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3D PRINTING TECHNOLOGY IN MICRONEEDLE FOR TRANSDERMAL DRUG DELIVERY

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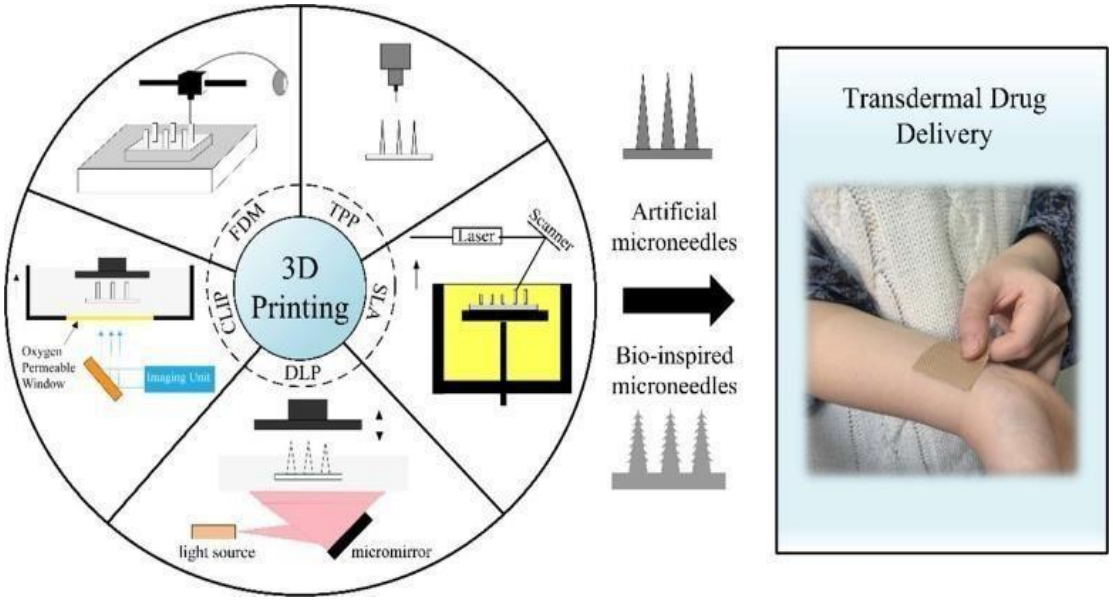
• ABSTRACT

Transdermal drug delivery helps by pass first-pass metabolism and ensures prolonged, controlled release of medications. However, its efficiency is hindered by the protective barrier of the stratum corneum Microneedles offer a modern transdermal system that is pain-free, minimally invasive, user-friendly, and capable of delivering drugs with enhanced bioavailability.[1] 3D printing is revolutionizing microneedle (MN) fabrication for transdermal drug delivery, offering noninvasive administration, better patient compliance, and bypassing first-pass metabolism. MNs, classified as solid, coated, hollow, and dissolving, enable delivery of drugs, vaccines, and biologics. 3D printing allows precise customization, rapid prototyping, complex designs, and controlled drug release, making MNs suitable for personalized treatments. Despite challenges like slow production, quality issues, and intellectual property concerns, advances in materials, automation, and scalable methods are expected to overcome these barriers. Applications extend to biosensing, cancer therapy, and chronic disease management, positioning 3D-printed MNs as a promising step toward personalized medicine.[2] Microneedles are gaining attention as advanced transdermal drug delivery systems due to improved patient compliance and self-administration compared to traditional injections. However, challenges in precise macroscales fabrication hinder their commercialization, especially for personalized medicine. Recent research highlights the use of 3D printing with various techniques and formulations to create synthetic carriers and bioinspired microneedles. This review outlines these advances, their benefits, limitations, and potential as nextgeneration drug delivery systems.[3]



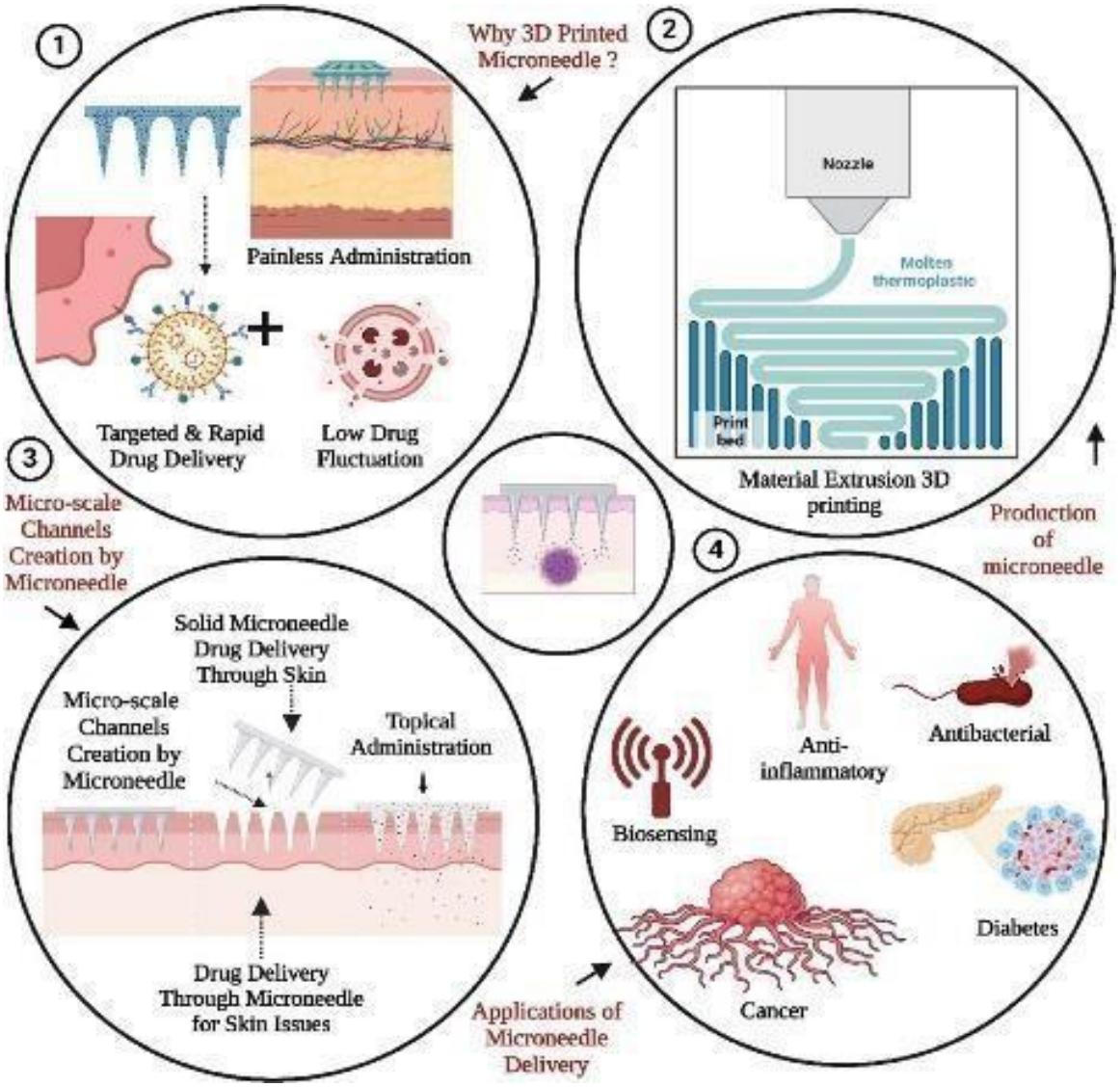
- **KEYWORDS**: Transdermal delivery, Controlled release, Microneedles, Minimally invasive, Bioavailability, 3D printing, Prototyping, Biosensing.

