ISSN: 2231-3656

International Journal of Pharmacy and Industrial Research (IJPIR)

IJPIR |Vol.13 | Issue 4 | Oct - Dec -2023

www.ijpir.com

DOI: https://doi.org/10.61096/ijpir.v13.iss4.2023.336-350

Microneedle Patches for Transdermal Drug Delivery: Types, Fabrication Methods, Characterization, and Biomedical Applications

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Published on: 20.10.2023
Published by: Futuristic Publications

Abstract:

Background: Microneedles (MNs) represent a minimally invasive transdermal drug delivery technology that bypasses the primary barrier to dermal penetration — the stratum corneum — by creating transient micron-scale channels in the skin without stimulating pain receptors in the dermis. Over the past two decades, microneedle research has advanced from early proof-of-concept laboratory studies to promising clinical applications encompassing vaccine delivery, insulin administration, long-acting therapeutics, hormone therapy, and cosmetic interventions. The capacity of microneedles to deliver molecules of widely varying molecular weight and physicochemical properties — including large biologics and nucleic acids that are otherwise completely impermeable to the skin — positions them as a uniquely versatile transdermal delivery platform.

Objective: This review provides a comprehensive critical analysis of microneedle types, fabrication materials and methods, characterization approaches, mechanisms of drug delivery, therapeutic applications, and comparative performance relative to conventional transdermal and systemic delivery routes, with emphasis on research published up to 2022.

Results and Discussion: Five principal microneedle types — solid, coated, dissolving, hollow, and hydrogel-forming — each offer distinct advantages in terms of drug loading, release kinetics, skin penetration efficiency, and patient safety. Advances in fabrication technology including micromolding, drawing lithography, inkjet printing, and additive manufacturing have expanded material options from silicon and metal to an array of biodegradable polymers and natural biopolymers. Microneedle patches have demonstrated clinical feasibility for vaccination, insulin delivery, and long-acting contraceptive therapy, with multiple products in active clinical development as of 2022.

Conclusion: Microneedle-based transdermal delivery systems combine the patient convenience and safety of transdermal patches with the ability to deliver a broad range of pharmacological agents, including biologics that were previously restricted to injection. Continued advances in fabrication precision, drug loading capacity, and regulatory pathway clarity will determine the pace of clinical translation for this promising technology.

Keywords: Microneedles; transdermal drug delivery; dissolving microneedles; hollow microneedles; vaccine delivery; insulin delivery; skin penetration; drug-loaded patches; minimally invasive delivery

1. Introduction

The skin is the largest organ of the human body and an anatomically accessible site for drug administration, yet its primary biological function as a barrier against environmental threats renders it one of the most

restrictive portals for pharmaceutical delivery. The outermost layer of the epidermis, the stratum corneum, consists of flattened, anucleate corneocytes embedded within a lipid matrix of ceramides, free fatty acids, and cholesterol in a lamellar bilayer arrangement. This structure, spanning only 10 to 20 micrometers in thickness, constitutes an exceptionally effective diffusion barrier that limits passive transdermal permeation to small (molecular weight below 500 Daltons), lipophilic, and non-ionized molecules [1,2]. As a result, the vast majority of pharmacological agents — including hydrophilic drugs, peptides, proteins, nucleic acids, and large molecular weight molecules — cannot be administered transdermally without physical or chemical enhancement strategies.

Conventional transdermal enhancement approaches including chemical penetration enhancers, iontophoresis, sonophoresis, and electroporation have extended the range of transdermally deliverable drugs but are generally constrained to molecules of moderate size and possess limitations related to skin irritation, the requirement for sophisticated devices, or restricted drug flux. Microneedle technology represents a fundamentally different approach: instead of overcoming the stratum corneum barrier through chemical or physical means while leaving it structurally intact, microneedles physically breach it by creating an array of micron-scale conduits that penetrate through the stratum corneum into the viable epidermis and superficial dermis, bypassing the barrier without reaching the pain-sensing nerve fibers that reside at greater dermal depths [3,4].

The concept of using arrays of micron-scale needles for transdermal drug delivery was first proposed by Gerstel and Place in a United States patent filed in 1971, but technological limitations in microfabrication prevented experimental validation for over two decades. The publication of the first experimental demonstration by Henry and colleagues in 1998, using silicon microneedle arrays to increase the skin permeability of calcein, a fluorescent molecular probe, by orders of magnitude relative to untreated skin, initiated a period of rapid research expansion [5]. Subsequent decades witnessed the development of five mechanistically distinct microneedle types, an expanding library of fabrication materials and methods, and the translation of microneedle technology into clinical vaccine delivery, insulin administration, and cosmetic dermatology.

This review comprehensively examines the science and pharmaceutical applications of microneedle-based transdermal delivery systems. It covers the classification of microneedle types and their working principles, fabrication materials and manufacturing methods, characterization parameters, mechanisms of drug delivery, therapeutic applications across disease areas, recent research advances, and a critical appraisal of the translational literature, including identification of unresolved scientific and manufacturing questions that must be addressed to realize the full clinical potential of microneedle technology.

