also been fabricated [138–140].

In contrast, plasma etching relies on the chemical etching of surfaces using reactive gases in the plasma state (see Fig. 6(b)) [141]. Neutral radical particles enable isotropic etching, providing uniform treatment over large areas. However, the high temperatures and pressures involved can damage materials, and the process is heavily equipment-dependent [142]. Plasma etching has been used to fabricate silicon-based HMNs, including cone, cylinder, pyramid, and syringe-shaped structures, with heights ranging from 150 to 1157 μm and hollow diameters of 25 μm [143,144].

A hybrid approach combining plasma etching and deep reactive-ion etching (DRIE) has also been explored. This method integrates isotropic and anisotropic etching, enabling the creation of multilayered structures [145], though its complexity remains a challenge. It has been applied to etch silicon, silicon oxide, and photoresists, producing cone-shaped HMNs with heights of 200–1000 μm and hollow diameters of 30–60 μm, as well as cylindrical and four-pronged pyramid structures [145–148].

Wet etching, illustrated in Fig. 6(c), uses chemical solutions such as KOH, HF, or BHF to etch material surfaces. This method is cost-effective and offers fast processing speeds, but its inherently isotropic nature limits the fabrication of intricate structures [149]. The choice of etching solution determines the range of materials that can be processed. Studies have demonstrated the wet etching of silicon, silicon oxide, and photoresists to produce HMNs with cone, cylinder, pyramid, syringe, triangular prism, and square prism structures [123,125,143,150–156]. The resulting HMNs have heights of 30–1540 μm and hollow diameters of 2–100 μm.

A notable advancement is the use of HfO₂ films, which are inert to wet etching, in combination with RIE [157]. This integrated approach can be used to fabricates HMNs from silicon, silicon oxide, pyrex, and photoresists, resulting in structures such as cones, cylinders, pyramids, triangular pyramids, octagonal pyramids, square prisms, and triangular cross-section columns. These structures exhibit heights ranging from 45 to 550 μm and hollow diameters of 3.5–70 μm [157–164]. Additionally, the combination of plasma and wet etching– has been used to produce HMNs with cylindrical structures with heights of 8.95–200 μm and hollow diameters of 2.49–30 μm from materials including silicon, silicon oxide, chromium, and nickel [165,166].