- **INTRODUCTION**

Transdermal drug delivery (TDD) has gained attention as a promising alternative to oral dosing and hypodermic injections, with increasing relevance in medical and pharmaceutical applications. Microneedles (MNs), a minimally invasive TDD strategy, are commonly used in healthcare and cosmetology. They create macroscales pathways from the stratum corneum to the dermis, enabling the delivery of hydrophilic and large-molecule drugs into the skin. Despite improving penetration, MNs alone cannot generate sufficient driving force for deeper drug transport. To overcome this limitation, researchers have developed a 3D-printed ultrasonic microneedle array (USMA), which integrates hollow MNs with an ultrasonic transducer. While the hollow MNs pierce the skin barrier, ultrasound transmitted through them enhances drug movement within tissues. Tests using methylene blue and bovine serum albumin on porcine skin showed that USMA markedly increased delivery efficiency. In addition, it lowered insertion force and minimized tissue injury, making the method safer and more comfortable. These results suggest that USMA has strong potential as a clinical drug delivery platform, offering both high efficiency and improved patient comfort.[4]

3D printing has effectively overcome the challenges of conventional microneedle fabrication by offering continuous, one-step manufacturing and the ability to achieve personalized designs. Known as additive manufacturing (AM), this technique uses computer-aided design (CAD) to build structures layer by layer, enabling the creation of highly complex geometries.

In the last decade, multiple 3D printing approaches—including material extrusion, photopolymerization, powder bed fusion, and material/binder jetting—have been employed to produce diverse drug dosage forms, such as oral "printlets" and targeted implants, showcasing its promise in pharmaceutical development, especially personalized medicine. More recently, 3D printing has been widely applied to fabricate both artificial and bio-inspired microneedles for minimally invasive transdermal drug delivery. This review presents an overview of 3D-printed microneedles, their benefits and limitations, as well as future perspectives on their role in the pharmaceutical industry. The literature was sourced from major databases (PubMed, SCOPUS, Web of Science, and Google Scholar) and cross-referenced, covering studies from January 2015 to September 2020, with notable earlier works also included. The keywords for the search were "3D printing," "microneedles," and "transdermal drug delivery".[3]



Transdermal drug delivery (TDD) delivers medications through the skin and offers a non-invasive substitute for oral and injectable routes. It provides painless administration, bypasses first-pass metabolism, enhances patient compliance, allows self-use, and ensures minimally invasive therapy. This pathway also improves drug bioavailability, making it effective for both local and systemic treatments. Various TDD systems, such as transdermal and iontophoretic patches, have been investigated, with several already approved for clinical use and available on the market.[5,6,7]

To study how drugs penetrate the skin, it is necessary to look at its structural organization. The skin consists of three main layers: the dermis, epidermis, and hypodermis. The epidermis is further divided into several layers—stratum granulosum, stratum corneum, stratum lucidum, stratum spinosum, and stratum basale. The stratum corneum, composed of dead keratinized cells and corneocytes, is highly hydrophobic and acts as the primary barrier that limits the passage of most drugs through the skin.[8] The skin serves as a defense barrier against harmful agents. Small, low-molecular-weight substances can penetrate it with ease, whereas larger molecules require advanced techniques for effective entry.[9]

Microneedles (MNs) are tiny needle structures that penetrate the skin in a minimally invasive manner to administer drugs, vaccines, and bioactive agents. They can be produced from various materials, including silicon, polymers, metals, and biomaterials, to effectively bypass the stratum corneum for therapeutic applications. In contrast to conventional hypodermic needles, MNs improve skin permeability and bioavailability while providing controlled drug release without inducing pain, fear, or discomfort.[10,11] 3D printing (3DP) is an emerging technology in the pharmaceutical field that enables the production of small-batch, customized medicines with specific doses, shapes, and release profiles. It supports personalized medicine throughout drug development, reducing risks of undertreatment or side effects and improving patient adherence. 3DP is especially beneficial for pediatric, geriatric, and dysphagic patients, offering accurate, cost-effective, and on-demand drug formulations that enhance accessibility, including in remote areas.[12,13]

A) Skin structure with MN structure and B) Passage of different TDDSs

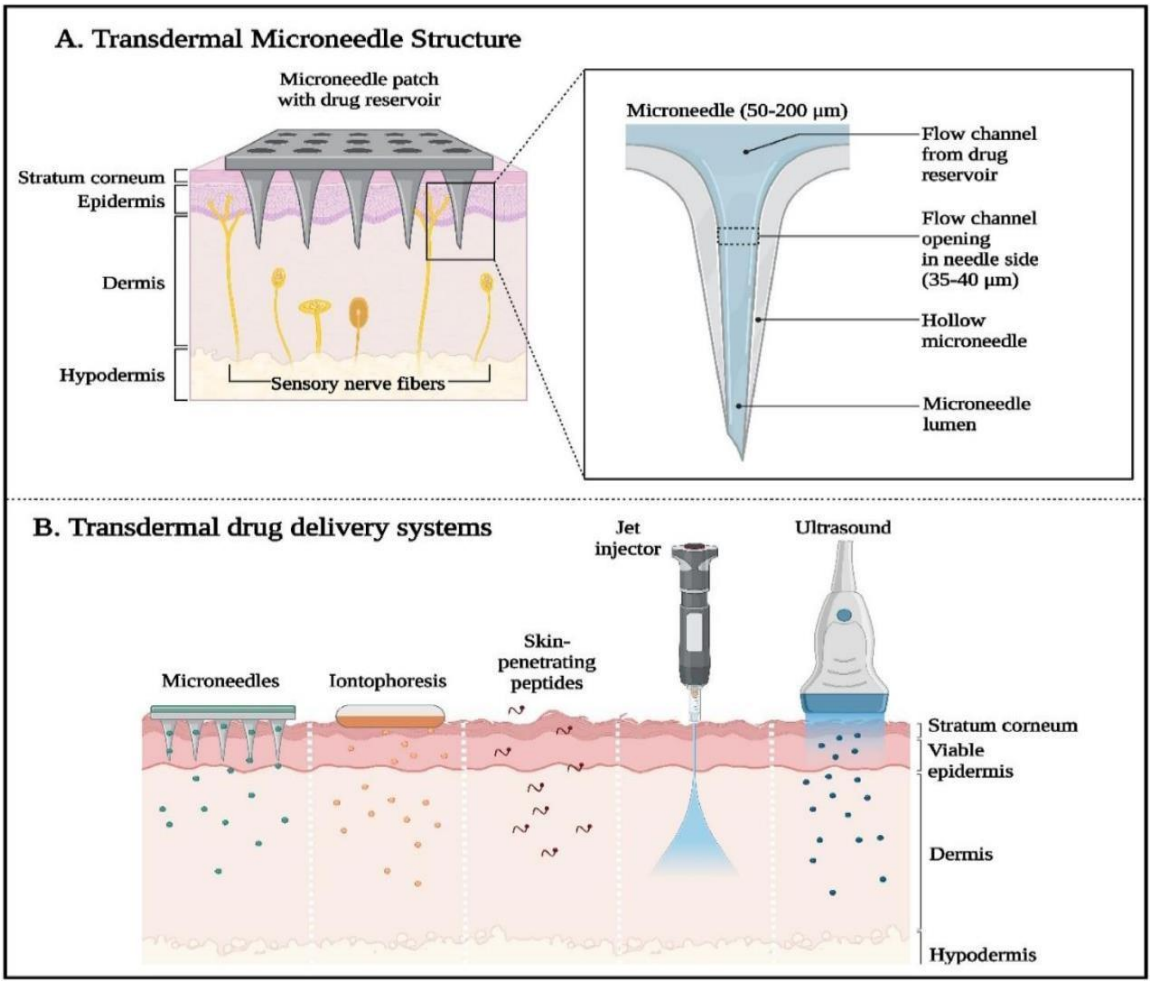


Fig. 1: A) Skin structure with MN structure B) Passage of different TDDSs.