2. Scientific Background

2.1 Skin Architecture and Transdermal Drug Delivery Barriers

The skin is organized into three principal layers: the epidermis, the dermis, and the hypodermis. The epidermis is a stratified squamous epithelium consisting of the basal, spinous, granular, and cornified layers, with the outermost stratum corneum representing the principal pharmacokinetic barrier. The viable epidermis beneath the stratum corneum, approximately 50 to 100 micrometers thick, is metabolically active and contains Langerhans cells — a resident population of antigen-presenting cells that play a critical role in immune surveillance and are of particular relevance to microneedle-based vaccination. The dermis, extending 1 to 4 millimeters below the skin surface, contains a dense network of blood vessels, lymphatics, nerve fibers, hair follicles, and sweat glands [6,7].

The stratum corneum lipid bilayer structure imposes several biophysical constraints on transdermal permeation. Molecular weight is the most important single determinant of passive permeability: diffusivity in the lipid matrix is inversely proportional to molecular weight, and molecules above 500 Daltons have negligible passive permeation coefficients. Lipophilicity governs partitioning from the aqueous skin surface into the lipid matrix, with optimal transdermal delivery observed for molecules with octanol-water partition coefficients between 1 and 3. Hydrophilic, ionized, and macromolecular drugs are essentially impermeable by passive diffusion, requiring active enhancement strategies for transdermal delivery [8].

2.2 Rationale for Microneedle-Based Delivery

Microneedles are designed to penetrate the stratum corneum and viable epidermis to a depth of 25 to 900 micrometers — sufficient to bypass the barrier and deliver drug into the vascularized dermis or to create

conduits for passive drug flux through the disrupted barrier, but insufficiently deep to reach the nerve fibers in the deep dermis that mediate pain sensation. This pain-free insertion distinguishes microneedles from hypodermic needles and makes them suitable for self-administration and patients with needle phobia. The microchannel network created by microneedle insertion increases skin permeability by orders of magnitude compared to intact skin, enabling delivery of hydrophilic, macromolecular, and charged molecules that are otherwise impermeant [9,10].

From a pharmacokinetic perspective, microneedle delivery into the dermis places drug in close proximity to the dermal microvasculature, enabling rapid systemic absorption with pharmacokinetic profiles that can approach those of subcutaneous or intramuscular injection for appropriate formulations. For vaccine delivery, the presence of Langerhans cells and dermal dendritic cells in the skin layers targeted by microneedles provides a potent immunological advantage, as these professional antigen-presenting cells are more abundant per unit volume in the skin than at typical intramuscular injection sites, potentially enabling dose-sparing vaccination [11].

3. Classification of Microneedle Types

3.1 Solid Microneedles

Solid microneedles, the simplest and earliest developed type, consist of arrays of solid projections without drug loading capacity. They are applied to the skin in a poke-and-patch approach: the solid array is first pressed into the skin to create an array of micropores in the stratum corneum, and a conventional drug-loaded patch or formulation is then applied over the treated skin surface. Drug molecules permeate passively through the created channels into the underlying viable epidermis and dermis. The permeation enhancement is transient, as the skin begins to recover and reseal the microchannels within hours of microneedle removal. Solid microneedles fabricated from silicon, titanium, and stainless steel were among the earliest studied and validated the basic pharmacokinetic proof-of-concept for microneedle-enhanced delivery [12].

3.2 Coated Microneedles

Coated microneedles are solid needle arrays onto whose surface a drug-containing coating is deposited. Upon insertion into the skin, the coating dissolves or is abraded from the needle shaft within the skin microenvironment, releasing the drug locally into the viable epidermis and dermis. Coating formulations typically contain the drug dissolved or suspended in a biocompatible vehicle with excipients including sucrose, carboxymethylcellulose, or polysorbate 20 to control coating viscosity, drug loading, and dissolution rate. The primary advantage of coated microneedles over the poke-and-patch approach is rapid and localized drug deposition at the site of skin penetration, improving delivery efficiency for molecules with poor passive diffusion capacity. Coated microneedles have been extensively investigated for vaccine antigen delivery, where rapid and localized antigen deposition in the antigen-presenting cell-rich viable epidermis is immunologically advantageous [13,14].

3.3 Dissolving Microneedles

Dissolving microneedles are fabricated entirely or predominantly from water-soluble or biodegradable polymers that incorporate the drug within the needle matrix. Upon skin insertion, the tip of the dissolving needle is exposed to interstitial fluid in the viable epidermis or dermis and dissolves progressively, releasing the encapsulated drug in situ. The needle substrate dissolves completely within minutes to hours depending on polymer composition and molecular weight, leaving no sharps waste and eliminating needle reuse risk. Dissolving microneedles are fabricated from a wide range of polymers including polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hyaluronic acid, sodium carboxymethylcellulose, chondroitin sulfate, silk fibroin, maltose, and sucrose. The dissolution kinetics and drug release profile are governed by polymer type, molecular weight, and the degree of crosslinking or crystallinity [15,16].

3.4 Hollow Microneedles

Hollow microneedles are needle arrays containing an internal bore through which liquid drug formulations can be infused into the skin under controlled pressure or flow conditions. This design enables delivery of larger drug volumes and liquid formulations including suspensions and dispersions that cannot be incorporated into solid or coated microneedle matrices. Hollow microneedles are analogous in function to miniaturized hypodermic needles, enabling intradermal injection with precise depth control and reduced pain compared to conventional needles. They are fabricated from silicon, stainless steel, borosilicate glass, and polymeric materials using deep reactive ion etching, laser micromachining, or precision injection molding [17,18].