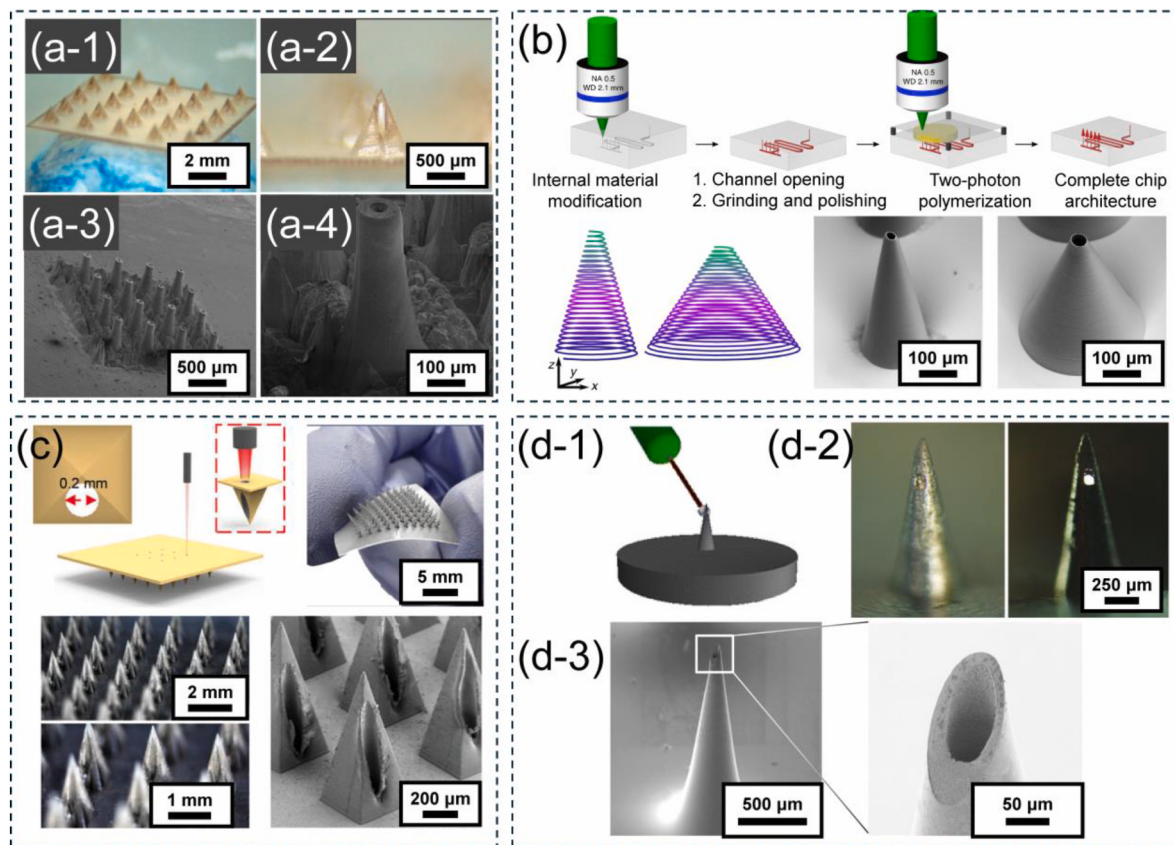


Fig. 4. Different laser-based processes for HMN fabrication. (a) Laser micromachining: (a-1,2) Reproduced with permission from Ref. [91], © 2022 Elsevier B.V; (a-3, 4) Reproduced with permission from Ref. [90], © 2016 IOP Publishing. (b) Laser writing and resulting HMN examples: reproduced with permission from Ref. [93], © 2019, Anika Trautmann et al. (c) Laser drilling and resulting HMN examples: Reproduced with permission from Ref. [104], © 2023 Advanced Materials published by Wiley-VCH GmbH. (d) Laser cutting and resulting HMN examples: (d-1,2) Reproduced with permission from Ref. [108], © 2012 Springer Science Business Media New York; (d-3) Reproduced with permission from Ref. [109], © 2020 The Japan Society of Applied Physics.

Table 3

Characteristics of various lithographic processes for HMN manufacturing.

Method	Parameter (μm)	HMN Materials	Pros	Cons	Ref.
X-ray Lithography	Shapes: cone, pyramid, triangular pyramid Heights: 350-1500 Hollow diameter: 10-84	Polymethyl Methacrylate (PMMA), polydimethylsiloxane (PDMS)	High achievable resolution, deep structure fabrication, minimal thermal deformation	Expensive equipment, radiation exposure risks, long exposure time, material limitations (photosensitive material)	[112–116]
UV Lithography	Shapes: cone, syringe, pyramid, triangular prism Heights: 400-1540 Hollow diameter: 2-150	Negative PR (SU-8), UV-curable PEG-DA solution	High productivity, cost-effectiveness	Resolution limits, precision restrictions, thickness limitations	[95, 117–125]
Drawing Lithography	Shape: syringe Heights: 2000 Hollow diameter: 50	Epoxy resin (IP-S)	No mask required, flexible pattern design, capable of creating needles of various thicknesses	Low productivity, high precision required, complex equipment	[96,126]
Centrifugal Lithography	Shapes: cone, syringe Heights: 460-8000 Hollow diameter: 30-233	Nickel, Metallic glasses (MGs)	Simple process, advantageous for forming symmetric structures, low cost	Resolution limitations, material restrictions	[127–130]
Unclassified	Shapes: cone, syringe Heights: 800-900 Hollow diameter: 15-50	Polymethyl Methacrylate (PMMA), Photosensitive resin	–	–	[131–134]

3.5. Replica molding-based fabrication of HMNs

Various fabrication methods using replica molding have been reported for the production of HMNs (Table 5). Replica molding typically involves the fabrication of a mold, followed by casting a material into

the mold and curing it through heating or UV exposure to form the final HMN structure. HMN fabrication using molds can be largely categorized into two approaches: embossed molds and intaglio molds, and mold fabrication can involve various techniques, including 3D printing, laser machining, lithography, and etching, as described in Sections 3.1 to 3.4.

