Review

Microneedle Technologies for Drug Delivery: Innovations, Applications, and Commercial Challenges

Kranthi Gattu , Deepika Godugu , Harsha Jain , Krishna Jadhav , Hyunah Cho , Satish Rojekar *

Posted Date: 3 December 2025

doi: 10.20944/preprints202512.0407.v1

Keywords: microneedle; transdermal delivery; drug delivery; biomaterials; vaccines; 3D printing

Review

Microneedle Technologies for Drug Delivery: Innovations, Applications, and Commercial Challenges

Kranthi Gattu [1], Deepika Godugu [2], Harsha Jain [3], Krishna Jadhav [4], Hyunah Cho [5] and Satish Rojekar [6,*]

[1] Industrial Pharmacy, Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Queens, NY 11439

[2] Department of Pharmacy, University College of Technology Sciences, Osmania University, Hyderabad, Telangana, India 500007

[3] College of Pharmacy, University of Iowa, Iowa City, IA 52242, United States

[4] Institute for Bioengineering of Catalonia (IBEC), Baldiri i Reixac 10-12, Barcelona,08028 Spain

[5] College of Pharmacy and Health Sciences, Fairleigh Dickinson University, New Jersey, 07932

[6] Institute for Translational Medicine and Pharmacology, Department of Pharmacological Sciences, Icahn School of Medicine, Mount Sinai, NY, 10029, USA

* Correspondence: rojekarsatish@gmail.com

Highlights

- Microneedles offer minimally invasive, painless transdermal and intradermal drug delivery for macromolecules.
- Diverse designs, such as solid, coated, dissolving, hollow, hydrogel-forming, and hybrid enable customized therapeutic solutions.
- Advances include 3D printing, stimuli-responsive polymers, and integration with biosensing for smart drug delivery.
- Expanded applications cover vaccines, insulin, cancer therapies, contraceptives, and cosmetics.
- Key barriers include scalable manufacturing, patient acceptance, and regulatory approval.

Abstract

Microneedle (MN) technologies have emerged as a groundbreaking platform for transdermal and intradermal drug delivery, offering a minimally invasive alternative to oral and parenteral routes. Unlike passive transdermal systems, MNs allow the permeation of hydrophilic macromolecules, such as peptides, proteins, and vaccines, by penetrating the stratum corneum barrier without causing pain or tissue damage, unlike hypodermic needles. Recent advances in materials science, microfabrication, and biomedical engineering have enabled the development of various MN types, including solid, coated, dissolving, hollow, hydrogel-forming, and hybrid designs. Each type has unique mechanisms, fabrication techniques, and pharmacokinetic profiles, providing customized solutions for a range of therapeutic applications. The integration of 3D printing technologies and stimulus-responsive polymers into microneedle systems has opened the door for patches that pair drug delivery with real-time physiological sensing. Over the years, microneedle applications have grown beyond vaccines to include the delivery of insulin, anticancer agents, contraceptives, and various cosmeceutical ingredients, highlighting the versatility of this platform. Despite this progress, broader clinical and commercial adoption is still limited by issues such as scalable and reliable manufacturing, patient acceptance, and meeting regulatory expectations. Overcoming these barriers will require coordinated efforts across engineering, clinical research, and regulatory science. This review thoroughly summarizes MN technologies, beginning with their classification and drug-delivery mechanisms, and then explores innovations, therapeutic uses, and translational challenges. It

 doi:10.20944/preprints202512.0407.v1

concludes with a critical analysis of clinical case studies and a future outlook for global healthcare. By comparing technological progress with regulatory and commercial hurdles, this article highlights the opportunities and limitations of MN systems as a next-generation drug-delivery platform.

Keywords: microneedle; transdermal delivery; drug delivery; biomaterials; vaccines; 3D printing

1. Introduction

Transdermal drug delivery has evolved from ancient topical remedies to sophisticated medical devices designed for controlled and efficient administration of therapeutics through the skin [1]. Over the past few decades, advances in microfabrication and material science have driven the emergence of microneedle (MN) technologies, representing a transformative leap that overcomes the limitations of oral and conventional parenteral drug delivery methods [2]. This technology enables minimally invasive, pain-free delivery of a wide range of drugs and biologics, improving patient compliance and therapeutic outcomes [3].

1.1. History of MN

MN technology has advanced considerably since its inception in the 1970s, with key innovations occurring in the 1990s, when microfabricated silicon microneedles were introduced as less-invasive instruments for transdermal drug delivery. This period initiated advanced manufacturing techniques utilizing materials including silicon, metals, and polymers [4]. The 2000s witnessed diversification into numerous MN forms, providing distinct benefits for the delivery of vaccines, small compounds, and biomacromolecules. Clinical translation advanced through trials that exhibited less pain, enhanced patient adherence, and expanded therapeutic possibilities, encompassing cosmetic uses [5,6].

Over the past decade, significant progress has been achieved through the integration of innovative materials and manufacturing methods, such as 3D printing, to facilitate scalable, precise production of microneedles. Innovative smart MN systems now integrate medication delivery with biosensing, personalized dosing, and closed-loop control capabilities [7]. From 2020 to 2030, MN technology is anticipated to evolve into a clinically feasible, market-ready platform that addresses critical obstacles in drug loading capacity, large-scale production, and regulatory approval. The continuous developments underscore the evolution of microneedles from experimental apparatus to multifunctional instruments pivotal to next-generation medicines and diagnostics [8] **(Figure 1)**.