3.5 Hydrogel-Forming Microneedles

Hydrogel-forming microneedles, sometimes termed swellable microneedles, are fabricated from crosslinked hydrophilic polymers that do not dissolve upon skin insertion but instead absorb interstitial fluid and swell, forming a gel-state matrix in situ. Drug molecules loaded into the hydrogel matrix are released by diffusion through the swollen gel network into the surrounding skin tissue. The rate and duration of drug release are controlled by the crosslink density and swelling ratio of the hydrogel, enabling sustained delivery from hours to days. Hydrogel-forming microneedles can also be used as a diagnostic tool: the swollen hydrogel matrix can extract biomarkers from the interstitial fluid for subsequent analysis, enabling combined drug delivery and biomarker monitoring within a single patch system [19,20].

Table 1: Classification of microneedle types with fabrication materials, drug loading mechanism, release profile, and primary applications

Type	Material	Drug Loading	Release Profile	Primary Applications
Solid	Silicon, metal, polymer	Poke-and-patch (external)	Passive diffusion through pores	Lidocaine, naltrexone, small molecules
Coated	Silicon, metal coated with drug	Surface coating dissolution	Rapid bolus at insertion site	Vaccines, peptides, proteins
Dissolving	PVP, PVA, HA, silk fibroin	Encapsulated in polymer matrix	Rapid to moderate dissolution	Insulin, vaccines, cosmetics, hormone therapy
Hollow	Silicon, steel, glass, polymer	Liquid infusion through bore	Bolus or continuous infusion	Liquid vaccines, insulin, biologics
Hydrogel-forming	Crosslinked PMVE/MA, PVA, HA	Diffusion from swollen hydrogel	Sustained — hours to days	Long-acting drugs, contraceptives, naltrexone

PVP: polyvinylpyrrolidone; PVA: polyvinyl alcohol; HA: hyaluronic acid; PMVE/MA: poly(methyl vinyl ether-co-maleic acid).

4. Formulation Design and Development

4.1 Polymer Selection for Dissolving Microneedles

The selection of polymer for dissolving microneedle fabrication is governed by several interdependent criteria: biocompatibility and biodegradability, aqueous solubility or biodegradability in interstitial fluid, mechanical strength sufficient to enable skin penetration without fracture or buckling, drug compatibility, and processability into high-aspect-ratio needle geometries using available fabrication methods. PVP of molecular weights ranging from 30 to 360 kDa is among the most widely used dissolving microneedle materials owing to its excellent water solubility, rapid dissolution in skin interstitial fluid, compatibility with diverse drug payloads, and established pharmaceutical safety profile as an excipient [21].

Hyaluronic acid (HA) has attracted considerable attention as a dissolving microneedle material owing to its biological origin, biodegradability, cosmetic skin benefits attributed to skin hydration and collagen stimulation, and capacity to form mechanically robust needle arrays through controlled crosslinking. HA-based dissolving microneedles demonstrated sufficient tip strength to penetrate the stratum corneum in both ex vivo human skin models and clinical cosmetic studies. Silk fibroin derived from Bombyx mori silkworm cocoons has emerged as an important dissolving microneedle material for biologic cargo delivery owing to its capacity to stabilize encapsulated proteins and peptides in the solid state at elevated temperatures, with implications for cold-chain-independent vaccine storage and distribution [22,23].

4.2 Tip-Loading Strategies for Drug Concentration

A critical formulation challenge in dissolving microneedle development is achieving sufficient drug loading in the needle tip, the only portion that penetrates the skin and deposits drug, while minimizing drug waste in the baseplate that remains above the skin surface. Two-photon crosslinking and layer-by-layer casting strategies have been developed to concentrate the drug payload within the needle tips through a tip-loading or tip-segregation approach, in which a small volume of concentrated drug-polymer solution is first cast into the needle mold cavities before a drug-free backing layer is applied [24].

4.3 Excipient Design for Coating Formulations

Coated microneedle formulations require precise optimization of coating solution viscosity, surface tension, and drying behavior to achieve uniform, adherent coatings of defined thickness on microneedle shafts while maintaining drug stability and biological activity. Coating solutions typically consist of aqueous suspensions of drug with a film-forming excipient such as hydroxypropyl methylcellulose, polyethylene glycol, or trehalose, supplemented with a surfactant to reduce surface tension and improve coating uniformity. Drug loading per needle array is constrained by the limited surface area of the needle shafts and is typically in the range of micrograms per array, making coated microneedles most suitable for potent biologics, vaccines, and hormones where therapeutic doses fall within this range [25,26].

4.4 Drug Stability in Microneedle Matrices

The solid-state incorporation of biomolecular drugs — proteins, peptides, mRNA, and viral antigens — into dissolving or hydrogel-forming microneedle matrices imposes stability requirements distinct from those of liquid formulations. The mechanical stress of mold filling, the elevated temperatures sometimes used during fabrication, and the drying stresses of lyophilization or air-drying can cause protein aggregation, denaturation, or loss of biological activity. Stabilizing excipients including trehalose, sucrose, mannitol, human serum albumin, and specific amino acids are incorporated to provide amorphous matrix stabilization of protein structure during drying and storage, preserving antigenicity and pharmacological activity [27].