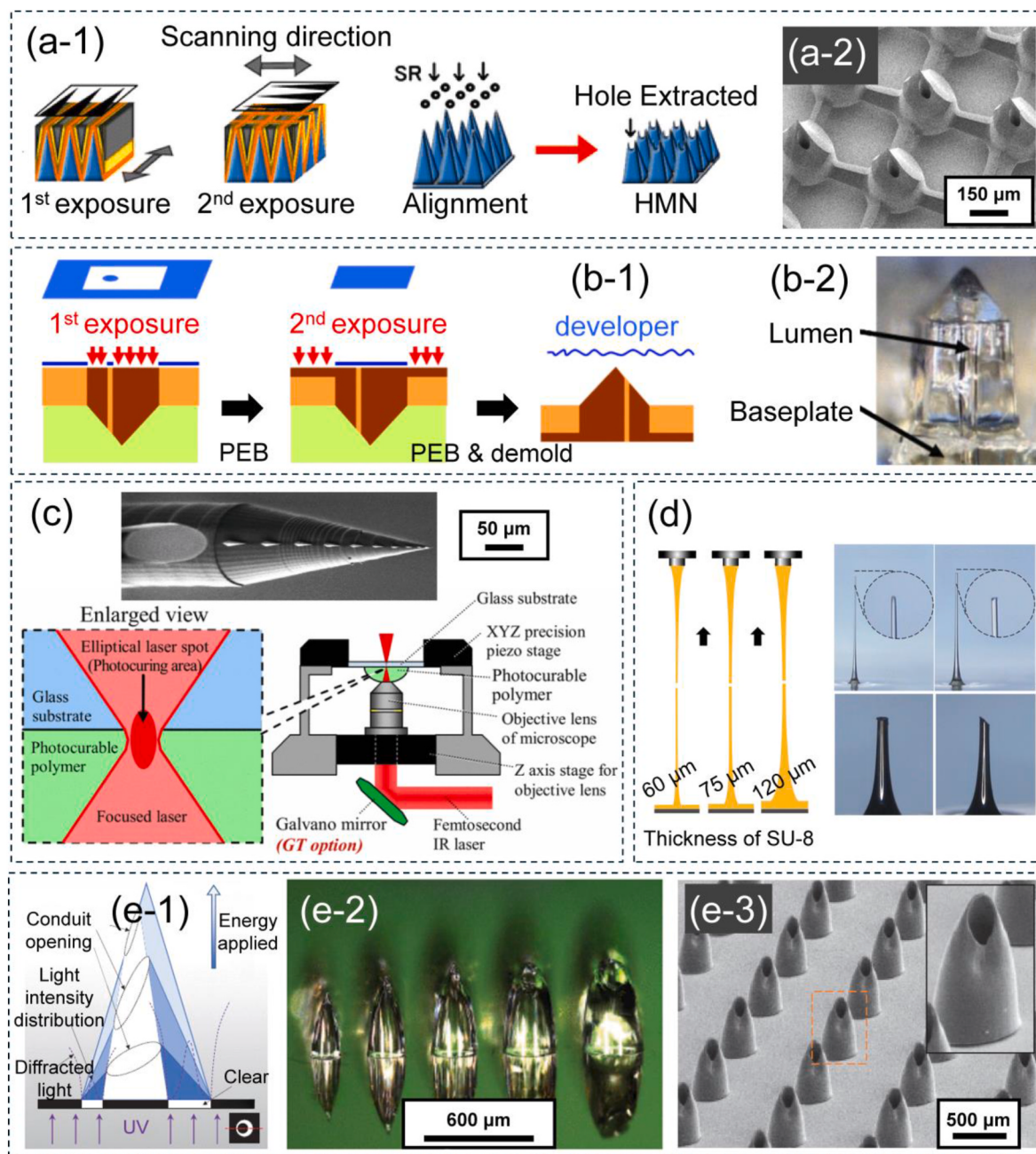


Fig. 5. Different lithographic processes for HMN fabrication. (a) X-ray lithography: (a-1,2) Reproduced with permission from Ref. [112], © 2006 Springer Nature. (b) UV lithography: Reproduced with permission from Ref. [118], © 2013 IEEE. (c) Drawing lithography: Reproduced with permission from Ref. [126], © 2015 IEEE. (d) Centrifugal lithography: Reproduced with permission from Ref. [107], © 2012 Springer Nature. (e) Diffraction lithography: Reproduced with permission from Ref. [131], © 2021 IEEE.

In the embossed mold approach, an initial master mold with protruding structures is created, and the surface of this mold is coated or deposited with another material to replicate the HMN shape. Since embossed molds have raised features, the mold geometry is easily visible and manageable during the fabrication process. However, coating or depositing materials onto the complex surfaces of embossed molds can be technically challenging due to difficulties in achieving uniform coverage. Notable examples include the use of sputtering to deposit a seed layer onto the embossed mold surface, followed by electroplating to build up the HMN structure [86]. Another example involves casting hyaluronic acid (HA) solution into an embossed mold and allowing it to dry over an extended period to form a core structure [109]. These methods have successfully produced HMNs with geometries such as

pyramidal structures with a height of 140 μm and a lumen diameter of 50 μm and conical structures with a height of 2000 μm and a lumen diameter of 50 μm , respectively.

Even when the initial mold is fabricated as an intaglio mold, it is possible to convert it into an embossed mold through double-casting processes. In this method, a secondary mold is fabricated using an elastic material, such as PDMS, to replicate the geometry of a rigid intaglio master [108]. This facilitates easier demolding after HMN fabrication. Using this approach, HMNs with a conical shape, 1100 μm in height, and a lumen diameter of 20 μm have been successfully fabricated [108].

Among replica molding methods, the use of intaglio molds is the most widely adopted. In this approach, a master mold is fabricated using

Table 4
Characteristics of various etching processes for HMN manufacturing.