 doi:10.20944/preprints202512.0407.v1

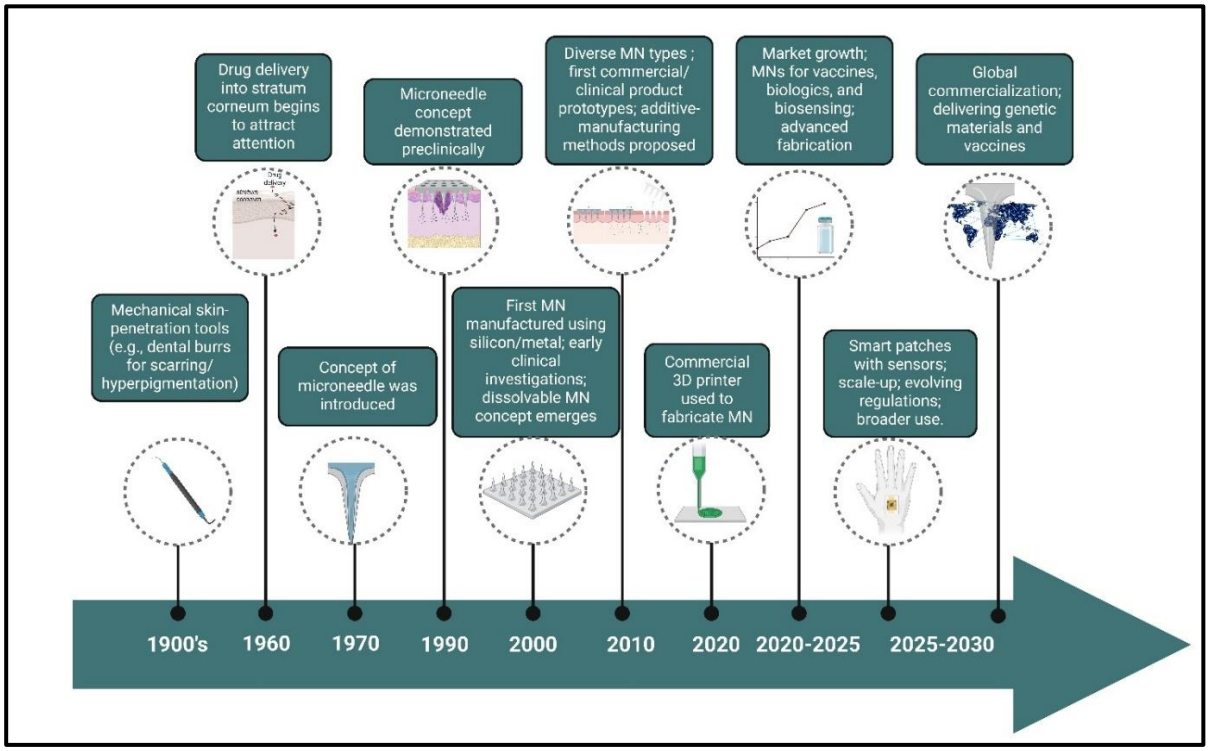
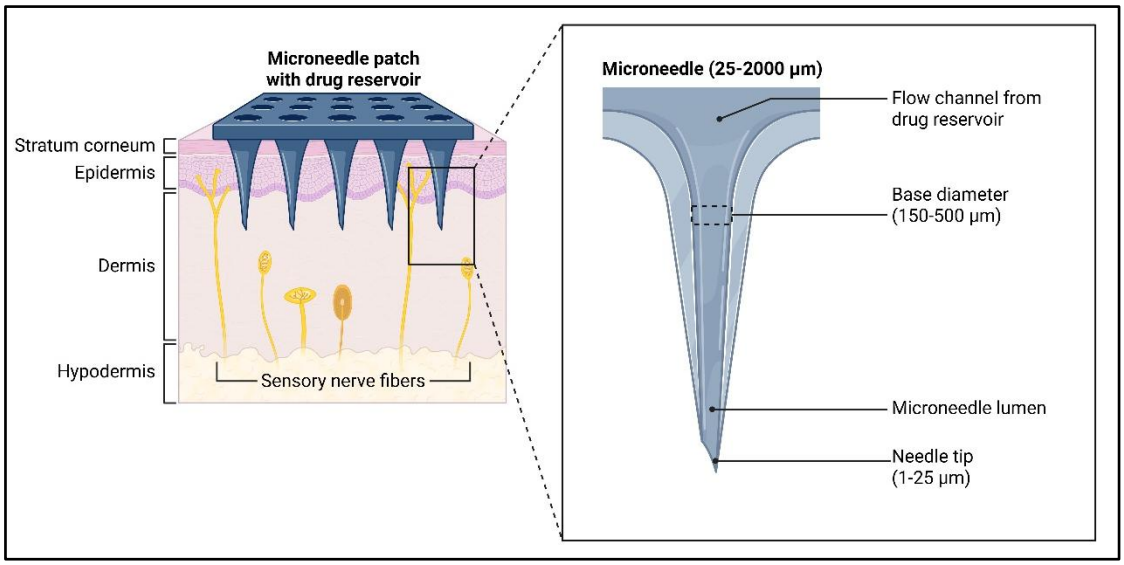


Figure 1. Timeline showing the evolution and projected future of MN technology from research to global commercialization (Created using Biorender).

1.2. Structure and Design Principles

Microneedles are arrays of microscale needles typically ranging in length from 25 micrometers (μm) to 2000 μm (2 millimeters), which corresponds approximately to the thickness of the human epidermis, including the stratum corneum [4]. The needle tip radius is designed to be sharp, ranging from 1 μm to 25 μm, to ensure efficient penetration through the skin barrier with minimal pain. The base diameter of individual microneedles typically ranges from 150 μm to 500 μm [9]. These are arranged in arrays commonly sized around 8 mm by 8 mm, with spacing (pitch) between needles approximately 500 μm (Figure 2) [10]. The needle height is carefully engineered to breach the outer skin layers without reaching pain receptors or blood vessels in the dermis, thereby providing a minimally invasive and painless drug delivery experience. These dimensions are crucial for achieving a balance between effective skin penetration and patient comfort and safety [11].



 doi:10.20944/preprints202512.0407.v1

Figure 2. Microneedle patch penetrating skin layers for transdermal drug delivery. Inset shows microneedle structure with lumen and delivery channel (Created using Biorender).

This review summarizes recent developments across different MN platforms, including their classification, modes of delivery, emerging technologies, therapeutic uses, commercial hurdles, and key illustrative examples. The goal is to offer a clear and balanced assessment of current progress and remaining challenges, providing readers with a practical guide to understanding and advancing work in this rapidly evolving area of drug-delivery research.

2. Classification of Microneedles

MNs can generally be grouped into five types: solid, coated, dissolving, hollow, and hydrogel-forming MNs, along with other hybrid types of MNs that have recently been developed based on their structure, materials, and methods of drug administration **(Table 1)** [12]. Different MNs have different fabrication methods, giving them specific mechanical properties and therapies that fit their properties [13,14]. Each type has its own optimizations and particular characteristics that optimize transdermal drug delivery, such as strengthening the drug's loading, improving its release kinetics, and maintaining the patient's overall safety, in addition to overcoming the barrier of the stratum corneum's impermeability [15].

2.1. Solid Microneedles

Solid MNs are the simplest type of interstitial MNs. These MNs can be fabricated from a range of biocompatible materials, including silicon, metals such as stainless steel and titanium, and biodegradable polymers such as polylactic acid (PLA). [16]. Their operation involves the "poke-and-patch" mechanism, in which the MN array pretreats the skin with a drug patch, creating microchannels (50 to 100 μm in depth). The needles can be made as long as 100 to 900 μm to ensure the dermal-epidermal border is not penetrated. These MNs are preferred for skin pretreatment during MN infiltration due to their mechanical stiffness and >90% reusability (costing less than 10 cents per unit at large scale) [15]. Fabrication methods include wet or dry etching of silicon, laser cutting of metals, and micro molding of polymers, with needle lengths of 100-900 μm to penetrate the viable epidermis without dermal vasculature [17]. Advantages include mechanical robustness, reusability, and inexpensive production, making them ideal for pretreatment applications in combination with iontophoresis or electroporation [1]. However, limitations include rapid channel closure (15-30 minutes reflecting skin elasticity), resulting in variable drug permeation rates and possible incomplete delivery in dynamic skin environments. Recent work has introduced bioactive coatings that actively maintain open pores, improving the overall performance of these systems [15].