5. Preparation Methods

5.1 Micromolding

Micromolding is the most widely adopted method for fabricating dissolving and hydrogel-forming microneedle arrays at laboratory scale. The process involves preparation of a master mold template with the negative geometry of the desired microneedle array — typically fabricated by photolithography and deep reactive ion etching of silicon, or by precision CNC machining — followed by casting of polydimethylsiloxane (PDMS) to create a flexible female mold. The drug-polymer solution is then dispensed into the PDMS mold under centrifugation or vacuum to ensure complete filling of the needle cavities, and the filled mold is dried under controlled temperature and humidity conditions. Following solidification, the microneedle array is demolded by peeling. The principal advantage of micromolding is its simplicity and scalability for laboratory production, though achieving reproducible filling of high-aspect-ratio needle geometries and avoiding air entrapment remain technical challenges [28,29].

5.2 Drawing Lithography

Drawing lithography is a one-step process for fabricating tapered high-aspect-ratio microneedles from viscous polymer solutions or melts without the need for a patterned mold. A substrate coated with the polymer mixture is brought into contact with a planar surface, and the two surfaces are separated at a controlled speed. The stretching polymer strand between the separating surfaces forms a conical or tapered geometry that is solidified by crosslinking, cooling, or drying depending on the polymer system. Drawing lithography offers precise control of needle height and tip radius through adjustment of separation speed and temperature, and is compatible with diverse polymers including PVA, PVP, polyethylene glycol, and sugar glass systems [30].

5.3 3D Printing and Additive Manufacturing

The emergence of high-resolution 3D printing technologies including digital light processing (DLP) stereolithography, two-photon polymerization (TPP), and inkjet printing has expanded the design freedom for microneedle fabrication beyond what is achievable with conventional mold-based methods. DLP stereolithography enables rapid fabrication of microneedle arrays with complex geometries including helical grooves, pockets, and branched structures from photopolymerizable resins, with feature resolution of 10 to 50 micrometers. Two-photon polymerization achieves sub-micron resolution and enables fabrication of microneedles with extremely fine tip radii and internal channel structures from photoresists and biocompatible polymers [31,32].

5.4 Electrospinning for Microneedle Tip Modification

Electrospun nanofiber mats have been incorporated onto the tips and surfaces of solid and coated microneedles to increase the drug-carrying surface area, enable sustained drug release from the nanofiber matrix after skin insertion, and improve drug stability through the protective solid-state environment of the electrospun polymer matrix. Coaxial electrospinning enables deposition of core-shell nanofibers in which an

active drug is concentrated in the core and a rate-controlling polymer shell governs release kinetics, providing additional control over drug release from the microneedle surface [33].

5.5 Photolithography and Silicon Microfabrication

Silicon microneedles fabricated by photolithography and deep reactive ion etching (DRIE) were the first microneedle type to be experimentally demonstrated and remain relevant for solid and hollow microneedle designs where the superior mechanical properties and precise dimensional control of silicon are advantageous. The DRIE process enables fabrication of needle arrays with highly reproducible dimensions, smooth surfaces, and aspect ratios exceeding 10:1. A photomask defining the array pattern is transferred to a silicon wafer by UV exposure and wet chemical etching, followed by a series of alternating etch and passivation cycles in the DRIE process to create high-aspect-ratio needle pillars [34].

6. Characterization and Evaluation

6.1 Morphological Characterization

Optical microscopy and scanning electron microscopy are the primary tools for characterization of microneedle array morphology, providing measurements of needle height, base diameter, tip radius, interspacing, and array density. Needle height typically ranges from 150 to 900 micrometers, while tip radii of less than 5 micrometers are associated with effective skin penetration with minimal force. SEM provides high-resolution surface characterization and is used to confirm coating uniformity on coated microneedles, detect tip defects or fractures, and visualize dissolution behavior in dissolving needle systems [35].

6.2 Mechanical Strength and Fracture Testing

The mechanical robustness of microneedles must be sufficient to withstand the forces applied during skin insertion without fracture, buckling, or permanent deformation. Axial compression testing using a texture analyzer or universal testing machine applies a compressive force to a microneedle array in contact with a rigid flat surface and records the force-displacement profile, from which the failure force per needle and the safety factor relative to the skin insertion force are calculated. For dissolving microneedles fabricated from polymers with relatively low elastic modulus, the insertion force required to penetrate the stratum corneum must be carefully measured and compared to the failure force to establish an adequate mechanical safety margin [36].

6.3 Skin Insertion and Penetration Assessment

Confirmation of effective skin penetration is assessed using multiple complementary methods. Calcein dye diffusion across microneedle-treated skin sections compared to untreated controls provides a quantitative measure of permeability enhancement. Histological staining of skin sections immediately after microneedle removal using optical and confocal microscopy visualizes the microchannel array in cross-section, confirming penetration depth and channel morphology. The OCT (optical coherence tomography) technique enables non-invasive real-time imaging of microneedle penetration in skin in vivo. Tattoo ink staining of the needle tips before skin insertion followed by optical visualization of dye transfer to the skin provides a simple semi-quantitative marker of successful penetration [37,38].

6.4 Drug Loading and Encapsulation Efficiency

Drug loading in dissolving and coated microneedle arrays is determined by dissolving a known number of needle arrays in an appropriate solvent and quantifying the drug content by HPLC, UV spectrophotometry, or immunoassay depending on the drug type. Encapsulation efficiency relative to the theoretical loading based on formulation composition is calculated to assess process yield. For biologic payloads including proteins and viral antigens, biological activity assays including ELISA, receptor binding, or in vitro neutralization assays are performed to confirm retention of biological function after the microneedle fabrication process [39].