Etching Type	Method	Parameter (μm)	HMN Materials	Pros	Cons	Etching Materials	Ref.
Dry	RIE (DRIE)	Shapes: cone, cylinder Heights: 42-1000 Hollow diameter: 1-150	Silicon, Negative PR (SU-8)	High achievable aspect ratio, high-resolution implementation	Long processing time, potential for surface damage, complex process sequence	Silicon, silicon dioxide, silicon oxide, pyrex, photo resist	[136–140, 143,150]
Dry	Plasma Etching	Shapes: cone, cylinder, pyramid, syringe Heights: 150-1157 Hollow diameter: 25	Silicon	Uniform processing of large areas	Equipment dependence, potential for thermal damage	Silicon	[143,144]
Dry	RIE + Plasma Etching	Shapes: cone, cylinder, 4-pronged pyramid Heights: 200-1000 Hollow diameter: 30-60	Silicon	Combination of isotropy and anisotropy, enabling multi-layer structure fabrication	Complex process steps	Silicon, silicon oxide, photo resist	[145–148]
Wet	Wet Etching	Shapes: cone, cylinder, pyramid, syringe, triangular prism, square prism Heights: 30-1540 Hollow diameter: 2-100	Silicon, Silicon dioxide, Negative PR (SU-8), Nickel	Fast speed, low cost, simple process	Isotropic etching, material limitations	Silicon, silicon oxide, photo resist	[123,125, 143, 150–156]
Dry + Wet	RIE + Wet Etching	Shapes: cone, cylinder, pyramid, triangular pyramid, octagonal pyramid, square prism, triangular cross-section column Heights: 45-550 Hollow diameter: 3.5–70	Silicon, Silicon dioxide, HfO_2 film, plastic	Composite structure capability	Difficulty in adjusting the speed difference between two processes	Silicon, silicon dioxide, silicon oxide, pyrex, photo resist, Si_3N_4	[157–164]
Dry + Wet	Plasma etching + Wet etching	Shape: cylinder Heights: 8.95–200 Hollow diameter: 2.49–30	Silicon, Chromium	Capable of generating uniform structures	Difficulty in stabilizing process conditions	Silicon, silicon oxide, chromium, nickel	[165,166]

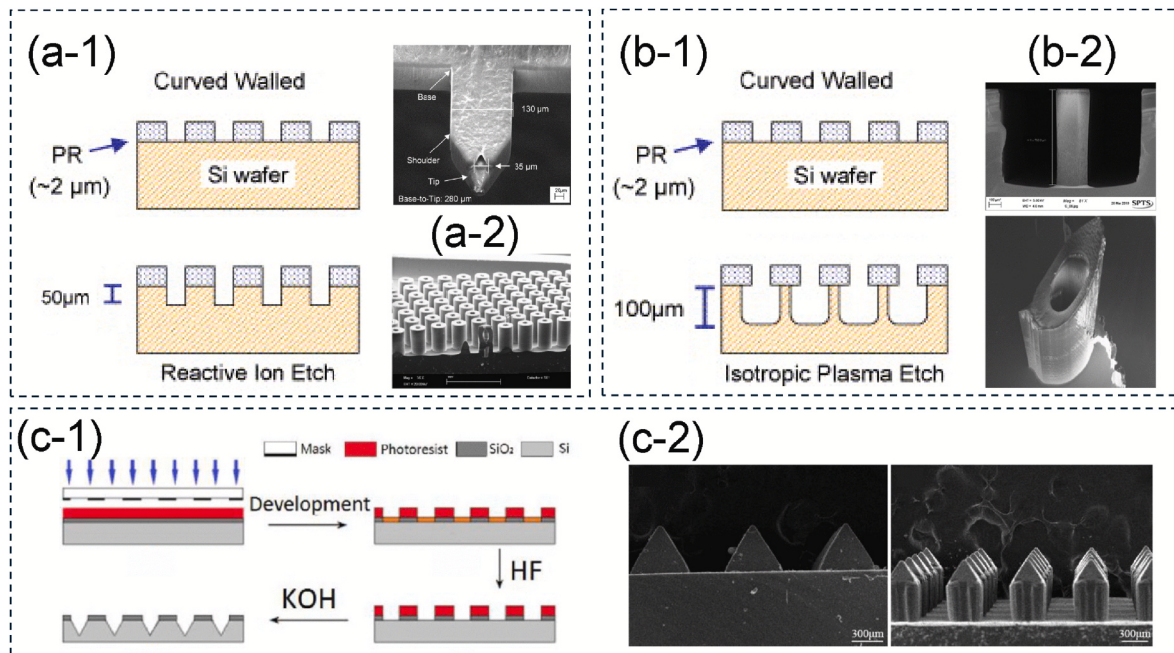


Fig. 6. Different etching processes for HMN fabrication. (a) Reactive ion etching: (a-1) Reproduced with permission from Ref. [163], © 2006 IOP Publishing; (a-2) Reproduced with permission from Ref. [136], © 2006 IOP Publishing. (b) Plasma etching: (b-1) Reproduced with permission from Ref. [163], © 2006 IOP Publishing; (b-2) Reproduced with permission from Ref. [144], © 2006 IOP Publishing. (c) Wet etching: Reproduced with permission from Ref. [155], © 2006 IOP Publishing.

techniques such as CO_2 laser machining, 3D printing, and lithography, and an intaglio mold is produced to define the cavity for the HMN structure [88,99–101]. The laser machining process, in particular, allows precise control over HMN geometries by adjusting parameters such as laser power and the focal distance between the target and the laser source.