2.2. Coated Microneedles

Coated microneedles are an advanced design based on solid microneedles, where drug formulations are layered onto the needle surface using techniques such as dip coating, spray coating, or inkjet printing. These designs employ biocompatible core materials like silicon, stainless steel, or polymers (e.g., PLA), with the active pharmaceutical agents adhering as uniform thin films [18]. Upon skin insertion, rapid dissolution or detachment of the coating delivers precise doses into microchannels approximately 50–150 microns deep, bypassing the stratum corneum and enabling efficient drug absorption [19]. Coating thickness and uniformity are critical and are often controlled by process parameters such as solution viscosity and withdrawal speed. Their primary benefits include immediate drug release, suitability for delivering low-dosage biotherapeutics, and versatility for vaccines, peptides, or hormones [20]. However, limitations involve challenges in achieving consistent coating coverage, dose loading, and stability during storage and transport. Recent innovations involve mucoadhesive, stimuli-responsive, and multilayer bioactive coatings that enhance skin permeation and therapeutic efficacy [21].

 doi:10.20944/preprints202512.0407.v1

2.3. Dissolving Microneedles

Dissolving MNs contain the drug in a water-soluble matrix, which is often made of biodegradable polymers (such as hyaluronic acid, polyvinylpyrrolidone, polyvinyl alcohol) or carbohydrates (such as sucrose, maltose) [22]. Once inserted into the skin, the MN dissolves in the interstitial fluid within 5–30 minutes, enabling controlled drug release while avoiding the generation of sharps waste. Fabrication techniques using micro molding or droplet-born air blowing provide arrays ranging from 100-600 μm and drug loading up to 1 mg/patch [23]. They are especially beneficial for biologics such as insulin or vaccines, because they provide accurate dosing and better patient compliance through painless and self-administration [24]. Limitations include mechanical fragility (fracture risk during insertion into dry skin) and the dissolution rate, which is affected by skin hydration or pH, potentially resulting in incomplete dissolution (efficiency of 70-95%). Recent formulations include ingredients such as chondroitin sulfate to provide greater strength [25].

2.4. Hollow Microneedles

Hollow MNs are similar to mini-hypodermic needles, with lumens connecting to the center to deliver liquid formulations into the dermis. They provide a chance for bolus or continuous delivery of larger drug volumes compared to other MNs, but require more complex production and insertion force [20,26].

2.5. Hydrogel-Forming Microneedles

Hydrogel-forming MNs use crosslinked, swellable polymers (e.g., poly(methyl vinyl ether-co-maleic anhydride) and polyethylene glycol diacrylate) that absorb interstitial fluid upon insertion, expanding 200-500% in volume to form drug-permeable conduits from an attached reservoir [27,28]. Unlike dissolving types, the matrix is not dissolved for removal after use, providing sustained release for hours to days through diffusion. Fabrication processes include casting or photopolymerization processes, often with integrated backings [13]. Benefits include zero-order kinetics for chronic therapies and minimal residue, but limitations include a slower onset (swelling time) and a bulkier reservoir, which may affect wearability. pH or enzyme-sensitive hydrogels provide an enhanced method of control [29].

2.6. Hybrid and Next-Generation Microneedles

Hybrid MNs incorporate components from many different classes, such as dissolving tips on hollow shafts or coated hydrogels, to combine benefits such as high loading with controlled infusion [30]. Next-generation design considers stimuli-responsive materials (e.g., thermos or glucose-sensitive polymers) [31]; nanoparticles (NPs) for targeted delivery [32]; bio-inspired structures (e.g., mosquito-like barbs) [33]; and additive manufacturing for personalization [34]. These provide versatility for theragnostic but are challenged in terms of scalability and regulation [8].

Table 1. Classification of microneedles: Mechanism, fabrication, advantages, and limitations.

Type	Fabrication materials/methods	Mechanism	Advantages	Limitations	Reference
Solid	Silicon, metals, polymers, etching, molding	Creates microchannels for passive diffusion	Simple design, low cost	Poor control of dosing	[12]
Coated	Dip-coating, spray-coating, and inkjet printing	Drug layered on the surface, dissolves upon insertion	Rapid release, suited for vaccines	Limited drug load	[18]

 doi:10.20944/preprints202512.0407.v1

Dissolving	Polymers (polyvinylpyrrolidone, hyaluronic acid) via micro molding	The biodegradable matrix dissolves in the skin, releasing the drug	No waste, suitable for biologics	Fragility, limited penetration	[35]
Hollow	Silicon, glass, stainless steel; laser micromachining	Drug infused through the central lumen	Larger volumes, controlled infusion	Complex design, higher cost	[36]
Hydrogel-forming	Crosslinked polymers (PEG, PHEMA)	Swellable polymers form drug-permeable conduits	Sustained release, reusable reservoir	Removal required, slower onset	[37,38]
Hybrid/Next-gen	Composite polymers, 3D printing, NPs	Combines multiple features; smart materials	High versatility, personalized therapy	Still experimental, scalability issues	[39]

3. Mechanisms of Drug Delivery via Microneedles

MNs enhance drug permeation across the skin by physically or chemically modulating the stratum corneum, the primary barrier to transdermal delivery. The mechanism of delivery depends on the MN type, formulation, and physicochemical properties of the drug [40,41].

3.1. Passive Diffusion via Solid Microneedles

Solid MNs work primarily by forming microchannels through the stratum corneum, facilitating the subsequent diffusion of topically applied drugs. The "poke-and-patch" approach relies on passive diffusion gradients, hydrophilicity, and hydration [15]. The formation of microchannels is rapid and reversible; microchannels usually close within hours due to the skin's elasticity and its mechanisms for repairing damaged skin. Studies have demonstrated enhanced delivery of small molecules, peptides, and vaccines using solid MN-mediated microchannels, with permeability enhancements ranging from 10 to 1000-fold compared to intact skin [42] **(Figure 3)**.

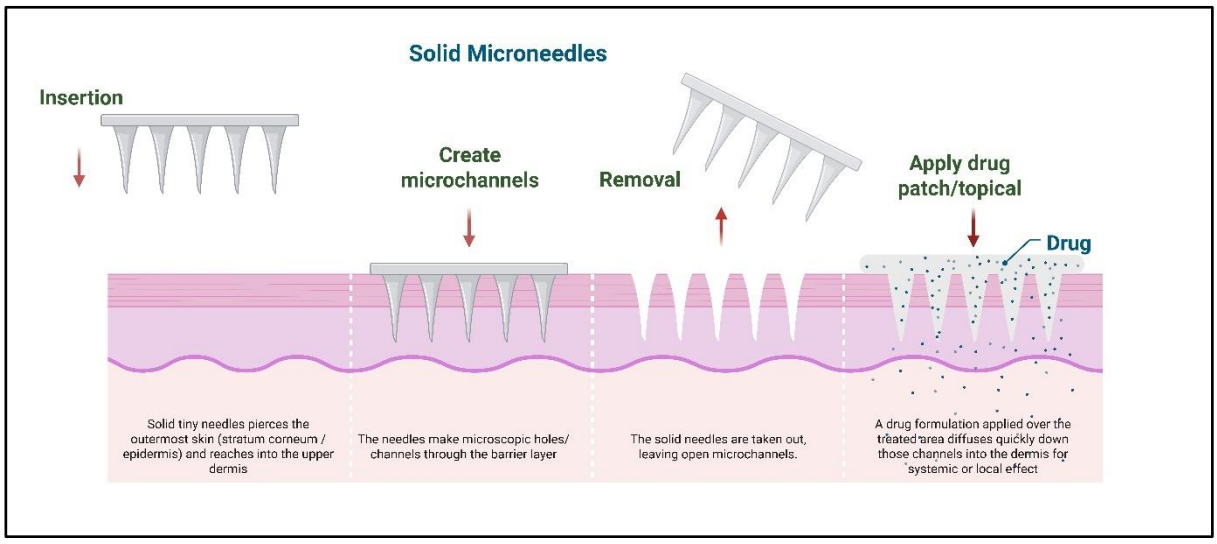


Figure 3. Schematic representation of Solid microneedles (poke-and-patch) and their mechanisms of drug delivery through the skin (Created using Biorender).