3D printing enables the creation of microneedles (MNs) with precise geometries, controlled drug release, and improved strength, making them more effective than traditional designs. This technology allows customized transdermal drug delivery systems (TDDSs) tailored to patient needs. Recent research has also extended MN use to brain-targeted nasal delivery. A dissolvable toothbrush-shaped MN patch, combined with cyclodextrin-based nanocarriers, showed rapid dissolution, sustained drug release, and significantly enhanced huperzine A delivery, improving outcomes in neurodegenerative models.[14]

• SKIN STRUCTURE AND VARIOUS LAYERS

The skin, the largest and most visible organ of the body, serves as a protective shield for internal organs, with a thickness ranging from 0.28 to 1.5 mm. It accounts for nearly one-third of the body's blood circulation and plays crucial roles in regulating temperature, maintaining electrolyte balance, and providing immune defense against microbes.

Additionally, it guards against harmful chemicals, radiation, and physical damage. Beyond these functions, the skin is also a valuable route for drug delivery, enabling therapeutic action with minimal side effects, even for potent compounds.

Anatomically, the skin is made up of the epidermis, dermis, hypodermis, subcutaneous tissues, blood vessels, sweat and sebaceous glands, hair follicles, nerves, and lymphatic vessels. The epidermis consists of five layers: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (SC). The SC, the outermost layer, is structurally distinct and acts as the primary barrier to drug absorption. It follows a "brick-and-mortar" structure, where keratinocytes (bricks) are embedded in lipid layers (mortar). Despite being flexible, this arrangement makes the SC relatively impermeable. Corneocytes are arranged in vertical, heptagonal columns within 15–22 organized lipid matrix layers, which largely control drug penetration through the skin.

Beneath the epidermis is the dermis, a 3–5 mm thick connective tissue layer containing blood vessels, lymphatics, and nerves. Below it lies the hypodermis or subcutaneous tissue, which serves as a fat reservoir, provides mechanical protection, nutritional support, and helps regulate body temperature. For drugs to enter systemic circulation, they must pass through all three layers. Despite these barriers, two main routes enable drug transport through the skin: direct penetration via the epidermis or through skin appendage channels.[15,16,17,18,19,20,21,22,23]

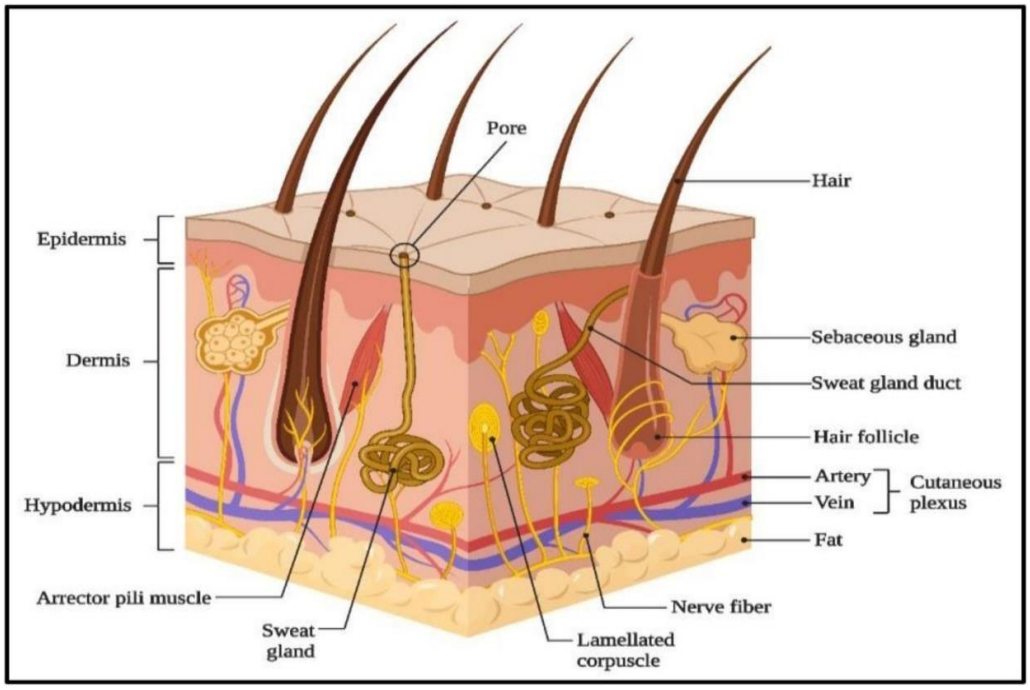


Fig. 2: Structure of skin including epidermis, dermis and hypodermis layers.

A) CHALLENGES IN SKIN DELIVERY

In recent years, drug delivery preferences have moved from oral administration to the transdermal route. Transdermal drug delivery systems (TDDS) increase drug permeation, boost patient adherence, and lower dosing frequency. Consequently, they offer multiple therapeutic benefits such as user-friendliness, prolonged release, non-invasive administration, reduced side effects, and minimal risk of infection without the need for applicators.

- **Stratum corneum acts as barrier**

The stratum corneum (SC), the outermost yet non-visible layer of the epidermis, makes up nearly 10% of body weight and receives a significant share of blood circulation. Though only 10–20 μm thick, it acts as the main barrier to drug penetration. Structurally, it consists of 10–15 compact lipid layers, corneocytes, and tight junctions, which restrict drug permeability. This barrier effect is strengthened by the steep drop in water content—from about 75% in the viable epidermis to 10–30% in the SC—leading to low hydration and reduced drug absorption. Drug movement through the SC occurs via two pathways: intracellular (through cells) and intercellular (between cells). Most drugs follow the intercellular lipid route through keratinocytes, requiring passage across both hydrophilic and lipophilic barriers, though resistance often develops rapidly.

- **Application pressure**

Microneedle (MN) systems offer a low-cost, customizable, and self-administered method that is easy to use and strong enough to penetrate the skin while staying attached for prolonged durations. They reduce tissue injury and pain by forming precise, stable channels for controlled drug delivery. To effectively cross the stratum corneum, each needle requires at least 0.08 N of force, and MNs must maintain their shape under pressure without breaking.[24]

- **Microneedles**

Microneedles (MNs) are an advancing technology in transdermal drug delivery systems (TDDS), providing a minimally invasive way to administer therapeutic agents. This approach helps overcome the limitations of traditional delivery methods, including oral, intravenous, and conventional transdermal routes. MNs are tiny needles at the micron scale, generally measuring 25–2500 μm in length, 1–25 μm at the tip, and 20– 250 μm in width.[25,26,27] Microneedles (MNs) may be configured as individual needles, in rows, or as array patches based on the application. By creating tiny pores in the skin, they allow macromolecular drugs

to cross the stratum corneum with minimal invasiveness, enhancing penetration and facilitating direct delivery to the dermis.[28]

- **Types of Microneedles**

Microneedles (MNs) differ in terms of application, materials, and drug delivery methods, enabling tailored designs to address specific medical requirements.[29,30,31] Microneedles are mainly made from metals, silicon, or biodegradable polymers, with each material providing distinct benefits suitable for specific drug delivery applications.