Intaglio molds can be used for both casting processes and

electroplating-based replication [88,100,118,121,122,125,155,167]. For example, electroplating using an intaglio mold has been used to fabricate HMNs with a conical shape, heights ranging from 250 to 500 μm , and lumen diameters between 30 and 75 μm . In another study, a positive master mold was first fabricated using a 3D printer, followed by PDMS casting to create an intaglio mold, which was then used with electroplating to fabricate pyramidal HMNs with a height of 650 μm and

Table 5
Characteristics of various molding processes for HMN manufacturing.

Mold type	Molding count	Method	Parameter (μm)	HMN Materials	Pros	Cons	Ref.
embossed mold	1st molding	Electroplating	Shape: pyramid Heights: 140 Hollow diameter: 50	Nickel	Easy to check structures during electroplating	Difficult to separate after electroplating	[153]
		Casting	Shape: cone Heights: 2000 Hollow diameter: 50	Hyaluronic acid	Easy mold fabrication using methods like 3D printing and imprinting, easy demolding	Mold type depends on the material used	[109]
	2nd molding	Electroplating	Shape: cone Heights: 1100 Hollow diameter: 20	Nickel	Easy to make first mold	Secondary molding must use if the first mold is hard	[108]
	Intaglio mold	1st molding	Shape: cone Heights: 250-500 Hollow diameter: 30-75	Nickel	Compatible with laser, imprinting and etching methods	Requires sputtering seed layer formation needed, mainly used with silicone-based materials due to separate	[88,100]
		Casting	Shapes: cone, pyramid, cylinder, syringe, triangular pyramid, triangular prism, triangular cross-section column Heights: 50-1540 Hollow diameter: 2-1054	Polymethyl methacrylate (PMMA), Polyglycolic acid (PGA), Polycarbonate (PC), Negative PR (SU-8)	Reusable, enables uniform pattern formation, can form complex structures	Pattern distortion possible, risk of bubble formation, potential infiltration issues	[99,101, 118,121, 122,125, 155,163, 167,169, 170]
		2nd molding	Shape: pyramid Heights: 650 Hollow diameter: 20-60	Nickel	Easy to form the second mold from the first mold Suitable for manufacturing	Requires soft materials like silicon for easy separation Mold type depends on the material used	[168]
		Casting	Shapes: syringe, triangular pyramid Heights: 500-886 Hollow diameter: 49-200	Polydimethylsiloxane, Polyimide (PI)			[86,114]

lumen diameters of 20–60 μm [168].

A particularly noteworthy method involves combining an intaglio mold with lithography [125]. In this case, the intaglio mold defines the HMN's lateral geometry, while the height can be freely adjusted by controlling the thickness of the photoresist (PR) layer deposited on the mold surface.

Additionally, a wide variety of HMN shapes have been fabricated using intaglio mold casting, including conical [101], pyramidal [169], syringe-like [86], triangular pyramidal [114,170], and triangular cross-section columnar structures [163].

4. Why should drugs be administered through HMNs?

Table 6 lists transdermal drugs approved by the FDA to date. Approval years and average molecular weights were sourced from DrugBank 6.0 [171], while the compounds' polarity and administration methods for injectable formulations were verified using multiple references.

To achieve therapeutic effects through intact skin, drugs must traverse three primary pathways: trans-appendageal, intracellular, and intercellular. Generally, an appropriate compound polarity and a molecular weight of 500 Da or less are required. However, additional factors, such as the application site of the transdermal preparation, histological thickness, and subcutaneous blood flow rate, must also be considered when quantifying systemic drug delivery [172]. Changes in skin structure or function caused by disease, as well as environmental factors like abrasions or wounds, can significantly impact transdermal drug delivery [173].

Unlike oral or injectable routes, transdermal drug dosages are expressed as drug concentrations per unit surface area. This highlights the importance of parameters such as the permeability coefficient, prescribed drug concentration, and application surface area, which

significantly influence efficacy. The physical and chemical processes governing dosage control in conventional transdermal systems are complex and vary widely across systems [174–178].

HMN technology offers a significant advantage by simplifying the complexity of dosage control. Once HMNs with an appropriate hollow size have been designed, actuators can effectively regulate the drug delivery rate per unit time. Integrating actuator control technologies with the selection and design of various hollow sizes, as outlined in the manufacturing processes, is essential (see Fig. 7(a)).

Another key advantage of HMNs is their flexibility in terms of drug delivery depth. The injectable formulations listed in Table 5 have various optimal delivery depths depending on the drug, ranging from the dermis to the subcutaneous and muscle layers. Delivery depth is a critical parameter affecting the absorption rate and must be carefully considered for effective systemic drug delivery [179]. Although typical HMNs target the epidermis and dermis, their flexibility in delivering controlled dosages tailored to absorption rates makes them more advantageous than other MN types. Designing needles of suitable lengths for specific targets and administration sites further emphasizes the utility of HMNs (see Fig. 7(b)).