3.2. Coating Dissolution Kinetics in Coated Microneedles

Coated MNs are used to deliver drugs via dissolution of a thin API layer coated onto the surface of the needle [43]. Drug release occurs minutes after insertion and is controlled by coating thickness, polymer excipient composition, and fluid dynamics in the skin's interstitial space [42]. This rapid

 doi:10.20944/preprints202512.0407.v1

release is suitable for vaccines and potent biologics, for which precise dosing and rapid onset are essential. The uniformity of coating and stability of adhesion during insertion are of great importance for reproducible delivery **(Figure 4)** [43].

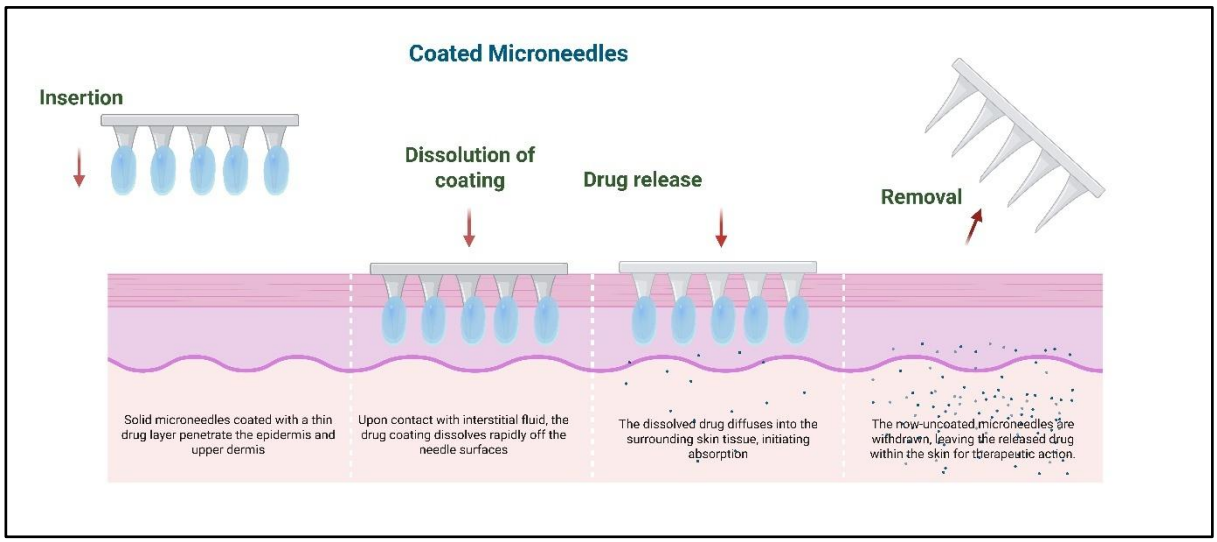
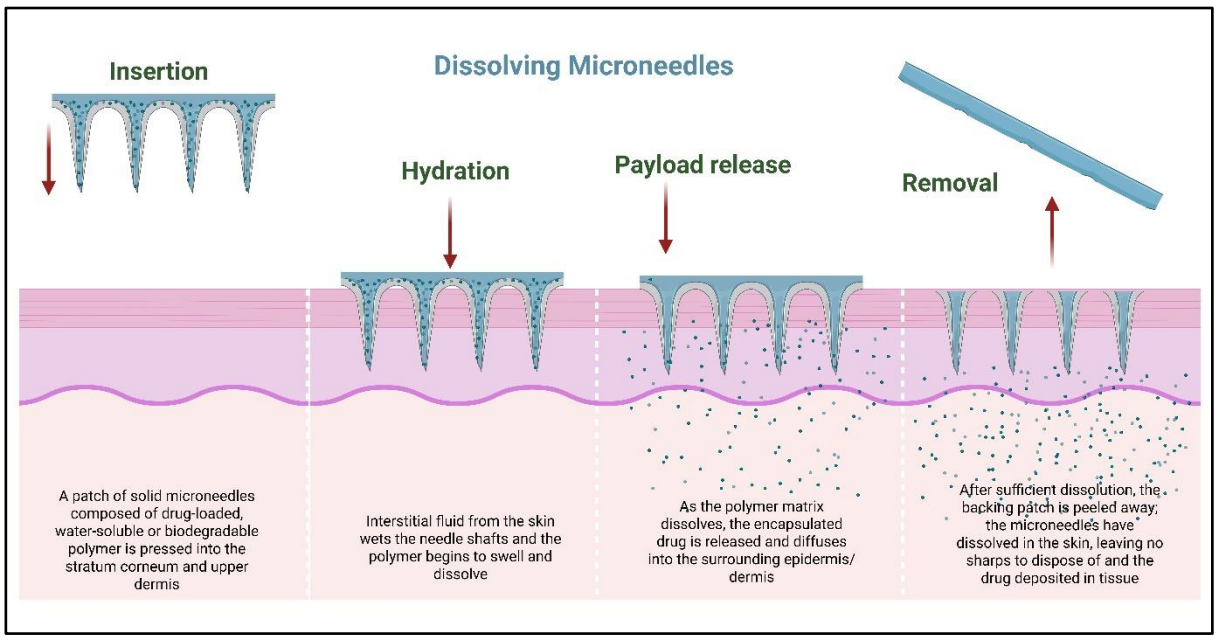


Figure 4. Illustrative mechanism of drug diffusion and release from coated microneedles into the dermal layer (Created using Biorender).

3.3. Biodegradable Matrix Dissolution in Dissolving Microneedles

Dissolving MNs encapsulate the API in a biodegradable polymer matrix (e.g., polyvinylpyrrolidone, hyaluronic acid, carboxymethyl cellulose) [44]. Upon insertion, interstitial fluid diffuses into the matrix, dissolving and releasing the encapsulated drug. The polymer molecular weight, degree of crosslinking, and needle geometry can manipulate release kinetics [45]. Dissolving MNs leaves no residual sharps and decreases biohazardous waste, and can stabilize thermolabile biologics in solid state formulations [46]. Clinical studies have demonstrated their efficacy for insulin and influenza vaccines, highlighting patient-friendly administration and improved compliance **(Figure 5)** [45].



 doi:10.20944/preprints202512.0407.v1

Figure 5. Representation of the insertion, hydration, and drug release mechanisms of dissolving microneedles for controlled drug delivery through the skin (Created using Biorender).

3.4. Infusion Through Hollow Microneedles

Hollow MNs contain a central lumen that allows direct infusion of liquid formulations into the dermis. Drug delivery can be given as a bolus, continuous infusion, or pulsatile dose with precise control of the pharmacokinetics [36]. The infusion rate is affected by the needle diameter, the lumen length, the depth of insertion, and skin backpressure. Hollow MNs can be used for a larger volume and viscous formulations suitable for biologics, monoclonal antibodies, and chemotherapeutics **(Figure 6)** [47].