1. Solid Microneedles

Solid microneedles (MNs), the first type developed, penetrate the stratum corneum to create microchannels, enhancing the absorption of topically applied drugs.[30] These microneedles (MNs) are drug-free, requiring a drug-containing patch or gel to be applied after insertion.[32] Solid microneedles (MNs) offer simple fabrication and reusability, though frequent use can lead to patient discomfort and skin irritation.[28,33]

2. Coated Microneedles

Coated microneedles (MNs) have a drug layer added by dip coating, inkjet printing, or spray drying, which rapidly dissolves after insertion to enable quick drug delivery[34,35].The main drawback is limited drugloading because of the thin coating, and variations in coating thickness can result in inconsistent dosing.[32,36]

3. Hollow Microneedles

Hollow microneedles (MNs) work as miniature syringes, enabling precise delivery of liquid drugs through their hollow channels. The procedure includes skin insertion, drug infusion using pressure or electrical force, and removal of the needles afterward. They are especially effective for delivering vaccines, insulin, and biologics, though drawbacks include fabrication challenges, blockage risks, and potential leakage.[37]

4. Dissolving Microneedles

Dissolving microneedles (MNs) are composed of biodegradable materials that incorporate the drug within their structure. Upon insertion, they dissolve completely, enabling single-step drug release. They are often fabricated using solution-cast micromolding, where a polydimethylsiloxane (PDMS) master mold is employed to form cavities. Their key

advantages include eliminating sharp waste and minimizing infection risk, though their drug-loading capacity is lower than that of hollow or porous microneedles.[38,39]

5. Porous Microneedles

Porous microneedles feature interconnected pores that facilitate drug diffusion through the needle structure. They are compatible with both solid and liquid formulations and enable sustained drug release. The increased surface area supports higher drug loading, but their fabrication is expensive and challenging, requiring precise control of pore size and distribution to ensure consistent dosing and efficacy.[40]

6. Separable Microneedles

Separable microneedles detach either completely or partially from the applicator after insertion, enabling prolonged drug delivery without requiring the patch to stay on the skin. They are especially advantageous for vaccines and hormone treatments, but issues such as uniform detachment and full dissolution still pose challenges.[41]

7. Cryogenic Microneedles

Cryogenic microneedles are fabricated under ultra-low temperatures, enabling the delivery of temperature-sensitive drugs such as peptides and proteins. They ensure drug stability and minimize discomfort during insertion, but their expensive production process and need for controlled storage conditions hinder broad application.[42,43]

8. Core-shell Microneedles

Core–shell microneedles are designed with a drug-filled inner core enclosed by a biodegradable shell. Upon insertion, the shell dissolves first, allowing the drug to be released in a controlled fashion. This approach enhances stability and sustains drug release, but fabricating precise core–shell structures remains technically difficult.[44]

9. Hydrogel Microneedles

Hydrogel microneedles (MNs) are made from swellable polymers that absorb interstitial fluid from the skin, creating pathways for drug transport. They are biocompatible, non-toxic, and effective for prolonged drug delivery. Typical materials include natural polymers like gelatin and synthetic copolymers such as poly(methyl vinyl ether-co-maleic acid) cross-linked with polyethylene glycol.[45] Their use is limited by low mechanical strength and a reduced capacity for drug loading.

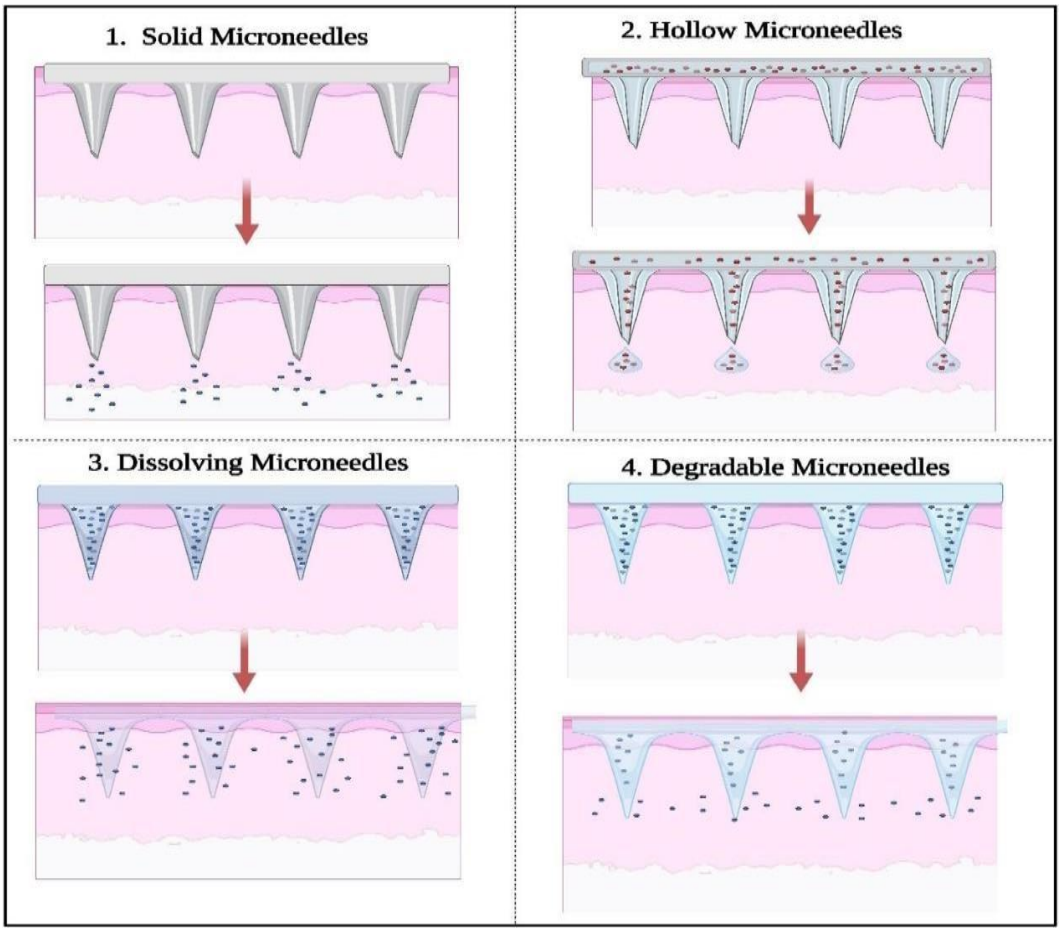


Fig. 3: Different types of Microneedles.