Additionally, HMNs facilitate the reuse of already approved drugs, offering significant advantages in drug development. Establishing optimal dosages and formulations based on the delivery method, while reevaluating compound properties, enables the effective repurposing of existing drugs. Given that drug development often takes over a decade [180,181], leveraging validated injectable formulations of existing compounds can save considerable time and resources.

In conclusion, the HMN delivery mechanism holds strong potential in the transdermal drug delivery market due to flexibility in managing dosage and speed, independent of the SC barrier. The ability to precisely adjust delivery rates across a wide range via needle size and actuators is unmatched among microneedle technologies. By integrating complex

Table 6
Summary of FDA-approved transdermal drugs.

Compound	FDA approval year	FDA-approved transdermal product	Type	Polarity	Average molecular weight	When used in injectable form			Ref.
						Administration route	Target	Dosage range	
Scopolamine	1979	Transderm-Scop®	Hormone	Hydrophilic	303.15	Subcutaneous	Subcutaneous layer	0.32–0.65 mg	[171,182,183]
Nitroglycerin	1981	Transderm-Nitro®	Hormone	Lipophilicity	227.00	Intravenous	Dermis	5 mcg/min	[171,182,184]
Clonidine	1984	Catapres-TTS®	Analgesic	Hydrophilic	229.02	Intravenous	Dermis	0.25–0.5 mcg/kg/hr	[171,182,185]
Estradiol	1986	Estraderm®	Hormone	Lipophilicity	272.18	Intramuscular	Muscle layer	10–20 mg	[171,182,186]
Fentanyl	1990	Duragesic®	Analgesic	Lipophilicity	336.22	Intramuscular, Intravenous	Muscle layer, Dermis	25–100 mcg	[171,182,187]
Nicotine	1991	Nicoderm®, Habitrol®, ProStep®	Hormone	Hydrophilic	162.12	Intravenous	Dermis	1–1.5 mg	[171,188,189]
Testosterone	1993	Androderm®, Testoderm®	Hormone	Lipophilicity	288.21	Intramuscular	Muscle layer	50–400 mg	[171,182,190]
Lidocaine/Epinephrine	1995	Iontocaine®	Analgesic	Hydrophilic	234.17/183.09	Intravenous	Dermis	7 mg/kg	[191,192]
Estradiol/Norethidrone	1998	Combipatch®	Hormone	Lipophilicity	272.18/298.19	No FDA-approved injectable drugs.			[193]
Lidocaine	1999	Lidoderm®	Analgesic	Hydrophilic	234.17	Intravenous	Dermis	4.5 mg/kg	[171,182,194]
Ethinyl estradiol/Norelgestromin	2001	Ortho Evra®	Hormone	Lipophilicity	296.18/327.22	No FDA-approved injectable drugs.			[182,195]
Estradiol/Levonorgestrel	2003	Climara Pro®	Hormone	Lipophilicity	272.18/312.21	No FDA-approved injectable drugs.			[180,182,196]
Oxybutynin	2003	Oxytrol®	Hormone	Hydrophilic	357.23	Intramuscular, Intravenous	Muscle layer, Dermis	0.3 mg/kg	[171,182,197]
Lidocaine/Tetracaine	2005	Synera®	Anesthetic	Hydrophilic	234.17/264.18	No FDA-approved injectable drugs.			[191,198]
Methylphenidate	2006	Daytrana®	Hormone	Hydrophilic	233.14	Intravenous	Dermis	0.5 mg/kg	[171,182,199]
Selegiline	2006	Emsam®	Hormone	Lipophilicity	187.14	Intravenous	Dermis	10 mg/kg	[171,182,200]
Fentanyl hydrochloride	2006	Ionsys®	Analgesic	Hydrophilic	372.20	Intravenous	Dermis	4.5 mg/kg	[201–204]
Diclofenac epolamine	2007	Flector®	Analgesic	Hydrophilic	411	No FDA-approved injectable drugs.			[182,205]
Rivastigmine	2007	Exelon®	Hormone	Lipophilicity	250.17	Intravenous	Dermis	12 mg/day	[171,182,206]
Rotigotine	2007	Neupro®	Hormone	Hydrophilic	315.17	Subcutaneous	Subcutaneous layer	1 mg/kg	[171,182,207]
Granisetron	2008	Sustol®, Sancuso®	Antiemetic	Hydrophilic	312.20	Intravenous	Dermis	3 mg	[171,182,208]
Menthol/Methylsalicylate	2008	Salonpas®	Analgesic	Lipophilicity	156.27/152.15	No FDA-approved injectable drugs.			[182,209]
Capsaicin	2009	Qutenza®	Analgesic	Lipophilicity	305.20	No FDA-approved injectable drugs.			[171,182,210]
Buprenorphine	2010	Butrans®	Analgesic	Lipophilicity	467.30	Intramuscular	Muscle layer	0.3 mg	[171,182,211]
Sumatriptan	2013	Zecuity®	Analgesic	Hydrophilic	295.14	Subcutaneous	Subcutaneous layer	6 mg	[171,182,212]
Asenapine	2019	Secuado®	Hormone	Lipophilicity	285.09	No FDA-approved injectable drugs.			[182,213]
Donepezil	2022	Adlarity®	Hormone	Hydrophilic	379.22	Intravenous	Dermis	1–2 mg	[171,214]

Note: The dosage range was investigated based on injectable formulations.

delivery forms and selectively administering drugs, HMNs are promising tools for effective and precise drug delivery. Advancing HMN technology to optimize dosage control and expand its applications is critical for maximizing its impact.