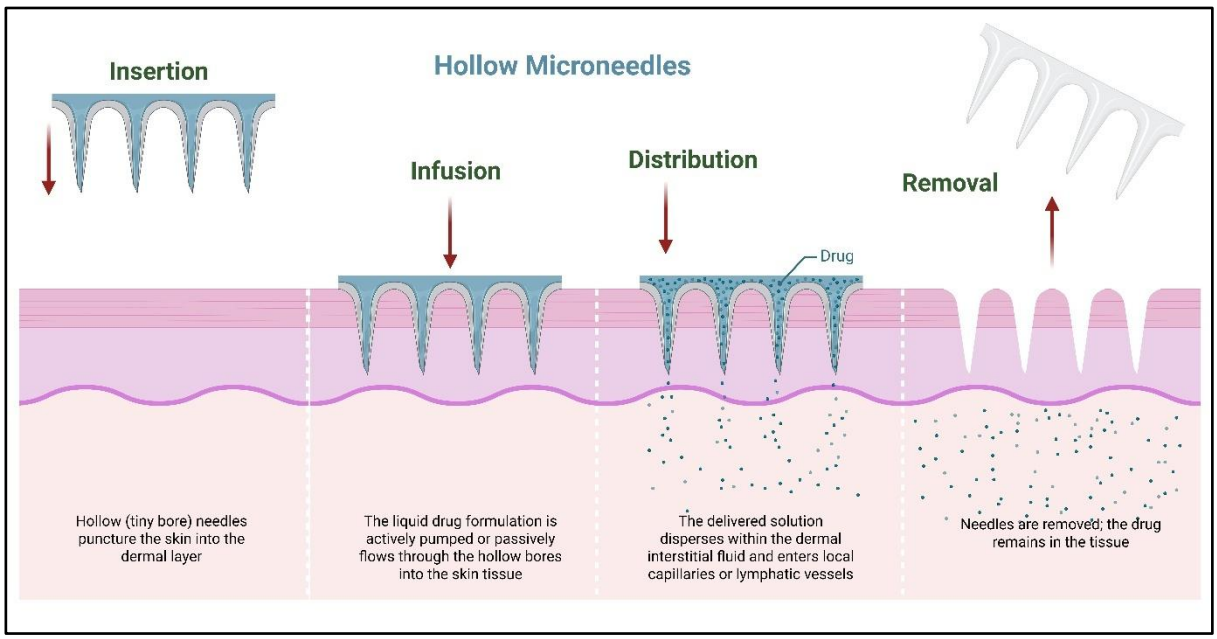


Figure 6. Diagram depicting the structure and drug distribution process of hollow microneedles across the skin barrier (Created using Biorender).

3.5. Swelling and Sustained Release via Hydrogel-Forming Microneedles

Hydrogel-forming MNs consist of crosslinked swellable polymers (e.g., PEG, polyHEMA) that absorb interstitial fluid to create conduits for the diffusion of drug species from an attached reservoir [48]. Sustained release can occur in hours to days, depending on the polymer composition and degree of crosslinking [13]. Unlike dissolving MNs, the hydrogel matrix is not dissolved after therapy, which helps to reduce deposition of residual polymer in the skin [49]. These hydrogel MNs have demonstrated potential for sustained insulin delivery, vaccines, and small molecule drug delivery, with enhanced pharmacokinetic profiles and reduced frequency of dosing **(Figure 7)** [50,51].

 doi:10.20944/preprints202512.0407.v1

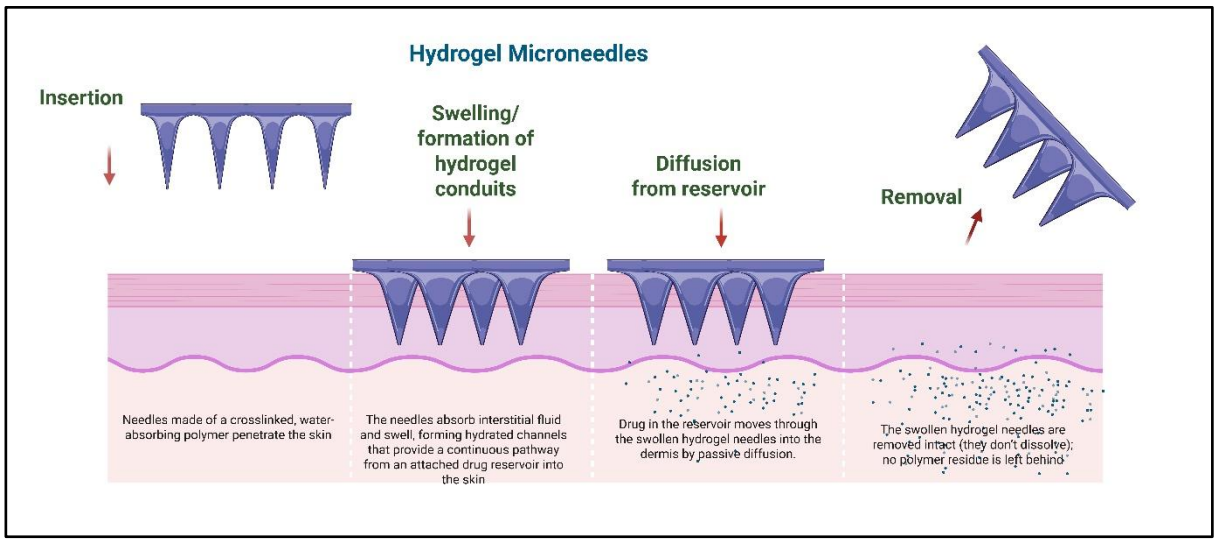


Figure 7. Schematic illustration of hydrogel-forming microneedles and their transdermal drug delivery mechanism (Created using Biorender).

3.6. Hybrid and Stimuli-Responsive Mechanisms

Next-generation MNs combine several mechanisms, usually dissolving tips and solid bases or adding stimuli-responsive polymers that unfold drugs (responsive to temperature, pH, or enzymatic activity) [52]. Nanoparticles, liposomes, or micelles may be incorporated in the matrix of the MN for targeted or controlled release [8]. Complex delivery profiles, such as pulsatile or on-demand release, can be achieved, and the MNs can be integrated with wearable electronics for feedback in real time [18,44].

4. Innovations in Microneedle Technologies

Technological advances in materials sciences, microfabrication, nanotechnology, and digital health are propelling MN systems beyond traditional transdermal drug delivery applications, moving them towards innovative, more precise, and more patient-centric solutions **(Table 2; Figure 8)** [53]. Recent developments focus on designs with multifunctionality from diagnostics, targeted therapy, and remote monitoring, as well as issues of bioavailability, patient adherence, and scalability [8]. Innovations in laser-ablation molds for the fabrication of polymer MNs and circularly polarized light optical vortices for metal microstructures provide enhancement of fabrication precision and mechanical properties [54]. These advancements are opening up the use of MN in wound healing, metabolic disorders, nucleic acid therapeutics, and even intraocular delivery, with projections for this technology in the market showing their use in next-generation pharmaceutics [55].

4.1. Stimuli-Responsive and Smart Polymers

Incorporating stimuli-responsive polymers into microneedles (MNs) enables dynamic, on-demand drug release controlled by environmental stimuli, representing a significant advancement in precision drug delivery [56]. These "smart" polymers respond to diverse stimuli, including pH, temperature, glucose, light, electrical, or magnetic fields, thereby modulating drug release kinetics for tailored therapeutic effects [57]. For instance, pH-responsive polymers such as poly(acrylic acid) facilitate targeted drug release within the acidic tumor microenvironment, enhancing chemotherapy efficacy while minimizing systemic toxicity [58]. Glucose-responsive MNs constructed from phenylboronic acid-based hydrogels exhibit swelling or shrinking behaviors in response to blood glucose concentrations, enabling closed-loop insulin delivery systems that effectively mimic pancreatic function for diabetes management [59].

 doi:10.20944/preprints202512.0407.v1

Recent developments include multi-stimuli responsive systems that combine thermo and enzyme-sensitivity for wound healing applications, where MNs release antimicrobials upon detecting infection-associated signals like elevated temperature or bacterial enzymes [60].The field has seen exponential growth in patent activity, particularly in integrating diagnostics and therapeutics, exemplified by light-activated MNs for photodynamic therapy in skin disease treatment [61]. Although these polymers enhance bioavailability by 2-5-fold in preclinical models, current challenges, such as response times ranging from seconds to minutes and biocompatibility concerns, are being mitigated through the use of hybrid copolymers that optimize performance and safety [62]. Together, these advances establish stimuli-responsive MNs as a cutting-edge platform for personalized and responsive drug delivery systems in clinical and translational medicine.

