Journal of Agriculture, Biology and Applied Statistics
Vol. 5, Nos. 1-2, 2026, pp. 77-90
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URL: www.arfjournals.com
https://doi.org/10.47509/JABAS.2026.v05i01-02.07

An Overview of Microneedle Mediated Transdermal Drug Delivery: Painless Passage Through the Skin Barrier

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To Cite this Article

Misba Anjum, Ashly Merin George & Agilandeswari Devarajan (2026). An Overview of Microneedle Mediated Transdermal Drug Delivery: Painless Passage through the Skin Barrier. *Journal of Agriculture, Biology and Applied Statistics,* 5: 1-2, pp. 77-90.

Abstract: The skin, the body's largest organ, comprises three primary layers: epidermis, dermis and hypodermis. The stratum corneum, the outermost epidermal layer (~10–20 μm), acts as the principal barrier to transdermal drug delivery. Its brick-and-mortar structure of corneocytes embedded in lipid matrices impedes permeation, particularly for hydrophilic or high-molecular-weight compounds (>500 Da). Conventional approaches patches, chemical enhancers, iontophoresis and electroporation often yield suboptimal flux.

Microneedles (MNs) represent a transformative strategy, mechanically bypassing the stratum corneum via microchannels without stimulating nociceptors, thus enabling painless, enhanced permeation (10–1000× increase). MN arrays are classified into five types: solid (pre-treatment), coated (surface-bound drug), dissolving (matrix-embedded, biodegradable), hollow (fluid infusion), and hydrogel-forming (swelling-mediated sustained release). Critical quality attributes include drug content uniformity, weight variation, swelling ratio and mechanical integrity (insertion and fracture force). Microscopic techniques (SEM, confocal) assess morphological fidelity, while DSC, FTIR and XRD evaluate drug–polymer interactions and stability. *In vitro* permeation studies using Franz diffusion cells and *ex vivo*/*in vivo* models validate efficacy and skin recovery kinetics. Microneedle systems offer a minimally invasive, patient-compliant platform for transdermal delivery of therapeutics, vaccines, cosmetics and diagnostics.

Keywords: Microneedles, Transdermal drug delivery, Stratum corneum, Dissolving microneedles, Mechanical characterization, Permeation enhancement.

1. INTRODUCTION

Transdermal drug delivery (TDD) represents a globally recognized alternative to oral and parenteral administration, offering distinct clinical advantages. These

Received : 10 September 2026 • **Revised :** 22 September 2026 • **Accepted :** 29 September 2026 • **Published :** 19 October 2026

include the avoidance of hepatic first-pass metabolism, bypass of gastrointestinal degradation, and a significant reduction in systemic side effects [1]. TDD systems provide a steady-state delivery profile, which is particularly beneficial for chronic disease management where patient compliance is often a challenge. However, the inherent barrier function of the skin, primarily centered in the stratum corneum, strictly regulates the permeability of exogenous substances [2]. This barrier typically restricts effective permeation to drug molecules with low molecular weight (<500 Da), moderate lipophilicity (log P 1–3) and high potency [3].

The limitations of passive diffusion have led to the development of various enhancement strategies, ranging from chemical enhancers and thermal ablation to physical methods such as iontophoresis, electroporation and sonophoresis. While these methods can increase permeability, they are often associated with skin irritation, require complex and expensive equipment, or fail to deliver larger biotherapeutics efficiently. Microneedles (MNs) offer a superior solution by mechanically creating micro-conduits that are large enough to allow drug transport but small enough to avoid stimulating dermal nociceptors and blood vessels [4]. This "painless" technology has the potential to transform the delivery of vaccines, hormonal therapies, and dermatological treatments. This review synthesizes the current advancements in microneedle design, fabrication, and characterization, providing a comprehensive roadmap for their successful clinical translation.

2. PHYSIOLOGY AND BARRIER FUNCTION OF THE SKIN

The skin is the largest organ of the human body, accounting for approximately 15% of total body weight. It serves as a crucial interface, providing protection against UV radiation, chemicals, and pathogens, while also performing roles in thermoregulation and immune surveillance [5].