5. Technologies shaping the future of healthcare systems: HMNs

Rapid advancements in MEMS processing during the late 1990s significantly facilitated the development of various types of MNs, thereby accelerating research in this field (Fig. 8(a)). The number of academic publications on MNs has steadily increased annually, with diverse MN types that can bypass the SC barrier a major topic of interest (Fig. 8(b)). Among these, HMNs have unique advantages including precise dosage control and the ability to deliver mixtures of various drug

formulations. Despite these benefits, HMNs have received relatively limited attention, underscoring the need to highlight their potential.

Unlike other MN types, HMN are uniquely capable of delivering drugs through their hollow interior, enabling precise dosage control. This capability supports personalized treatments and is particularly advantageous for managing complex diseases where careful adjustment of drug dosages and concentrations is critical.

The flexible dosage control provided by HMNs is essential for chronic disease management. Precisely calibrated drug delivery helps maintain patient stability while minimizing side effects by optimizing drug concentrations [215]. Additionally, in emergency situations, HMNs allow for immediate dosage adjustments, ensuring rapid and effective treatment.

Another notable advantage of HMNs is their compatibility with a

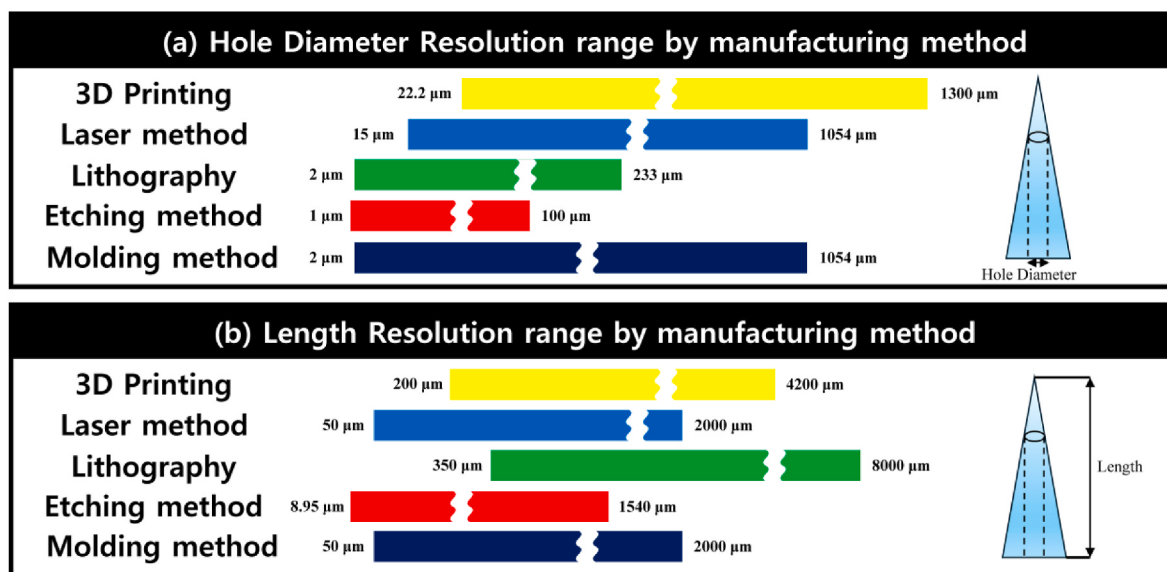


Fig. 7. Morphological parameters of HMN. (a) Hole diameter and (b) length resolution ranges by manufacturing method.

wide range of drug formulations. While traditional solid or dissolvable microneedles can only deliver specific formulations, HMNs can deliver liquids, suspensions, and highly viscous drugs, enabling diverse therapeutic applications. This versatility is particularly useful for combination therapies, such as cancer treatments [216], where different drugs can be delivered either sequentially or simultaneously to maximize efficacy.

Beyond drug delivery, HMNs are emerging as platforms capable of integrating fluid extraction and analytical functionalities [217]. This positions HMNs as a promising foundation for integrated diagnostic–therapeutic systems that combine drug administration with real-time biosignal monitoring. For instance, HMN-based systems for glucose monitoring and automatic insulin delivery could revolutionize daily health management for patients [218].