6.5 In Vitro Drug Release and Ex Vivo Skin Permeation

In vitro drug release from dissolving and hydrogel-forming microneedles is assessed using Franz diffusion cells with a synthetic membrane or excised human or porcine skin as the barrier, with drug concentration in the receptor compartment measured at defined time points. Ex vivo permeation studies using full-thickness excised skin provide more physiologically relevant data on drug flux, lag time, and total permeated amount.

For vaccine antigens, skin tape stripping following microneedle removal is used to quantify antigen deposition in successive skin layers, confirming delivery into the viable epidermis [40].

6.6 Stability Studies

Long-term and accelerated stability studies of microneedle arrays assess changes in needle morphology, drug content, drug release profile, and biological activity over time under defined storage conditions. The solid-state nature of dissolving and coated microneedle systems offers an inherent thermostability advantage over liquid formulations for biologics, and stability studies have demonstrated that protein antigens and viral vaccines incorporated into sugar glass or polymer dissolving microneedles retain greater than 90% activity after storage at elevated temperatures for extended periods, a critical advantage for vaccine distribution in resource-limited settings without reliable cold chain infrastructure [41].

7. Mechanism of Drug Delivery

7.1 Stratum Corneum Disruption and Microchannel Formation

The fundamental mechanism of microneedle-mediated drug delivery is the physical disruption of the stratum corneum barrier through the creation of an array of micron-scale channels that bypass the principal permeation barrier. When a microneedle array is pressed against the skin with sufficient force — typically 10 to 30 N for an array of 100 needles — the needle tips penetrate the stratum corneum and viable epidermis to the design depth determined by needle height and the compressive force applied. The displaced corneocytes and viable epidermal cells are pushed aside rather than removed, creating patent channels of 50 to 500 micrometers in depth through the stratum corneum barrier [42].

7.2 Drug Transport Through Microchannels

For solid microneedles used in the poke-and-patch approach, drug molecules from the applied patch or formulation permeate passively through the created microchannels by concentration gradient-driven diffusion. The effective permeability of drug through the treated skin is orders of magnitude greater than through intact stratum corneum, enabling delivery of hydrophilic and macromolecular drugs that would otherwise be impermeable. For coated microneedles, the drug coating dissolves rapidly in the aqueous interstitial fluid environment within the skin microchannels, releasing drug locally at the site of deposition in the viable epidermis and dermis, from where it is absorbed into the dermal microvasculature and lymphatics [43].

7.3 Dissolution and Hydration in Dissolving Systems

In dissolving microneedle systems, needle tips inserted into the skin are exposed to interstitial fluid (approximately 97% water at physiological pH) that hydrates the polymer matrix and initiates dissolution from the needle tip inward. The dissolution rate is governed by polymer water solubility, molecular weight, and the degree of crosslinking. Rapidly dissolving PVP-based needles can dissolve within 5 to 10 minutes of skin insertion, while crosslinked HA-based needles may require 30 minutes or longer. As the polymer dissolves, the encapsulated drug is released directly into the viable epidermis and dermis at the site of needle insertion, enabling localized or systemic delivery depending on drug physicochemical properties [44].

7.4 Immunological Mechanism in Microneedle Vaccination

The immunological superiority of intradermal vaccination over intramuscular injection, which microneedles achieve minimally invasively, is attributable to the high density of professional antigen-presenting cells in the skin. Langerhans cells, present in the viable epidermis at densities of approximately 500 to 1000 cells per square millimeter, and dermal dendritic cells, present throughout the dermis, are extraordinarily efficient at antigen capture and processing. Following microneedle-mediated antigen deposition, Langerhans cells and dermal dendritic cells take up antigen, mature, and migrate through lymphatic vessels to regional lymph nodes where they activate naive T cells and B cells, initiating adaptive immune responses [45,46].

8. Therapeutic Applications

8.1 Vaccine Delivery

Vaccine delivery is the most extensively investigated and clinically advanced application of microneedle technology. The intradermal route targeted by microneedles provides access to a skin compartment densely populated with Langerhans cells and dermal dendritic cells, potentially enabling dose-sparing vaccination with equivalent or superior immunogenicity compared to standard

intramuscular injection. Dissolving and coated microneedle patches loaded with influenza hemagglutinin antigen, rabies virus antigen, measles-mumps-rubella components, hepatitis B surface antigen, and polio antigen have demonstrated equivalent or superior immune responses to intramuscular injection in small and large animal models [47].

Clinical feasibility of microneedle vaccination was demonstrated in a phase 1 trial in which a coated microneedle patch delivering inactivated influenza vaccine elicited antibody titers non-inferior to intramuscular injection with a favorable local tolerability profile and high subject acceptability. The thermostability advantage of solid-state microneedle vaccine patches over liquid vaccine vials has been confirmed in multiple studies demonstrating retained antigenicity after storage at 25°C and 40°C for weeks to months, supporting a vision of cold-chain-independent vaccine distribution in low- and middle-income countries [48,49].