2.1. Epidermal Layers and the Stratum Corneum

The epidermis is the superficial, non-vascularized layer, ranging in thickness from 50 μm to 1.5 mm. It is composed primarily of keratinocytes in various differentiation stages. The outermost layer, the stratum corneum (SC), is the most significant barrier to drug diffusion. The SC consists of 15 to 20 layers of non-viable, flattened corneocytes densely packed with keratin filaments [6]. These cells are surrounded by a continuous lipid matrix composed of ceramides, free fatty acids, and cholesterol. This "brick-and-mortar" structure is remarkably impermeable to most substances, particularly polar and high-molecular-weight molecules [7].

2.2. Dermis and the Vascular Network

The dermis, located beneath the epidermis, is a thicker (0.5 to 3 mm) layer composed of collagen and elastin fibers. It contains blood vessels, lymphatic vessels, hair follicles, sweat glands, and nerve endings. The papillary dermis, adjacent to the epidermis, is rich in capillaries, making it the primary target for systemic drug absorption once the SC barrier is breached [8].

2.3. Molecular Transport and the Rationale For Microneedles

Drug transport through the skin occurs primarily via passive diffusion, governed by Fick's First Law: $J = -D (dc/dx) $, where J is the flux and D is the diffusion coefficient. The SC's low diffusion coefficient is the primary bottleneck for systemic delivery. Microneedles circumvent this by physically removing the SC barrier in localized areas, effectively creating "macro-pores" through which drugs can diffuse at rates several orders of magnitude higher than passive permeation [9, 10]. This mechanical disruption is temporary; the skin's barrier function typically restores itself within 24 to 72 hours through natural repair mechanisms.

3. CLASSIFICATION OF MICRONEEDLE SYSTEMS

Microneedles are categorized based on their structural design and the method by which they facilitate drug delivery, each offering specific advantages for different therapeutic needs.

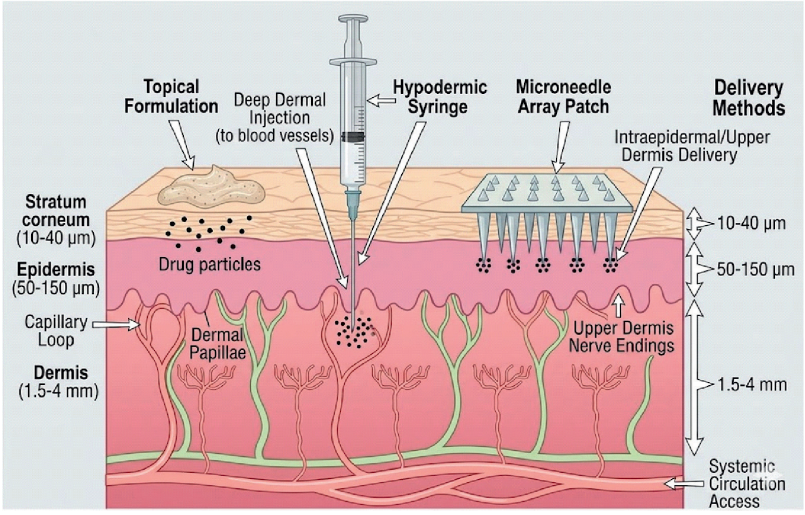


Fig. 1: Microneedle delivery methods

3.1. Solid Microneedles

Solid MNs are the simplest form of the technology, typically fabricated from silicon, stainless steel, or titanium. They are utilized in a "poke-and-patch" method: the array is applied to the skin to create micro-pores and then removed, followed by the application of a drug-loaded patch or topical formulation [11,12,13]. This pre-treatment significantly enhances the flux of large or hydrophilic molecules.

Advantages: High mechanical strength, robust penetration, and compatibility with various drug formulations.

Disadvantages: Two-step application process, risk of contamination during the interval between poking and patching, and the potential for patient error [14].

3.2. Coated Microneedles

Coated MNs utilize a "coat-and-poke" approach, where the therapeutic agent is applied as a dry film to the surface of solid microneedle shafts. Techniques such as dip-coating or spray-coating are used to ensure precise drug loading. Upon insertion into the skin, the coating dissolves in the interstitial fluid, rapidly releasing the drug [15].

Advantages: Rapid drug release, suitable for low-dose therapeutics like vaccines and potent biologics.

Disadvantages: Limited drug loading capacity determined by surface area, and potential for coating instability during storage [16].

3.3. Dissolving Microneedles

Dissolving MNs are fabricated from water-soluble or biodegradable polymers (e.g., PVP, HA, sugars) that encapsulate the drug within the needle matrix. Upon insertion, the needles dissolve completely, releasing the drug cargo and leaving no sharp waste behind [17].