- **3D printing technology in Microneedles**

3D printing has transformed microneedle (MN) fabrication, becoming central to the progress of minimally invasive drug delivery technologies. These systems deliver drugs like vaccines and insulin transdermally by gently piercing the skin's outermost layer without causing pain.[29] Traditional approaches such as molding and microfabrication are often costly, complex, and time-consuming. By comparison, 3D printing offers a quicker, more versatile solution, allowing accurate customization of microneedle (MN) structures for specific therapeutic uses.[46] In addition to allowing intricate MN geometries, 3D printing accommodates a variety of materials that enhance drug delivery and biosensing performance. Research indicates that 3D-printed MN arrays attain precise sharpness much faster than traditional methods, reducing overall development time.[29] Although 3D-printed microneedles (MNs) offer many benefits, concerns about material compatibility and biocompatibility continue to limit their clinical use. Still, integrating 3D printing with MN technology has significant potential to promote personalized medicine and deliver innovative drug therapies.[47,48]

- **APPLICATION OF 3D – PRINTD MICRONEEDLES**

i. Extraction of biological fluids

Xie et al. designed 3D-printed hollow microneedle (MN) array patches to collect interstitial fluid (ISF) efficiently and without pain. When attached to a vacuum tube, the MNs apply negative pressure, allowing the painless extraction of approximately 18.42 ± 1.02 μL of ISF without affecting dermal pain receptors or blood vessels.[49] Miller et al. fabricated microneedles (MNs) for interstitial fluid (ISF) collection using a Becton Dickinson ultrafine pen needle, with a glass capillary attached to the MN backing. The collected ISF was clear and colorless, showing no blood cells or cellular material, which indicates that MN insertion caused no tissue damage.[50] Grooved microneedles created through photopolymerization 3D printing feature smooth, precise surfaces. Their non-swellable grooves facilitate interstitial fluid (ISF) extraction by capillary action, allowing the MN array to efficiently collect 20–30 μL of ISF without including other tissue components.[51]

ii. Bio-sensing

MN-based biosensors allow for real-time analysis and serve as revolutionary devices in disease diagnosis, facilitating early-stage detection.[52] Volecker et al. combined photopolymerization-based 3D printing with soft lithography to fabricate sophisticated microneedle (MN) arrays. These MNs are capable of detecting metabolites and proteins within a linear range, providing a platform for biomarker assessment in both healthy individuals and patients.[53]

iii. Cancer

Tumor heterogeneity, characterized by variations among cells within a single tumor, poses a significant obstacle to standardized cancer treatment. By considering patient-specific factors, 3D printing provides a personalized therapy platform that delivers drugs effectively while minimizing side effects.[54] Uddin et al. created 3D-printed cisplatin microneedle (MN) patches by first fabricating biocompatible polymer structures and then applying cisplatin via polymeric inkjet coating. The hydrophilic polymer blend of polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol facilitated fast delivery of the hydrophobic cisplatin into the epidermis. These cisplatin-loaded MN patches successfully eradicated cancer, resulting in 100% survival in animal studies.[55] Lahiji et al. fabricated self-locking dissolvable microneedles (MNs) using 3D printing techniques, specifically projection micro-stereolithography combined with digital light processing (DLP). With a sharp tip and broad

base design, these MNs remain firmly anchored in the skin after insertion. They showed significantly improved immune-modulatory drug delivery compared to traditional delivery methods.[56]

iv. Diabetes

Insulin microneedles (MNs) composed of an organic–inorganic bioceramic composite were prepared via a template method using hydroxyapatite and gelatin. They demonstrated minimal cytotoxicity, strong mechanical properties, and extended insulin delivery compared to subcutaneous injections. Thus, these MNs provide a more efficient and sustained-release option than traditional, painful subcutaneous administration.[57,58,59] Seong et al. developed a novel strategy for transdermal protein delivery using bullet-shaped, double-layered microneedle (MN) arrays with water-swellable tips. These MNs enable sustained insulin release and deliver the drug beneath the epidermis via interlocking skin adhesion. The bullet-shaped, double-layered design provides a controlled, long-lasting insulin release, maintaining blood glucose levels efficiently over time without causing pain, bursting, or inflammation.[60,61,62] Using a digital micromirror device (DMD) with static optical projection lithography (SOPL), hollow insulin microneedle (MN) patches were quickly and precisely fabricated. These patches showed excellent biocompatibility and mechanical strength, maintaining their shape during application. They penetrated the skin effectively, with microprobes closing after removal and full skin recovery within 120 minutes. The MNs successfully reduced blood glucose levels, supported rapid healing, and caused minimal tissue disruption.[44]

v. Anti-fungal

Clotrimazole is crystalline, poorly soluble in water, and carries high systemic toxicity when taken orally. In topical forms, it mostly stays within the epidermis, leading to limited bioavailability. To improve delivery, microneedles (MNs) were 3D-printed using Phrozen Aqua-Blue photocurable resin and dip-coated with a hydrogel solution composed of Carbopol EZ-3 Polymer (Lubrizol), glycerol, and triisopropanolamine. This method increased drug release and effectively suppressed the growth of *Candida albicans.*[63,42]

Amphotericin B, which has poor bioavailability, was formulated into microneedles (MNs) using laser-assisted matrix pulsed laser evaporation printing. MNs composed of polyvinylpyrrolidone and dimethyl sulfoxide exhibited concentration-dependent suppression of Candida albicans.[64] Terbinafine hydrochloride, known for its potential liver toxicity when

administered systemically, was incorporated into different microneedle (MN) patches using a combination of 3D laser cutting and solvent casting techniques. Three formulations were prepared: F1 (polyvinyl alcohol, Kollicoat IR, ethylene glycol, and gelatin), F2 (F1 with poloxamer 338), and F3 (chitosan, gelatin, and ethylene glycol). Cone-shaped MN patches achieved skin penetration rates of 74%, 42%, and 96.3%, respectively, indicating improved permeability.[65]

vi. Anti-inflammatory

Microneedles (MNs) were fabricated by employing the 3D printing digital light processing (DLP) technique to photopolymerize and cross-link polyethylene glycol diacrylate (PEGDA) hydrogel. The developed MNs showed improved mechanical strength and were sensitive to external stimuli, including pH and temperature. In vitro and ex vivo evaluations revealed a significant enhancement in drug release.[66] Fucoidan, a sulfated heteropolysaccharide extracted from brown algae, is traditionally used to treat ailments such as wind-dampness, paralysis, rheumatism, knee swelling, itching, and skin injuries. Fucoidan nanoparticles were linked with reactive oxygen species– responsive thioketal and loaded with Sinomenine, a drug with low water solubility, before being incorporated into soluble microneedles (MNs). These MNs enhanced drug concentration at the targeted site, providing an effective therapeutic effect.[67] MN scaffolds containing MXene and spidroin were created using extrusion 3D printing. These scaffolds exhibited self-healing capabilities and photothermal sensitivity, promoting wound healing. The findings indicate that 3D-printed multifunctional scaffolds have considerable potential for advancing wound repair.[68]

vii. Anti-Bacterial

High-GelMA (gelatin methacryloyl) is a biodegradable and biocompatible material with superior mechanical strength. Amoxicillin-loaded GelMA microneedles (MNs) were quickly produced with high resolution using DLP 3D printing. These antibacterial MNs demonstrated strong inhibitory effects against Staphylococcus aureus and Escherichia coli.[69] Ceftriaxone sodium, a broad-spectrum antibiotic (MW 554.58 g/mol), has poor bioavailability and is unstable in gastric conditions. Microneedles (MNs) were produced using stereolithography via vatphotopolymerization. Biocompatible, curable, and photo-crosslinkable resins were utilized to fabricate MNs with sufficient mechanical strength and low insertion force. In animal studies, these MNs showed enhanced bioavailability and efficient skin penetration.[70] Heat-sensitive Amoxicillin–Vancomycin-loaded solid polymeric hydrogel microneedles