4.2. Nanoparticle Incorporation and Multifunctional Microneedles

Incorporating nanoparticles, liposomes, nanosuspension, micelles, or dendrimers within MN matrices not only improves the stability of encapsulated drugs but also facilitates targeted delivery to specific cells or tissues. Additionally, this approach allows for the integration of multiple therapeutic or diagnostic functions, broadening the scope and versatility of MN-based delivery systems.[63]. Moreover, NPs help protect labile biologics against degradation, thus facilitating co-delivery of therapeutics and adjuvants for synergistic effects [64]. In cancer treatment, gold or silica NPs/loaded MNs can be used for photothermal ablation with chemotherapy, with tumor regression rates as high as 80% in murine models [65]. For vaccines, lipid NPs encapsulate mRNA molecules, which improves stability and immune response on nucleic acid delivery via dissolving MNs. Multifunctional MNs incorporate biosensing, including electrochemical detection of biomarkers in interstitial fluid (ISF) using NP-based sensing for real-time monitoring during the drug release [66,67]. Recent innovations include stimuli-responsive NPs for gene therapy, where magnetic NPs provide guided delivery under external fields for a more precise expression for metabolic disorders. These systems increase drug loading by 30-50%, while also decreasing their off-target effects, although scalability in NP-MN integration remains challenging [68].

4.3. D Printing and Advanced Microfabrication

3D printing technologies such as stereolithography (SLA), two-photon polymerization (2PP), and fused deposition modeling (FDM) enable unprecedented control over the geometry of the MN, as well as its porosity and internal structures [69,70]. These techniques enable rapid prototyping of customizable arrays with hollow channels, microreservoirs, or hybrid designs, which are impossible with traditional etching or molding processes. For example, 3D-printed hollow MNs with integrated ultrasonic atomizers enable on-demand drug atomization, improving drug bioavailability in remote healthcare applications. Advancements in materials, including biocompatible resins, e.g., PEGDA, to support complex release profiles (sequential multi-drug release for wound healing) [71,72] and additions of 2PP-printed MNs for brain-targeted delivery for crossing the blood-brain barrier with tailored tips for precision neuroscience. High-resolution printing (< 10 μm) enables patient-specific design and reduces fabrication time (hours) and costs [73,74]. Challenges such as material biocompatibility are overcome with graphene composites, providing a 3-fold increase in mechanical strength [75]. Overall, 3D printing accelerates the entire process from the laboratory to the clinic, enabling personalized medicine [76].

4.4. Wearable Patches and Digital Health Integration

Wearable MN patches combine drug delivery with biosensing and Internet of Things (IoT) connectivity to create “closed loop” systems for continuous health management [77]. These platforms detect biomarkers in ISF, such as glucose, electrolytes, or cfDNA, using integrated electrodes or optical sensors, and can automatically initiate dosing based on the detected physiological signals.[78,79]. For example, systems based on hydrogel, such as mPatch, have used a set of sensors

 doi:10.20944/preprints202512.0407.v1

(CMOS) to monitor the optical concentration of Ca^{2+} ions, to provide real-time feedback in metabolic disorders [80]. Recent advances include graphene-composite MN patches for painless, non-bleeding monitoring, connected to smartphones for remote data processing and warnings. Integration with AI algorithms can be used to optimize therapy, for example, in patches known as continuous glucose monitoring (CGM), which adjust insulin release to optimize glucose control, improving glycemic control by 40% in trials [81,82]. Cloud-based systems help provide telemedicine, enhancing adherence to diabetes and cardiovascular diseases. Miniaturized designs ensure comfort, with battery life >24 hours, though power efficiency and sensor accuracy in dynamic environments are ongoing focuses [83,84].

4.5. Personalized and Controlled Release Designs

Progress in polymer chemistry and MN architecture paves the way for customized release kinetics and allows the drugs to have precision medicine and individualized pharmacokinetics [85]. Dissolving MNs with multi-layered tips allows for the sequential release of actives, which is ideal for the combination therapy approach in photoaging or infections [74]. Hydrogel MNs provide extended delivery for days through swelling-controlled diffusion, and hybrid formulations include pulsatile or on-demand delivery pumps [86]. Bioinspired innovations, such as mosquito-proboscis mimics, offer minimally invasive and self-administered solutions [87], site-specific MNs for wounds or tumors with customizable porosity for zero-order kinetics. These designs expand beyond transdermal to ocular or gastrointestinal applications, with efficacy gains of 50-100% over conventional patches [18,88]. Future personalization via AI-driven fabrication promises adaptive therapy, though regulatory standardization is needed [89].

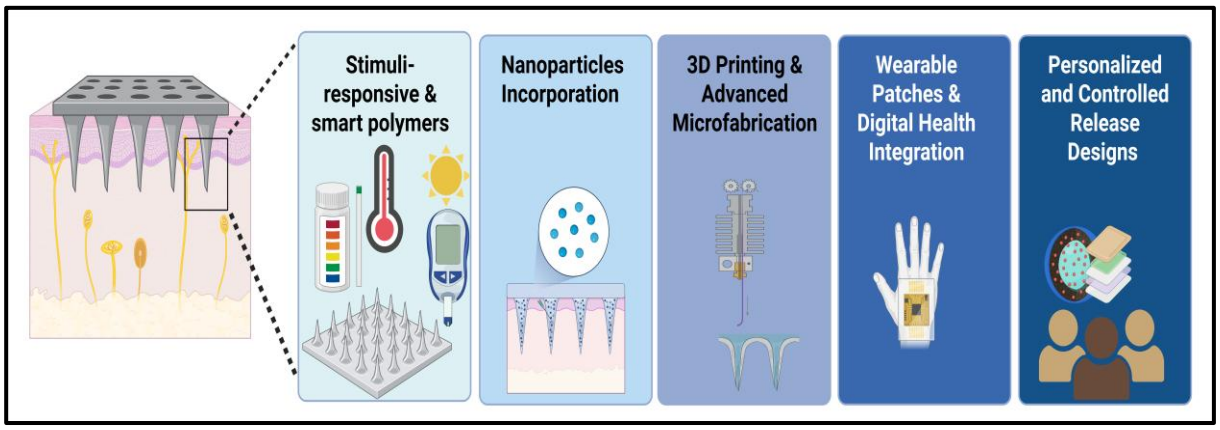


Figure 8. Schematic illustration of advanced microneedle technologies for transdermal delivery, highlighting smart polymers, nanoparticles, 3D printing, wearable integration, and personalized release features.

Table 2. Innovations in Microneedle Technologies: Features and Applications.