Advantages: Self-disposable (no sharp waste), ideal for home use, and the ability to load drugs specifically in the needle tips ("tip-loading") for maximum efficiency.

Disadvantages: Lower mechanical strength compared to metals, sensitive to environmental humidity, and loading limits for very high-dose drugs [18].

3.4. Hollow Microneedles

Hollow MNs resemble miniaturized hypodermic needles, featuring an internal lumen for the active infusion of liquid drug formulations. This allows for the delivery

of larger volumes (up to 200 µl) and provides control over the delivery rate using pumps or pressurized reservoirs [19].

Advantages: Delivery of large volumes and high-dose biologics (e.g., insulin), and precise control over infusion rates.

Disadvantages: Prone to clogging by skin tissue (coring), requires specialized insertion devices, and higher complexity in fabrication [20].

3.5. Hydrogel-Forming Microneedles

Hydrogel MNs are made of cross-linked polymers that do not dissolve but instead swell upon contact with interstitial fluid. This swelling creates a continuous aqueous conduit for the drug to diffuse from an external reservoir into the skin [21].

Advantages: Delivery of high doses over extended periods, can be removed intact, and potential for biosensing applications.

Disadvantages: Slower onset of action compared to dissolving MNs, and the need for a separate drug reservoir [22].

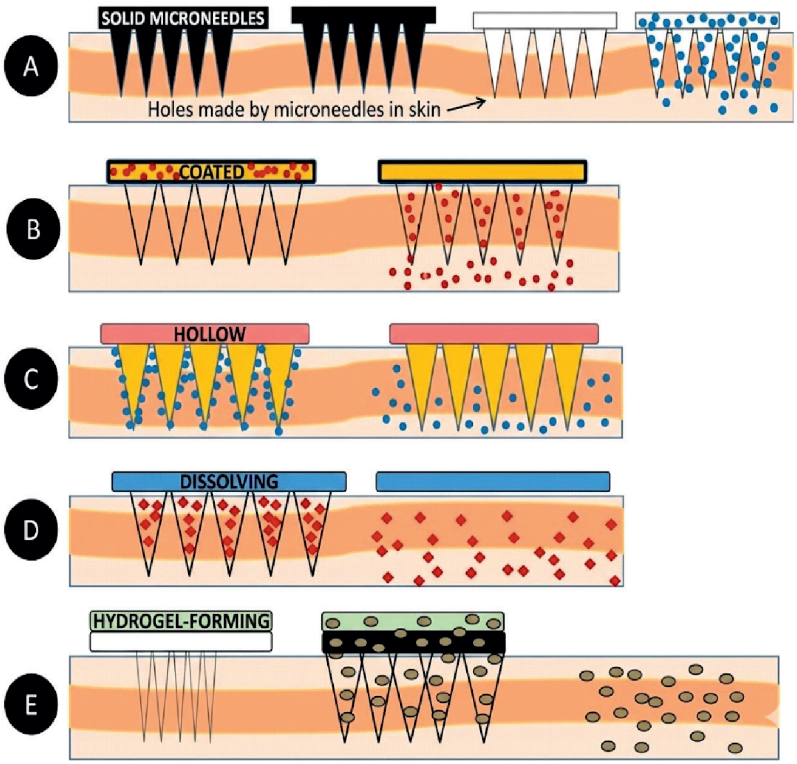


Fig. 2: Mechanism of Microneedle

4. FABRICATION STRATEGIES FOR MICRONEEDLE ARRAYS

The fabrication of microneedles requires sub-micron precision to ensure needle sharpness, structural integrity, and consistency across the array. The choice of technique is determined by the material properties and the intended application [23,24].

4.1. Micro Moulding and Casting

Micromoulding is the most prevalent technique for producing polymeric and dissolving microneedles. The process begins with the creation of a "master mould" using high-precision techniques like laser machining or photolithography [25,26]. The polymer solution, containing the therapeutic agent and stabilizers, is dispensed into the PDMS mould. To ensure the viscous solution fills the sharp needle tips, vacuum or centrifugal forces (e.g., 4000 RPM for 10 minutes) are applied [27]. The solvent is evaporated under controlled conditions (e.g., 25°C, 40% RH) for approximately 24 hours. A backing membrane is then added to provide mechanical support. This method is highly scalable and cost-effective for mass production [28, 29].