(MNs) were fabricated using low-force stereolithography 3D printing. The MN arrays were biocompatible, non-toxic, and strong enough to endure insertion. Cross-linking agents controlled the MNs' swelling properties, maintaining therapeutic effectiveness. These antibiotic-loaded hydrogel MNs showed improved efficacy against bacteria like Staphylococcus aureus and Escherichia coli.[71]

Viii Anti-wrinkle

Microneedles (MNs) are ideal for anti-wrinkle applications because they offer excellent permeability, safe and nontoxic skin penetration. They have been designed for both treatment and cosmetic purposes.[72] Microneedles (MNs) have been widely used to deliver drugs effectively to targeted skin areas in cosmetic applications. Acetyl hexapeptide-3, a small peptide, is recognized for its potent and safe anti-wrinkle effects. Using CAD and DLP techniques, MNs were designed with a blend of biocompatible monomers—polyethylene glycol diacrylate (PEGDA) and vinyl pyrrolidone (VP) in a 3:7 ratio. The resulting MNs successfully penetrated human cadaver skin, exhibited minimal polymer toxicity, and maintained structural integrity under compression.[73] Complex polypeptide-loaded dissolving microneedles (MNs) were developed using oligopeptide-1, acetyl hexapeptide-8, and palmitoyl pentapeptide-4 to target wrinkle reduction. Hyaluronic acid (HA) and polyvinylpyrrolidone (PVP) served as the primary matrix materials due to their biocompatibility and skin-friendly nature. The MNs exhibited no cytotoxicity, and in vivo evaluations showed significant improvement in forehead lines, eyebrow lines, under-eye lines, nasoorbital folds, and frown lines.[74] A marked decrease In wrinkles and enhanced skin rejuvenation were seen in a wide range of individuals, including those with different skin types and thicknesses.[75]

Ix. Others

Microneedles (MNs) incorporating vaccines were produced through 3D printing using continuous liquid interface production (CLIP). They were designed to co-deliver various antigens (proteins, RNAs, DNAs, etc.) to trigger antibody generation. This approach enhanced overall IgG levels, maintained a balanced IgG1/IgG2 ratio, and induced a robust humoral immune response, contributing to the formation of a localized immune-competent environment.[76]

- **CHALLENGES AND FUTURE PERPECTIVE**

Advancements in 3D printing for microneedles (MNs) bring both promise and obstacles. The technology supports complex structures and personalized therapeutic delivery, yet challenges remain in terms of material suitability, production expenses, and design optimization. Limited biocompatibility of many 3D-printed materials restricts their medical application, emphasizing the need for research into biodegradable polymers, hydrogels, and hybrid materials to improve safety and drug release profiles. Moreover, the high manufacturing cost remains a major barrier to large-scale use, highlighting the importance of affordable approaches such as automated microfabrication, rolltoroll methods, and shared production facilities to bridge the gap from prototype to clinical translation.[77] The integration of AI-based computational modeling and machine learning offers great potential to refine microneedle (MN) design, improving penetration performance and achieving more controlled drug release. Yet, intellectual property rights (IPR) pose difficulties, as overlapping patents and unclear regulations can hinder commercialization. Approaches such as establishing patent pools, fostering collaborations between academia and industry, and developing transparent regulatory pathways may ease technology transfer. Looking ahead, the convergence of artificial intelligence with 4D printing could enable adaptive MN systems capable of responding to physiological changes. Despite these hurdles, steady progress in 3D printing is likely to advance innovation, ultimately making MN-based drug delivery more effective and widely available.[78]

- **RECENT RESEARCHES**

Current research on 3D printing for microneedles (MNs) in transdermal drug delivery (TDD) highlights the creation of customizable, sophisticated, and multifunctional MN systems aimed at improving personalized therapy. Advances include the use of multi-material printing for biomimetic structures, incorporation of sensing technologies, and the design of smart patches capable of simultaneous drug release and health monitoring. While 3D printing offers benefits such as precision, scalability, and personalization, challenges remain in regulatory approval and large-scale manufacturing.

Recent research underscores the role of 3D printing in creating sophisticated, patient-tailored microneedle (MN) arrays for transdermal drug delivery (TDD), offering enhanced mechanical stability, precise drug release, and opportunities for personalized therapy. Methods such as stereolithography (SLA) and multi-material printing facilitate the fabrication

of advanced MN designs, including biomimetic structures and eutectogel-based systems that improve drug loading, alongside multifunctional platforms equipped with sensors and wireless monitoring. Although issues with material biocompatibility and large-scale production persist, 3D-printed MNs are emerging as a groundbreaking solution for delivering drugs in a painless, efficient, and customizable manner.

• CONCLUSION

The adoption of three-dimensional (3D) printing for microneedle (MN) fabrication marks a significant step forward in transdermal drug delivery. This technology enables the creation of customized MNs tailored to individual patients, offering accurate drug delivery with minimal pain. Among its major benefits are rapid prototyping that accelerates product development, reduced production expenses, and the ability to construct intricate designs that conventional methods cannot achieve. However, issues such as material compatibility, appropriate biological responses, and regulatory challenges still hinder widespread clinical use. Ongoing research is necessary to address these barriers and refine MN design. As advancements continue, 3D-printed MNs are expected to play an essential role in the future of personalized medicine and the evolution of modern healthcare technologies.

• REFERENCES

1. Jung JH, Ji SG. Microneedle for transdermal drug delivery: current trends and fabrication. J Pharm Investig, 2021; 51(5): 503–517.
2. Prajapat M, Gholap AD, Shinde S, Padhiyar D, Butani S, Shah S, Rajput AS. 3D printing technology in microneedles: an emerging era in transdermal drug delivery.
3. Yang Q, Zhong W, Xu L, Li H, Yan Q, She Y, Yang G. Recent progress of 3printed microneedles for transdermal drug delivery. Int J Pharm., 2021; 593: 12010.
4. Chen Z, Wu H, Zhao S, Chen X, Wei T, Peng H, Chen Z. 3D-printed integrated ultrasonic microneedle array for rapid transdermal drug delivery.
5. Ali R, Mehta P, Arshad MS, Kucuk I, Chang MW, Ahmad Z. Transdermal microneedles – a material perspective. AAPS PharmSciTech., 2020; 21: 12.
6. Hegde NR, Kaveri SV, Bayry J. Recent advances in the administration of vaccines for infectious diseases: microneedles as painless delivery devices for mass vaccination. Drug Discov Today, 2011; 16: 1061–1068.
7. Aich K, Singh T, Dang S. Advances in microneedle-based transdermal delivery for drugs and peptides. Drug Deliv Transl Res., 2022; 12: 1556–1568.