Innovation	Feature	Application	Advantage	Examples	References
Stimuli-responsive MNs	pH, glucose, temperature-sensitive polymers	Insulin, targeted cancer therapy	On-demand, closed-loop release	glucose-responsive insulin MN patches for insulin delivery; pH-responsive MNs releasing doxorubicin or cisplatin selectively in acidic tumor tissue in murine xenograft models	[90]

 doi:10.20944/preprints202512.0407.v1

Nanoparticle-loaded MNs	Drug-loaded nanoparticles or liposomes	Vaccines, biologics, gene therapy	Improved stability, targeted delivery	Poly(lactic-co-glycolic acid) (PLGA) nanoparticle-loaded MNs for influenza or SARS-CoV-2 subunit/DNA vaccines, showing enhanced humoral and cellular immunity vs intramuscular injection	[91]
3D-printed MNs	Customized geometry, multi-layered	Personalized medicine, combination therapy	High precision, rapid prototyping	3D-printed hollow MNs for individualized intradermal vaccination and sampling	[92]
Wearable MN patches	Integrated sensors and electronics	Chronic disease monitoring, digital health	Remote monitoring, automated dosing	Wearable MN patch from UC San Diego monitoring glucose, alcohol, and lactate simultaneously in interstitial fluid with electrochemical readout and wireless transmission	[93]
Hybrid MNs	Combination of dissolving, solid, hydrogel	Multi-drug or sequential release	Optimized pharmacokinetics, patient-tailored therapy	Hybrid dissolving–hydrogel MNs for biphasic release of small molecules such as ibuprofen (fast initial release from dissolving tips followed by sustained release from swelling base	[13]

4.6. Advances in Smart Microneedle Design: 4D Printing and AI Optimization

Recently, the fabrication of microneedles has advanced significantly, driven by 4D printing and bio-inspired designs, to address the longstanding challenge of balancing mechanical strength and biocompatibility. Researchers have developed MN arrays made from dual-sensitive polymers using projection micro-stereolithography, which respond to physiological stimuli, such as moisture, by deploying backward-facing barbs inspired by creatures like parasites and honeybees. This dynamic shape change greatly improves tissue adhesion, reducing the "pop-off" effect and enhancing the utility of microneedles for applications like sustained drug release and continuous biosensing [94].

Concurrently, machine learning techniques are revolutionizing microneedle design by integrating finite element analysis with Gaussian Process Regression to optimize needle geometry and achieve maximum safety margins, ensuring reliable skin penetration without mechanical failure. These scientific and computational innovations mark a shift from static to smart, bioinspired microneedle architectures with optimized functionality and patient compliance [95].

5. Therapeutic Applications of Microneedles

MN technologies have expanded beyond simple transdermal delivery of therapeutics and provide versatile platforms for a broad range of therapeutic applications [96]. The unique combination of minimally invasive delivery, greater patient compliance, and improved

 doi:10.20944/preprints202512.0407.v1

bioavailability has made MNs a promising alternative for vaccines, biologics, chronic disease therapeutics, oncology, and cosmetic interventions **(Figure 9)** [5].

5.1. Vaccines and Immunotherapy

Vaccination represents one of the earliest and most extensively studied applications of MNs [97]. Coated and dissolving MNs have been used for the delivery of influenza, measles, rubella, and hepatitis B vaccines, as well as novel candidates for the administration of the COVID-19 vaccines [98]. MN-mediated delivery targets antigen-presenting cells in the epidermis and dermis, which results in robust humoral and cellular immune reactions at lower antigen doses as compared to intramuscular injection [99]. MN patches provide essential benefits for vaccination, such as dose sparing, which allows smaller amounts of vaccine antigen to achieve comparable immunity to traditional injections. This is especially valuable for costly or limited supply vaccines [98,100]. Additionally, MN vaccination is painless, making it a more appealing option for patients, especially children. This aspect can lead to increased overall patient compliance [101]. Another significant advantage of MN technology is its thermostability. By stabilizing vaccines in a solid-state MN matrix, it eliminates the need for a continuous cold chain, facilitating distribution to remote or resource-limited areas [102]. Clinical trials have already shown that MN influenza vaccines are highly effective, and research into their potential for mass immunization is currently underway [103]. Beyond traditional vaccines, MN technology is also being explored for cancer immunotherapy, where it can deliver various therapeutic agents directly to specific sites to modulate the immune system [104].

5.2. Diabetes and Peptide Delivery

Insulin and other peptide therapeutics greatly benefit from MN-mediated delivery. Dissolving and hydrogel-forming MNs offer extended-release profiles without requiring frequent subcutaneous injections [105]. Glucose-responsive MNs enable better therapeutic control by releasing insulin when glucose levels are elevated, similar to how the body regulates these levels through pancreatic function [8]. Clinical studies have shown that insulin patches can improve glycemic control and increase patient compliance. Additionally, other peptide therapeutics, such as glucagon-like peptide-1 (GLP-1) analogs and parathyroid hormone fragments, have been successfully delivered using MNs. This approach offers the potential to treat chronic diseases without the pain or anxiety associated with traditional injections [106].

5.3. Cancer Therapy and Chemotherapy

The MN technologies have been modified for localized delivery of chemotherapeutics, immunomodulators, and gene therapy vectors. Hollow and dissolving MNs enable the controlled delivery of cytogenic drugs with less systemic toxicity and enhanced tumor targeting [107]. For example, MN-mediated delivery of doxorubicin, paclitaxel, and cisplatin-loaded NPs has shown the enhancement of penetration into skin tumors and reduced systemic exposure [108]. MN-based immunotherapy, such as checkpoint inhibitors and vaccine adjuvants, has also shown promise in preclinical models of melanoma and breast cancer [109]. Hybrid MN systems combining nanoparticles and stimuli-responsive matrices facilitate spatiotemporal control of drug release, which may further optimize anti-cancer efficacy [110].

5.4. Hormonal and Contraceptive Delivery

MN patches are an alternative route for hormonal therapies, such as contraception, hormone replacement, and fertility treatments. Dissolving MNs have been developed to release levonorgestrel, estradiol, and progesterone with sustained kinetics for weekly or monthly dosing [111]. The advantages include enhancing adherence to therapy due to lower GI metabolism and patient convenience. MNs also address the need for repeated injections, which increases accessibility in low-resource settings [112].

 doi:10.20944/preprints202512.0407.v1

5.5. Cosmeceuticals and Dermatology

The cosmetic and dermatology sector has embraced MNs for skin rejuvenation, pigmentation correction, and transdermal delivery of growth factors, peptides, and vitamins. MNs increase the penetration of actives such as hyaluronic acid, retinoids, and antioxidants, which have poor dermal absorption [113]. Dissolving MNs allows for the delivery of these compounds without pain, while inducing collagen generation and skin reorganization [114]. The use of MN-based cosmeceuticals has become increasingly popular, due to the minimally invasive and office-free application techniques, with less risk of infection, compared to traditional microneedling [27].

5.6. Infectious Disease Therapeutics

Beyond vaccination, MNs are being explored for antiviral and antibacterial therapies. Dissolving MNs may deliver antiviral peptides, nucleic acids, or antibiotics directly to the dermis, leading to increased local efficacy and reduced systemic side effects [115]. Delivery using MNs has been studied for herpes simplex virus, human papillomavirus, and bacterial skin infections and has shown increased local drug concentration and therapeutic effect [116]. Furthermore, long-acting antiretroviral therapy can be effectively delivered via intradermal administration with dissolving or implantable microneedle patches, overcoming adherence challenges associated with oral and injectable dosing. Incorporation of etravirine and rilpivirine nanosuspensions into dissolving arrays has demonstrated efficient transdermal deposition of drug nanocrystals and markedly enhanced systemic and lymphatic exposure *in vivo* [117,118]. Subsequent designs co-loading cabotegravir and rilpivirine have yielded sustained plasma concentrations for several weeks following a single application, with repeat dosing maintaining prolonged therapeutic levels [119]. More recent systems embedding bictegravir and tenofovir alafenamide further confirmed that microneedle-mediated intradermal delivery can achieve sustained systemic concentrations of integrase inhibitors while enabling rapid conversion of prodrugs, highlighting the platform's strong potential for long-acting treatment and pre-exposure prophylaxis [120].