4.2. Photolithography and Etching

Photolithography is the gold standard for fabricating silicon and metal microneedles. The process involves coating a silicon wafer with a light-sensitive photoresist and exposing it to UV light through a mask to define the needle patterns. Deep Reactive Ion Etching (DRIE) is then used to remove material, creating high-aspect-ratio shafts with vertical walls. Tapered needles can be produced using wet chemical etching, which takes advantage of the crystal orientation of the silicon [29]. While these methods provide exceptional dimensional accuracy, the high cost of equipment and the fragility of silicon have led researchers to explore more robust alternatives like stainless steel and polymers.

4.3. 3D Printing And Additive Manufacturing

Stereolithography (SLA): Uses a UV laser to cure photosensitive resin layer-by-layer. SLA can produce MNs with diverse shapes and sizes with a resolution of ~25 μm.

Two-Photon Polymerization (2PP): This technique uses a highly focused femtosecond laser to trigger polymerization only at the focal point. With a resolution

of less than 100 nm, 2PP can produce needles with incredibly sharp tips and complex internal architectures, such as porous or barbed shafts [30].

Digital Light Processing (DLP): Offers faster printing speeds than SLA by projecting an entire layer of light at once. This makes it more suitable for small-scale production of customized clinical devices.

4.4. Thermal Processing and Laser Ablation

Micro-injection molding is used for high-volume production of thermoplastic MNs, such as those made from polycarbonate. Molten polymer is injected into a cooled micro-mould under high pressure, allowing for rapid cycle times. Laser ablation, using high-power femtosecond or nanosecond lasers, is employed to cut microneedle shapes directly from thin metal or polymer sheets. This method is highly versatile and does not require expensive masks or molds [31].

5. ADVANCED CHARACTERIZATION OF MICRONEEDLE SYSTEMS

5.1. Mechanical Characterization [32,33,34]

The mechanical performance of MNs is the primary determinant of their ability to successfully penetrate the skin barrier without breaking.

Axial Compression Testing: A single needle or array is compressed against a hard surface using a texture analyzer. The force-displacement curve is monitored to identify the failure point (buckling or fracture). For a 600 μm needle, a fracture force exceeding 0.5 N per needle is typically required to ensure penetration [35,36, 37].

Insertion Force: Measured by pressing the MN array against a skin mimic or excised skin. The force at which the first "pop" or drop in resistance occurs represents the insertion threshold. This value should be low (0.1 to 3 N for an array) to allow for manual application [37, 38].

Safety Factor: Defined as the ratio of the fracture force to the insertion force. A safety factor of at least 5 is recommended for clinical applications to prevent needle breakage during handling or misapplication.

5.2. Morphological and Dimensional Evaluation

Scanning Electron Microscopy (SEM): SEM provides detailed images of the needle surface, allowing researchers to verify tip sharpness and the fidelity of the fabrication process. It is used to identify defects such as rounded tips, shaft cracks, or surface roughness [39,40].

Confocal Laser Scanning Microscopy (CLSM): CLSM allows for the non-invasive visualization of the MNs in the skin. By labeling the drug with a fluorescent dye, researchers can map the three-dimensional distribution and penetration depth (typically 100 to 350 μm) of the drug within the epidermis

Optical Microscopy: Research microscopes (e.g., Olympus SZX16) equipped with digital cameras allow for rapid screening and quantitative measurements of array dimensions.

5.3. Physicochemical Stability and Drug Loading

Drug Content Uniformity: Assessed by dissolving MN patches in a suitable solvent and analyzing the solution via HPLC or UV-Vis spectrophotometry. High uniformity (±5%) is essential for consistent clinical dosing.

Weight Variation and Swelling: Patches are individually weighed to ensure batch-to-batch consistency. Swelling index testing for hydrogel MNs measures the capacity to absorb interstitial fluid, which directly correlates with the diffusion-based drug release rate [40, 41].

FTIR Spectroscopy: Used to identify potential chemical interactions (e.g., hydrogen bonding) between the drug and the polymer matrix by analyzing shifts in characteristic absorption peaks [42].

Differential Scanning Calorimetry (DSC): Evaluates the thermal properties and physical state of the drug within the MNs. The disappearance of a drug's crystalline melting peak suggests the formation of a stable amorphous dispersion, which can enhance solubility and release [43,44].