8. Ita K. Transdermal delivery of drugs with microneedles – potential and challenges. Pharmaceutics, 2015; 7: 90–105.
9. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. Biomater Res., 2021; 25: 24.
10. Bird D, Ravindra NM. Transdermal drug delivery and patches – an overview. Med Devices Sensors, 2020; 3: e10069.
11. Dabbagh SR, Sarabi MR, Rahbarghazi R, Sokullu E, Yetisen AK, Tasoglu S. 3D-printed microneedles in biomedical applications. iScience, 2021; 24.
12. Chen G, Xu Y, Kwok PCL, Kang L. Pharmaceutical applications of 3D printing. Addit Manuf., 2020; 34: 101209.
13. Trenfield SJ, Awad A, Goyanes A, Gaisford S, Basit AW. 3D printing pharmaceuticals: drug development to frontline care. Trends Pharmacol Sci., 2018; 39: 440–451.
14. Loh JM, Lim YJL, Tay JT, Cheng HM, Tey HL, Liang K. Design and fabrication of customizable microneedles enabled by 3D printing for biomedical applications. Bioact Mater., 2024; 32: 222–241.
15. Azmana M, Mahmood S, Hilles AR, Mandal UK, Al-Japairai KAS, Raman S. Transdermal drug delivery system through polymeric microneedle: a recent update. J Drug Deliv Sci Technol., 2020; 60: 101877.
16. Dehdashtian A, Stringer TP, Warren AJ, Mu EW, Amirlak B, Shahabi L. Anatomy and physiology of the skin. Melanoma: Modern Multidisciplinary Approach, 2018: 15–26.
17. Gilaberte Y, Prieto-Torres L, Pastushenko I, Juarranz Á. Anatomy and function of the skin. Nanoscience in Dermatology, 2016; 1–14.
18. Li Z, Fang X, Yu D. Transdermal drug delivery systems and their use in obesity treatment. Int J Mol Sci., 2021; 22: 12754.
19. Wang FY, Chen Y, Huang YY, Cheng CM. Transdermal drug delivery systems for fighting common viral infectious diseases. Drug Deliv Transl Res., 2021; 11: 1498–1508.
20. Wong R, Geyer S, Weninger W, Guimberteau JC, Wong JK. The dynamic anatomy and patterning of skin. Exp Dermatol, 2016; 25: 92–98.
21. Wysocki AB. Skin anatomy, physiology, and pathophysiology. Nurs Clin., 1999; 34: 777–97.
22. Yadav N, Parveen S, Chakravarty S, Banerjee M. Skin anatomy and morphology, 2019; 1–10.
23. Zwirner J, Hammer N. Anatomy and physiology of the skin. In: Scars: A Practical Guide for Scar Therapy. Springer, 2024; 3–9.

24. Rajesh NU, Coates I, Driskill MM, Dulay MT, Hsiao K, Ilyin D, Jacobson GB, Kwak JW, Lawrence M, Perry J. 3D-printed microarray patches for transdermal applications. JACS Au., 2022; 2: 2426–45.
25. Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug delivery system. J Pharm Pharmacol, 2012; 64: 11–29.
26. Le Z, Yu J, Quek YJ, Bai B, Li X, Shou Y, Myint B, Xu C, Tay A. Design principles of microneedles for drug delivery and sampling applications. Mater Today, 2023; 63: 137–69.
27. Wu C, Yu Q, Huang C, Li F, Zhang L, Zhu D. Microneedles as transdermal drug delivery system for enhancing skin disease treatment. Acta Pharm Sin B., 2024; 14(12): 5161–80.
28. Oliveira C, Teixeira JA, Oliveira N, Ferreira S, Botelho CM. Microneedles' device: design, fabrication, and applications. Macromol, 2024; 4: 320–55.
29. Al-Nimry SS, Daghmash RM. Three-dimensional printing and its applications focusing on microneedles for drug delivery. Pharmaceutics, 2023; 15: 1597.
30. Aldawood FK, Andar A, Desai S. A comprehensive review of microneedles: types, materials, processes, characterizations and applications. Polymers, 2021; 13: 2815.
31. Rajput A, Kulkarni M, Deshmukh P, Pingale P, Garkal A, Gandhi S, Butani S. A key role by polymers in microneedle technology: a new era. Drug Dev Ind Pharm., 2021; 47: 1713–1732.
32. Peng T, Chen Y, Hu W, Huang Y, Zhang M, Lu C, Pan X, Wu C. Microneedles for enhanced topical treatment of skin disorders: applications, challenges, and prospects. Engineering, 2023; 30: 170–189.
33. Parhi R. Recent advances in 3D printed microneedles and their skin delivery application in the treatment of various diseases. J Drug Deliv Sci Technol, 2023; 84: 104395.
34. Alimardani V, Abolmaali SS, Yousefi G, Rahiminezhad Z, Abedi M, Tamaddon A, Ahadian S. Microneedle arrays combined with nanomedicine approaches for transdermal delivery of therapeutics. J Clin Med., 2021; 10: 181.
35. Bilal M, Mehmood S, Raza A, Hayat U, Rasheed T, Iqbal HM. Microneedles in smart drug delivery. Adv Wound Care., 2021; 10: 204–219.
36. Avcil M, Çelik A. Microneedles in drug delivery: progress and challenges. Micromachines, 2021; 12: 1321.
37. Gade S, Glover K, Mishra D, Sharma S, Guy O, Donnelly RF, Vora LK, Thakur RRS. Hollow microneedles for ocular drug delivery. J Control Release, 2024; 371: 43–66.

38. Kulkarni D, Damiri F, Rojekar S, Zehravi M, Ramproshad S, Dhoke D, Musale S, Mulani AA, Modak P, Paradhi R. Recent advancements in microneedle technology for multifaceted biomedical applications. Pharmaceutics, 2022; 14: 1097.
39. Vora LK, Courtenay AJ, Tekko IA, Larrañeta E, Donnelly RF. Pullulan-based dissolving microneedle arrays for enhanced transdermal delivery of small and large biomolecules. Int J Biol Macromol, 2020; 146: 290–298.
40. He YT, Liang L, Zhao ZQ, Hu LF, Fei WM, Chen BZ, Cui Y, Guo XD. Advances in porous microneedle systems for drug delivery and biomarker detection: a mini review. J Drug Deliv Sci Technol, 2022; 74: 103518.
41. Wang C, Jiang X, Zeng Y, Terry RN, Li W. Rapidly separable microneedle patches for controlled release of therapeutics for long-acting therapies. Med Drug Discov, 2022; 13: 100118.
42. Chang H, Chew SW, Zheng M, Lio DCS, Wiraja C, Mei Y, Ning X, Cui M, Than A, Shi P. Cryomicroneedles for transdermal cell delivery. Nat Biomed Eng., 2021; 5: 1008–1018.
43. Zheng M, Hu T, Yang Y, Qie X, Yang H, Zhang Y, Zhang Q, Yong KT, Liu W, Xu C. In situ-formed cryomicroneedles for intradermal cell delivery. NPG Asia Mater., 2024; 16: 11.
44. Li R, Liu X, Yuan X, Wu S, Li L, Jiang X, Li B, Jiang X, Gou M. Fast customization of hollow microneedle patches for insulin delivery. Int J Bioprinting, 2022; 8: 1–10.
45. Hou X, Li J, Hong Y, Ruan H, Long M, Feng N, Zhang Y. Advances and prospects for hydrogelforming microneedles in transdermal drug delivery. Biomedicines, 2023; 11: 2119.
46. Johnson AR, Procopio AT. Low cost additive manufacturing of microneedle masters. 3D Print Med., 2019; 5: 1–10.
47. Fu X, Gu J, Ma M, Liu R, Bi S, Zhang X, Zhang Y. Unique benefits and challenges of 3D-printed microneedles. Int J Bioprinting, 2024; 1896: 1–10.
48. Olowe M, Parupelli SK, Desai S. A review of 3D-printing of microneedles. Pharmaceutics, 2022; 14: 2693.
49. Xie Y, He J, He W, Iftikhar T, Zhang C, Su L, Zhang X. Enhanced interstitial fluid extraction and rapid analysis via vacuum tube-integrated microneedle array device. Adv Sci., 2024; 10: 2308716.