Future advancements in HMN technology are expected to involve the integration of microfluidic systems, micropumps, and biosensors, paving the way for smart, adaptive drug delivery platforms. The incorporation of microfluidic channels can enable precise, programmable drug release, improving both treatment efficacy and patient compliance. Additionally, micropumps could facilitate on-demand drug administration, ensuring that medication is delivered at optimal times based on

individual patient needs. Furthermore, biosensors embedded within the HMN system could provide real-time physiological data, such as glucose levels or inflammatory markers, enabling feedback-controlled drug delivery for personalized treatment. These technological advancements could transform HMN from a conventional drug delivery tool into an intelligent, automated platform capable of responding dynamically to real-time physiological conditions. Future research should focus on optimizing these integrated systems to enhance their efficiency, reliability, and user-friendliness, ultimately contributing to next-generation healthcare solutions.

HMNs also play a pivotal role in public health by enabling minimally invasive vaccine delivery. This approach can enhance patient compliance during large-scale immunization campaigns, particularly during pandemics, while minimizing pain, reducing infection risks, and simplifying the vaccination process. Furthermore, when paired with drug pumps, HMNs can serve as long-term controlled drug-release systems, making them ideal for chronic disease management.

Despite these advantages, the regulatory framework for HMN-based drug delivery systems remains underdeveloped. The FDA's 2020 guidance on microneedling products outlines general considerations for safety and efficacy evaluation, including needle length, density,

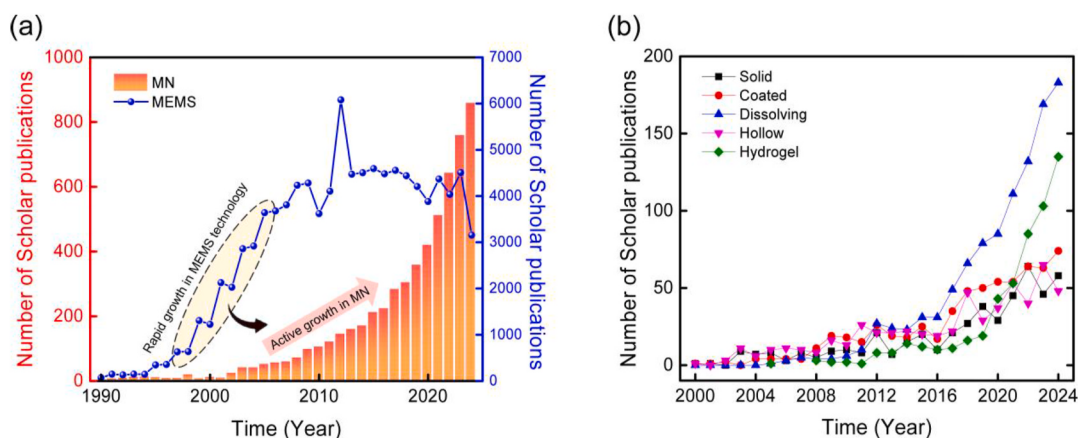


Fig. 8. (a) Chronology of MN and MEMS development. Publications were investigated using the “Web of Science” filtering with the keywords “microneedle” and “MEMS”. (b) Chronology of publications on microneedles, categorized by type of drug delivery method. Solid (solid), coated (coated, coating), dissolving (dissolving, dissolved), hollow (hollow), hydrogel (hydrogel) microneedles were investigated using the Web of Science with the keywords of (“microneedle” and (“Component 1” or “Component 2”). Results include studies conducted as of December 2024.

penetration depth control, and mechanical performance [219]. However, specific quantitative criteria and standardized evaluation protocols have yet to be established, leading to a case-by-case regulatory assessment. Given this uncertainty, early-stage discussions with regulatory bodies are crucial to ensuring compliance and facilitating the commercialization of HMN technologies. Future research should focus not only on optimizing HMN design and integration with diagnostic systems but also on establishing standardized guidelines to support their clinical translation.

In conclusion, HMNs offer unmatched precision and flexibility for drug delivery, overcoming the limitations of traditional treatment methods. This non-invasive and safe platform can facilitate tailored healthcare solutions, underscoring the potential for HMNs to play a central role in future healthcare systems. By integrating HMN with smart microfluidic and biosensing technologies, future drug delivery systems can evolve into highly adaptive, patient-specific platforms, marking a significant leap forward in personalized medicine.

6. Conclusion

HMNs have the potential to address the limitations of existing medical technologies through their precise and flexible drug delivery capabilities. Current transdermal drug delivery systems often require varying dosages and delivery depths depending on their complex pharmacokinetic mechanisms. HMNs stand out as unique platforms due to their high compatibility with a wide range of drug formulations, enabling them to meet complex therapeutic demands. Additionally, they facilitate patient-specific designs with minimal invasiveness through advanced manufacturing processes. Despite these advantages, the development of HMN technology has lagged behind that of other drug delivery systems, with limited research and industrial focus. Continuous efforts and increased support are essential to unlock the full potential of HMNs and realize their transformative impact on healthcare.

CRedit authorship contribution statement

Jongwon Kim: Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Jaehoon Jeong:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jung Ki Jo:** Writing – review & editing, Validation, Supervision, Formal analysis. **Hongyun So:** Writing – review & editing, Supervision, Resources, Funding acquisition.

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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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