6. BIOLOGICAL EVALUATION AND PERMEATION METRICS

6.1. *In Vitro* Drug Release and Permeation Studies

Franz diffusion cells are utilized to model the release of drugs from MNs into the body. This setup consists of a donor and a receptor compartment separated by a semi-permeable membrane. The MN patch is applied to a pre-conditioned dialysis membrane or excised skin (porcine or human). The receptor compartment is filled with phosphate-buffered saline (PBS) at pH 6.8 or 7.4, maintained at a physiological temperature of 32°C to 37°C. The receiver phase is stirred using a magnetic bead to maintain sink conditions. Samples are withdrawn at regular intervals (e.g., 0.5, 1, 2, 4, 8, 12, and 24 hours) and analyzed for drug concentration via validated HPLC or UV-Vis methods [45, 46]. This allows researchers to calculate the cumulative drug

release and determine the release kinetics (e.g., zero-order, first-order, or Higuchi model).

6.2. In Vivo Animal Model Studies: Safety and Efficacy

Transepidermal Water Loss (TEWL): TEWL is monitored using a vapometer before and after MN application. An increase in TEWL indicates successful disruption of the stratum corneum barrier. Monitoring the return of TEWL to baseline (typically within 24–72 hours) allows for the assessment of skin recovery kinetics

Histological Evaluation: Skin biopsies are taken post-treatment, stained with Hematoxylin and Eosin (H&E), and examined under a microscope. This confirms the depth of needle penetration and ensures that no permanent tissue damage or significant inflammatory response has occurred.

Pharmacokinetic (PK) Analysis: Serial blood samples are collected and analyzed via HPLC or LC-MS/MS. Key parameters include the time to reach maximum concentration (T_max), the peak concentration (C_max), and the area under the curve (AUC), which reflects the total systemic exposure. These PK profiles are compared with traditional injections to evaluate the relative efficiency of MN delivery.

7. THERAPEUTIC APPLICATIONS AND FUTURE PERSPECTIVES

7.1. Vaccination and Global Health

The skin is rich in antigen-presenting cells (APCs), such as Langerhans cells. Delivering vaccines via MNs targets these cells directly, often resulting in a more robust immune response compared to traditional intramuscular injections. This "dose-sparing" effect allows for the use of smaller amounts of antigen to achieve protective immunity [47, 48]. Furthermore, the stability of vaccines in solid-state MN patches eliminates the need for a cold chain, significantly reducing the cost and logistical challenges of mass vaccination campaigns in developing countries.

7.2. Chronic Disease Management and Hormonal Therapy

For patients with chronic conditions requiring daily injections, such as diabetes (insulin) or growth hormone deficiencies, MNs offer a painless and patient-friendly alternative. Sustained-release hydrogel MNs are particularly promising for maintaining steady hormone levels over several days or weeks [48,49]. Integration with biosensors could lead to closed-loop systems that monitor biomarkers and deliver drugs accordingly.

7.3. Oncology and Targeted Therapy

Microneedles are being investigated for the local delivery of chemotherapeutic agents directly into tumor sites, particularly for skin cancers like melanoma. This approach maximizes the local drug concentration while minimizing systemic toxicity [50,51,52]. Furthermore, MNs can deliver immunotherapeutic agents to modulate the tumor microenvironment.

7.4. Dermatology and Cosmetics

In the cosmetic industry, MN patches are used to deliver anti-aging compounds (e.g., hyaluronic acid, peptides) and treatments for skin disorders like alopecia and hyperpigmentation. MNs also show potential in scar management by delivering drugs directly into the fibrotic tissue [53,54].

7.5. Challenges in Clinical Translation and Regulatory Hurdles

Despite their potential, several hurdles remain for the widespread adoption of microneedles. Moving from laboratory-scale micromoulding to high-throughput industrial manufacturing requires standardized processes and robust quality control. As combination products (device + drug), microneedles must satisfy both medical device and pharmaceutical regulations, requiring extensive safety and stability data. Sterilization methods must be validated to ensure they do not degrade the drug or the polymer matrix.

8. CONCLUSION

Microneedle technology stands at the forefront of the next generation of drug delivery systems. By merging the benefits of needle-based and needle-free delivery, it provides a minimally invasive, efficient, and patient-compliant platform for a vast range of therapeutics. Continued advancements in microfabrication, polymer science, and biosensing will likely address current limitations in drug loading and scalability, paving the way for microneedles to become a standard of care in global vaccination campaigns and chronic disease management. The transition from purely physical penetration to intelligent, responsive delivery systems marks the beginning of a new era in personalized medicine.

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