50. Miller PR, Taylor RM, Tran BQ, Boyd G, Glaros T, Chavez VH, Krishnakumar R, Sinha A, Poorey K, Williams KP. Extraction and biomolecular analysis of dermal interstitial fluid collected with hollow microneedles. Commun Biol., 2018; 1: 173.
51. Leng F, Zheng M, Xu C. 3D-printed microneedles with open groove channels for liquid extraction. Explor, 2021; 1: 20210109.
52. Dervisevic M, Harberts J, Sánchez-Salcedo R, Voelcker NH. 3D polymeric lattice microstructurebased microneedle array for transdermal electrochemical biosensing. Adv Mater, 2024; 36: 2412999.
53. Keirouz A, Mustafa YL, Turner JG, Lay E, Jungwirth U, Marken F, Leese HS. Conductive polymercoated 3D printed microneedles: biocompatible platforms for minimally invasive biosensing interfaces. Small, 2023; 19: 2206301.
54. Bhuskute H, Shende P, Prabhakar B. 3D printed personalized medicine for cancer: applications for betterment of diagnosis, prognosis and treatment. AAPS PharmSciTech., 2022; 23: 1–12.
55. Jiang T, Xu G, Chen G, Zheng Y, He B, Gu Z. Progress in transdermal drug delivery systems for cancer therapy. Nano Res., 2020; 13: 1810–1824.
56. Joo SH, Kim J, Hong J, Lahiji SF, Kim YH. Dissolvable self-locking microneedle patches integrated with immunomodulators for cancer immunotherapy. Adv Mater., 2023; 35: 2209966.
57. Cegla J. Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucoseresponsive insulin delivery. Ann Clin Biochem, 2015; 52: 720.
58. Jiang C, Chang JY. Unfolding and breakdown of insulin in the presence of endogenous thiols. FEBS Lett., 2005; 579: 3927–3931.
59. Yu W, Jiang G, Liu D, Li L, Tong Z, Yao J, Kong X. Transdermal delivery of insulin with bioceramic composite microneedles fabricated by gelatin and hydroxyapatite. Mater Sci Eng C., 2017; 73: 425–428.
60. Liu S, Jin MN, Quan YS, Kamiyama F, Katsumi H, Sakane T, Yamamoto A. The development and characteristics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insulin. J Control Release, 2012; 161: 933–941.
61. Owens DR. Optimising glycaemic control—the role of long-acting insulin analogues in basal insulin therapy. Br J Diabetes Vasc Dis., 2002; 2: 403–406.

62. Seong KY, Seo MS, Hwang DY, O'Cearbhaill ED, Sreenan S, Karp JM, Yang SY. A self-adherent, bullet-shaped microneedle patch for controlled transdermal delivery of insulin. J Control Release, 2017; 265: 48–56.
63. Jadach B, Nowak A, Długaszewska J, Kordyl O, Budnik I, Osmałek T. Coated microneedle system for delivery of clotrimazole in deep-skin mycoses. Gels., 2024; 10: 264.
64. Sachan R, Jaipan P, Zhang JY, Degan S, Erdmann D, Tedesco J, Vanderwal L, Stafslien SJ, Negut I, Visan A. Printing amphotericin B on microneedles using matrix-assisted pulsed laser evaporation. Int J Bioprinting, 2017; 3.
65. Albarahmieh EA, AbuAmmouneh L, Kaddoura Z, AbuHantash F, Alkhalidi BA, Al-Halhouli A. Fabrication of dissolvable microneedle patches using an innovative laser-cut mould design to shortlist potentially transungual delivery systems: in vitro evaluation. AAPS PharmSciTech., 2019; 20: 1–14.
66. Tunçel E, Tort S, Han S, Yücel Ç, Tırnaksız F. Development and optimization of hydrogel-forming microneedles fabricated with 3D-printed molds for enhanced dermal diclofenac sodium delivery: a comprehensive in vitro, ex vivo, and in vivo study. Drug Deliv Transl Res., 2024; 1–30.
67. Liu X, Diao N, Song S, Wang W, Cao M, Yang W, Guo C, Chen D. Inflammatory macrophage reprogramming strategy of fucoidan microneedles-mediated ROS-responsive polymers for rheumatoid arthritis. Int J Biol Macromol, 2024; 271: 132442.
68. Shao Y, Dong K, Lu X, Gao B, He B. Bioinspired 3D-printed MXene and spidroin-based nearinfrared light-responsive microneedle scaffolds for efficient wound management. ACS Appl Mater Interfaces, 2022; 14: 56525–56534.
69. Erkus H, Bedir T, Kaya E, Tinaz GB, Gunduz O, Chifiriuc MC, Ustundag CB. Innovative transdermal drug delivery system based on amoxicillin-loaded gelatin methacryloyl microneedles obtained by 3D printing. Materialia, 2023; 27: 101700.
70. Kawre S, Suryavanshi P, Lalchandani DS, Deka MK, Porwal PK, Kaity S, Roy S, Banerjee S. Bioinspired labrum-shaped stereolithography (SLA) assisted 3D printed hollow microneedles (HMNs) for effectual delivery of ceftriaxone sodium. Eur Polym J., 2024; 204: 112702.
71. Turner JG, Laabei M, Li S, Estrela P, Leese HS. Antimicrobial releasing hydrogel forming microneedles. Biomater Adv., 2023; 151: 213467.

72. Islam H, Poly TS, Tisha ZT, Rahman S, Naveed AIJ, Ahmed A, Ahmed SN, Hassan J, Uddin MJ, Das DB. 3D printed hollow microneedles for treating skin wrinkles using different anti-wrinkle agents: a possible futuristic approach. Cosmetics, 2023; 10: 41.
73. Lim SH, Tiew WJ, Zhang J, Ho PCL, Kachouie NN, Kang L. Geometrical optimisation of a personalised microneedle eye patch for transdermal delivery of anti-wrinkle small peptide. Biofabrication, 2020; 12: 035003.
74. Xing M, Liu H, Meng F, Ma Y, Zhang S, Gao Y. Design and evaluation of complex polypeptideloaded dissolving microneedles for improving facial wrinkles in different areas. Polymers, 2022; 14: 4475.
75. Hong JY, Ko EJ, Choi SY, Li K, Kim AR, Park JO, Kim BJ. Efficacy and safety of a novel, soluble microneedle patch for the improvement of facial wrinkle. J Cosmet Dermatol, 2018; 17: 235–241.
76. Caudill C, Perry JL, Iliadis K, Tessema AT, Lee BJ, Mecham BS, Tian S, DeSimone JM. Transdermal vaccination via 3D-printed microneedles induces potent humoral and cellular immunity. Proc Natl Acad Sci U S A., 2021; 118: e2102595118.
77. Bg PK, Mehrotra S, Marques SM, Kumar L, Verma R. 3D printing in personalized medicines: a focus on applications of the technology. Mater Today Commun, 2023; 35: 105875.
78. Nyaboke Y. Intellectual property rights in the era of artificial intelligence. J Mod Law Policy, 2024; 4: 57–72.