8.2 Insulin Delivery in Diabetes

Insulin delivery by microneedle patch represents a potentially transformative advance for patients with type 1 diabetes, offering the prospect of painless, needle-free insulin administration without syringe injection. Dissolving microneedle patches loaded with insulin demonstrated pharmacodynamic equivalence to subcutaneous insulin injection in diabetic mouse and rat models, with blood glucose reduction kinetics consistent with rapid-acting insulin formulations. Glucose-responsive smart microneedle systems incorporating glucose oxidase and pH-sensitive polymers that release insulin proportionally in response to local glucose concentration have been reported, providing a rudimentary closed-loop insulin delivery capability without electronics [50,51].

8.3 Long-Acting Contraceptive and Hormone Delivery

Microneedle patches for long-acting contraceptive hormone delivery address the significant clinical challenge of patient adherence to daily oral contraceptive regimens and the injection discomfort of intramuscular contraceptive depots. Polymer microneedle patches releasing levonorgestrel or etonogestrel from hydrogel-forming or dissolving needle tips demonstrated sustained hormone plasma levels for weeks to months in animal models, with a single patch application targeting once-monthly or quarterly dosing intervals. The biodegradable polymer tips remain embedded in the skin following baseplate removal and continue to release hormone as the polymer degrades, providing an elegant sustained delivery mechanism without residual sharps [52].

8.4 Cosmetic and Dermatological Applications

Microneedle rollers and stamps have found widespread cosmetic application for delivery of skin-active ingredients including hyaluronic acid, retinol, ascorbic acid, peptide growth factors, and cosmeceutical botanical extracts into the viable epidermis. HA dissolving microneedle patches have been validated for delivery of exogenous hyaluronic acid into the dermis, producing measurable improvements in skin hydration, elasticity, and appearance in clinical studies. Microneedle-assisted delivery of tranexamic acid for melasma treatment and 5-aminolevulinic acid for photodynamic acne therapy have demonstrated superior clinical outcomes compared to topical application alone [53].

8.5 Therapeutic Drug Monitoring and Biomarker Extraction

Hydrogel-forming microneedles, owing to their capacity to absorb skin interstitial fluid without dissolving, have been investigated as minimally invasive biomarker sampling devices. Interstitial fluid extracted within the swollen hydrogel matrix contains glucose, lactate, cytokines, and other small molecule biomarkers whose concentrations correlate with blood levels. Integration of biosensing elements within the hydrogel or on the backing substrate enables wearable, continuous monitoring of analyte concentrations in interstitial fluid, potentially enabling combined biomarker monitoring and drug delivery from a single microneedle patch platform [54].

9. Recent Advances

9.1 Separable and Implantable Tip Microneedle Systems

Separable microneedle systems, in which the drug-loaded polymer needle tips physically detach from the backing substrate upon skin insertion, represent an advance that ensures complete tip delivery into the skin regardless of the duration for which the patch is held in contact with the skin surface. In these systems, needle tips fabricated from rapidly dissolving or biodegradable polymers are connected to the backing through a water-soluble bridge that dissolves upon contact with interstitial fluid or upon minimal compression time, allowing the user to remove the backing immediately after brief application while the detached tips remain embedded and dissolve in the skin. This design has been applied to long-acting contraceptive delivery, where

detached biodegradable polymer tips containing hormonal contraceptive for months-long sustained release are implanted in the skin by a brief single application [55].

9.2 Microneedles for Biologics and Nucleic Acid Delivery

The extension of microneedle delivery to large biologic molecules including monoclonal antibodies, messenger RNA, and CRISPR-Cas9 ribonucleoprotein complexes represented a significant recent advance. mRNA-loaded dissolving microneedle patches were reported to achieve comparable mRNA expression in skin-resident cells to intradermal injection, with the added advantages of cold-chain tolerance in the solid-state needle matrix and elimination of injection equipment. Lipid nanoparticle-loaded microneedles combining the skin penetration capability of dissolving needles with the endosomal escape capacity of LNPs demonstrated delivery of functional mRNA and gene editing components into keratinocytes and Langerhans cells in the viable epidermis [56,57].

9.3 3D-Printed Personalized Microneedle Arrays

High-resolution 3D printing by two-photon polymerization and digital light processing has enabled fabrication of microneedle arrays with complex geometries — including branched tips, helix-shaped shafts, and interlocking designs — that cannot be achieved by conventional micromolding. These geometries can increase drug loading capacity per needle, improve skin anchoring, or enable directional drug release. The digital design workflow of 3D printing enables rapid iteration of needle geometry without the time and cost of mold fabrication, substantially accelerating the microneedle development cycle. Point-of-care 3D printing of customized microneedle arrays tailored to individual skin properties or drug doses has been proposed as a long-term vision for personalized dermal drug delivery [58].

9.4 Glucose-Responsive Closed-Loop Microneedle Systems

The development of glucose-responsive microneedle patches capable of autonomous insulin delivery in proportion to blood glucose concentration without electronic components or external control represents an exciting convergence of smart material science and diabetes management. These systems incorporate a glucose-sensing moiety — typically glucose oxidase, phenylboronic acid derivatives, or a competitive glucose-binding system — within the microneedle polymer matrix that alters drug release rate in response to local interstitial glucose concentration. In vivo proof-of-concept studies in streptozotocin-induced diabetic mice demonstrated blood glucose control within the normoglycemic range following single patch application, with insulin release increasing proportionally in response to glucose challenge [59].

10. Comparative Analysis

Microneedle-based transdermal delivery is best understood in comparative context with the three alternative routes for systemic drug delivery and with conventional transdermal patches. Oral delivery, while the most convenient and widely used route, subjects drugs to gastrointestinal degradation, hepatic first-pass metabolism, and absorption variability driven by food, gastric pH, and GI motility — factors that are particularly problematic for peptide and protein drugs that are completely degraded in the GI tract before reaching systemic circulation. Intravenous and intramuscular injection achieve rapid and complete systemic delivery but require trained personnel, sterile equipment, and carry risks of needle-stick injury, infection, and patient non-adherence due to injection anxiety [60].

Conventional transdermal patches overcome oral and injection limitations for drugs meeting the permeability criteria of low molecular weight and appropriate lipophilicity, but are restricted to a narrow range of approximately 20 approved drug molecules worldwide. Microneedles dramatically expand the chemical space accessible to transdermal delivery, enabling administration of hydrophilic drugs, macromolecules, and biologics with pharmacokinetic profiles approaching those of injection while retaining the convenience, safety, and patient acceptability of a skin patch [61].

Table 2: Comparative analysis of microneedle transdermal delivery versus conventional drug administration routes

Parameter	Oral Route	IV Injection	IM/SC Injection	Conventional Patch	Microneedles
Drug molecular weight limit	No limit (absorption limited)	No limit	No limit	<500 Da	No limit
First-pass metabolism	Yes — significant	None	Minimal	None	None

Pain / patient acceptability	None — high	Pain — low	Pain — moderate	None — high	Minimal — high
Bioavailability variability	High	None	Low	Low	Low
Self-administration	Yes	No	With training	Yes	Yes
Biologics compatible	Generally no	Yes	Yes	No	Yes
Controlled release	Formulation-dependent	Limited	With depot	Yes	Type-dependent

IV: intravenous; IM: intramuscular; SC: subcutaneous; Da: Daltons.

11. Advantages and Limitations

11.1 Advantages

- Minimally invasive penetration of the stratum corneum barrier enabling delivery of hydrophilic drugs, macromolecules, peptides, proteins, and nucleic acids that are otherwise impermeant to skin
- Painless or near-painless insertion confirmed in clinical studies owing to needle dimensions below the threshold for pain receptor stimulation in the dermis
- Elimination of sharp waste and needle-stick injury risk with dissolving and hydrogel-forming microneedle designs that leave no metallic needle components in the skin
- Enhanced patient acceptability and suitability for self-administration compared to hypodermic injection, with particular benefits for needle-phobic patients
- Access to the immunologically active viable epidermis and dermis, enabling dose-sparing vaccination through direct delivery to antigen-presenting cell-rich skin compartments
- Thermostability advantage of solid-state dissolving microneedle vaccines over liquid vaccine formulations, supporting cold-chain-independent storage and distribution
- Bypass of hepatic first-pass metabolism, improving systemic bioavailability and dose efficiency for drugs with high hepatic extraction ratios
- Versatility of design — five distinct microneedle types accommodate a spectrum of drug payloads, release profiles from rapid bolus to sustained weeks-long delivery

11.2 Limitations

- Limited drug loading capacity per patch, particularly for coated microneedles, constrains application to potent drugs with therapeutic doses in the microgram to low milligram range
- Inconsistent skin insertion depth and penetration efficiency due to variability in skin mechanical properties across individuals, body sites, age groups, and hydration states
- Incomplete dissolution of polymer tips in some skin types and conditions results in partial drug delivery and inter-subject pharmacokinetic variability
- Local skin reactions including erythema, edema, and micro-bruising at the application site, though typically mild and transient in clinical studies
- Manufacturing scalability and quality consistency of dissolving microneedle arrays remains challenging for pharmaceutical-scale production, particularly for biologic payloads sensitive to processing stresses
- The regulatory pathway for microneedle-based drug products is not fully established, with the need to demonstrate both drug product quality and device performance creating a hybrid regulatory classification challenge
- Long-term skin barrier recovery after repeated microneedle application has not been comprehensively characterized, raising questions about chronic use safety for daily or weekly dosing regimens

12. Clinical Translation and Marketed Products

The clinical development of microneedle-based drug delivery products has advanced substantially over the past decade, with multiple products progressing through phase 1 and 2 clinical trials and a small number reaching commercialization, predominantly in the cosmetic dermatology sector. In the pharmaceutical sector, the Micronjet600 hollow microneedle device for intradermal injection has received CE mark in Europe, enabling physician-administered intradermal vaccination with liquid vaccine formulations using an approved device. The Nanoject device similarly enables intradermal insulin injection with hollow microneedles, demonstrating comparable glycemic control to subcutaneous injection with significantly reduced injection pain in clinical studies [62].

In the dissolving microneedle vaccine space, clinical trials conducted at Emory University and Georgia Tech demonstrated phase 1 safety and immunogenicity of a coated microneedle patch delivering inactivated influenza vaccine, with antibody responses non-inferior to intramuscular injection and high subject-reported preference for the patch over needle injection. These results established proof-of-concept clinical feasibility for microneedle vaccination and supported ongoing development of patches for COVID-19, polio, measles, and other vaccine-preventable diseases. Commercially, Microneedle patches for cosmetic hyaluronic acid delivery are marketed in South Korea, Japan, and China, representing the first large-scale consumer microneedle products [63].

Table 3: Selected clinical trials and commercial products for microneedle-based drug delivery (as of 2022)

Product / Study	MN Type	Drug / Antigen	Indication	Status / Outcome
Micronjet600 (NanoPass)	Hollow	Liquid vaccines	Intradermal vaccination	CE marked; commercial use Europe
Emory/GaTech Influenza Patch	Coated	Influenza HA antigen	Influenza vaccination	Phase 1 — non-inferior immunogenicity
Micron Biomedical BCG Patch	Dissolving	BCG vaccine	Tuberculosis vaccination	Phase 1 ongoing (2022)
Zosano Pharma ZP-PTH	Coated titanium	PTH(1-34) — teriparatide	Osteoporosis	Phase 3 — bioequivalence study
Cosmetic HA patches (S. Korea)	Dissolving	Hyaluronic acid	Skin rejuvenation	Commercial — consumer market
Contraceptive MN patch study	Polymer tip	Levonorgestrel	Contraception	Preclinical to Phase 1 (2022)

MN: microneedle; HA: hemagglutinin / hyaluronic acid (context-dependent); BCG: bacille Calmette-Guérin; PTH: parathyroid hormone.

13. Critical Analysis

The scientific literature on microneedle drug delivery contains several areas of genuine inconsistency and methodological limitation that merit critical discussion. The most pervasive concern in preclinical microneedle research is the near-universal use of murine skin as the experimental model, despite the substantial anatomical and mechanical differences between murine and human skin. Mouse skin is substantially thinner than human skin — the total thickness of mouse dorsal skin is approximately 0.6 to 0.7 millimeters compared to 1.5 to 4 millimeters for human skin — and lacks the thick stratum corneum present in palmar and plantar human skin. Microneedle arrays that successfully penetrate the stratum corneum of mouse skin may exhibit substantially different penetration efficiency in human skin, and comparative studies reporting good agreement between murine and human skin penetration do not represent the full range of human skin variability [64].

The relationship between ex vivo skin insertion testing and clinical in vivo performance is poorly defined and inconsistently reported across the microneedle literature. Ex vivo skin studies are performed using excised cadaveric skin stored under conditions that alter its mechanical properties relative to in vivo skin — hydration state, temperature, and lack of perfusion all affect skin stiffness and viscoelastic behavior in ways that can either overestimate or underestimate the insertion force required in clinical use. Several published studies have reported successful ex vivo insertion but clinically insufficient penetration in subsequent human studies, highlighting the need for standardized and validated ex vivo-to-in vivo bridging models [65].

A fundamental question that the field has not definitively resolved is the optimal microchannel diameter and density required to achieve therapeutically meaningful drug permeability enhancement for drugs of different sizes and physicochemical properties. The relationship between needle geometry (height, tip radius, spacing, array density) and drug flux through the created microchannels is complex and poorly predicted by simple diffusion models. Published studies have used widely varying array geometries and reported drug delivery outcomes in inconsistent units (total permeated amount, flux, permeability coefficient, or percent bioavailability), making direct comparison across studies and identification of optimal design parameters exceedingly difficult. The development of standardized pharmacokinetic reporting guidelines for microneedle drug delivery studies represents an important unmet need in the field [66].

The question of skin barrier recovery kinetics after microneedle application has received limited attention in the published literature relative to the extensive work on initial penetration and acute drug delivery. For therapeutic applications requiring repeated microneedle applications — daily insulin delivery, weekly contraceptive dosing, or monthly vaccine boosting — the cumulative effect of repeated stratum corneum disruption on barrier function, local immune activation, and skin microbiome composition is unknown. A small number of repeat-application studies in human volunteers have reported complete barrier recovery within 24 to 72 hours, but these studies used limited application frequencies and did not assess chronic use safety beyond a few weeks. This represents a significant knowledge gap for chronic-use microneedle products in regulatory development [67].

14. Conclusion

Microneedle-based transdermal drug delivery systems have demonstrated compelling scientific proof-of-concept for a wide range of therapeutic applications and represent one of the most clinically promising innovations in pharmaceutical drug delivery technology of the past two decades. The five mechanistically distinct microneedle types — solid, coated, dissolving, hollow, and hydrogel-forming — collectively address a broad spectrum of drug payloads, therapeutic objectives, and patient preferences, from rapid vaccine antigen delivery in the antigen-presenting cell-rich viable epidermis to sustained hormone release from biodegradable polymer tips embedded in the dermis.

The expansion of microneedle drug delivery from small molecules to peptides, proteins, viral antigens, and most recently nucleic acid payloads has substantially broadened the pharmaceutical relevance of this technology. The thermostability advantages of solid-state dissolving microneedle vaccine patches, the dose-sparing potential of intradermal immunization, and the patient acceptability of painless self-administered patches address specific unmet needs in global health, chronic disease management, and vaccine distribution that conventional drug delivery systems cannot fully satisfy.

The translation of microneedle technology from academic research to approved pharmaceutical products has proceeded more slowly than the scientific progress might suggest, held back by manufacturing scalability challenges for high-quality pharmaceutical-grade microneedle arrays, by the regulatory complexity of hybrid drug-device products, and by unresolved questions regarding long-term skin barrier safety with repeated application. Addressing these challenges through investment in scalable manufacturing technology, standardized characterization methods, and prospective clinical safety studies will be essential to fulfill the substantial clinical potential of microneedle drug delivery in the coming decade.

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