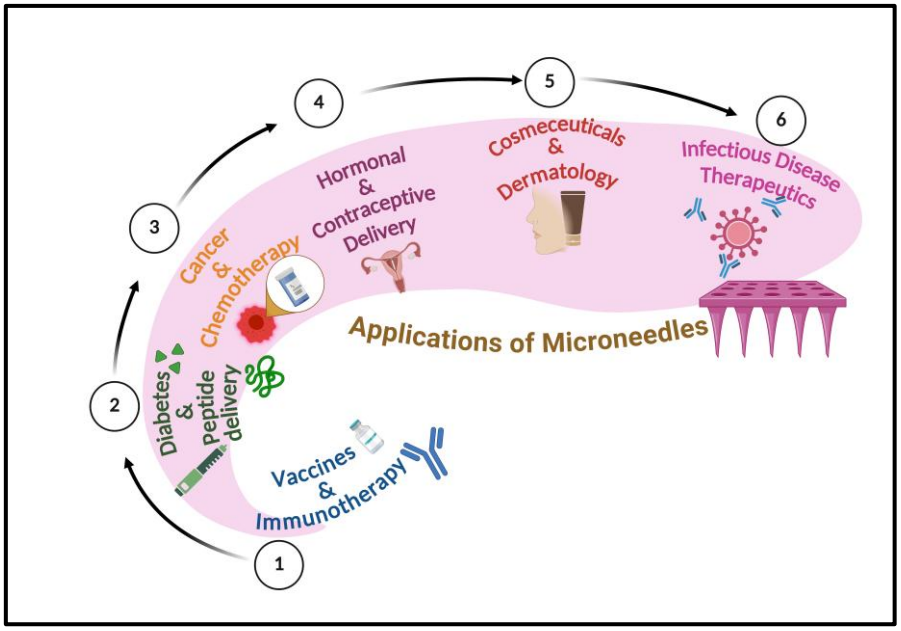


Figure 9. Overview of major applications of microneedles in biomedical and pharmaceutical fields.

6. Commercial Challenges, Regulatory Pathways, and Case Studies

Despite the promising therapeutic potential of MN technologies, translation from laboratory prototypes to commercially viable products faces several technical, regulatory, and market-based

 doi:10.20944/preprints202512.0407.v1

challenges [121]. Addressing these barriers is critical for widespread adoption in clinical and consumer settings **(Figure 10).**

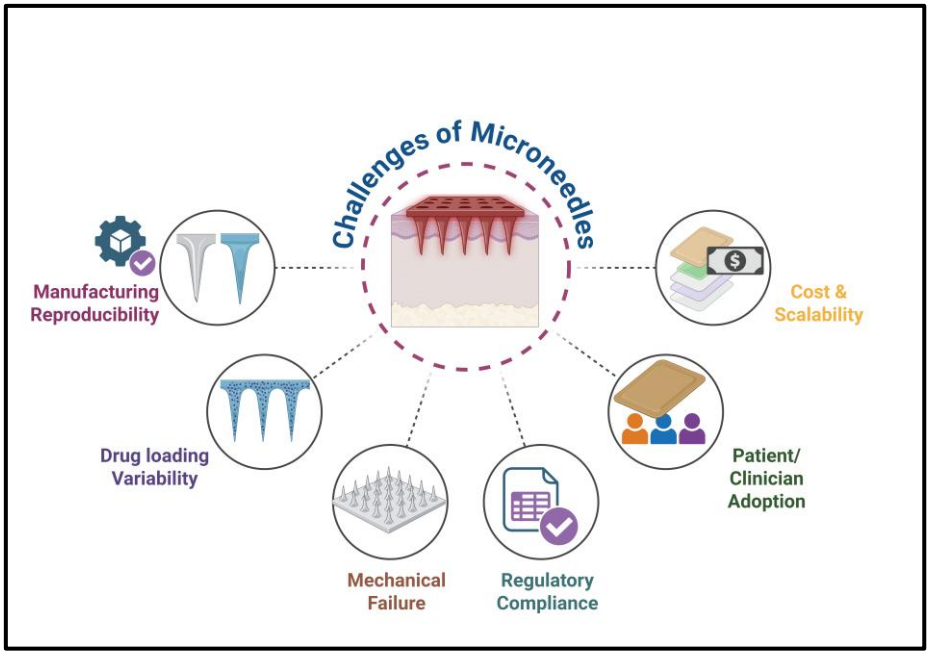


Figure 10. Key Challenges in Microneedle Technology Development.

6.1. Manufacturing and Scalability Challenges

A key obstacle to scaling up microneedle (MN) production is consistently achieving uniform quality and performance across large batches. Ensuring that MN arrays maintain precise dimensions, consistent sharpness, and intact tips throughout manufacturing is critical [122]. For dissolving or coated MNs, it is equally important to control polymer consistency and drug loading to secure reliable drug release profiles [123]. Transitioning from laboratory-scale fabrication to industrial production presents significant challenges, especially with complex MN designs [124]. While advanced manufacturing techniques like automated molding, roll-to-roll processing, and 3D printing offer promising solutions, their high costs pose limitations [125]. Furthermore, maintaining the mechanical robustness and drug stability of MNs, particularly those containing delicate biologic agents, is vital for prolonged shelf life. Despite promising clinical outcomes, large-scale manufacturing remains a significant bottleneck [47]. Additional concerns include the need for aseptic processing to produce vaccine-loaded MNs, which is more intricate and expensive than conventional sterilization methods. Companies such as Vaxxas and Micron Biomedical are heavily investing in the commercial scale-up process, attempting to shift from small-batch molding to high-volume manufacturing methods [47]. Moreover, ensuring consistent application force through standardized applicators, like the spring-loaded devices used by Vaxxas, is becoming a regulatory expectation to reduce variability in insertion depth and minimize user errors [47].

6.2. Safety and Clinical Validation

Before widespread use, MN products must be thoroughly validated for safety. This involves assessing short-term problems, such as mild skin reactions (erythema, edema) at the insertion site, as well as potential long-term dermatological effects [51]. Ensuring patient safety is of utmost importance, which requires strict sterilization protocols and the adoption of single-use MN designs. For biologics and vaccines, it is particularly critical to balance efficient delivery with the need to avoid triggering adverse immune reactions or systemic toxicity. [126]. Another significant safety concern is mechanical failure, such as incomplete insertion or needle breakage, which can impact drug delivery

 doi:10.20944/preprints202512.0407.v1

[27]. Although clinical trials have shown favorable safety profiles for products like MN influenza vaccines, post-marketing surveillance on a larger scale is essential [127].

6.3. Regulatory Approval Pathways

The regulatory process for combination products involving medicinal and non-medicinal components is complex due to their classification as drug-device combinations [128]. In the United States, the FDA requires a comprehensive dataset to support MN product approval. This includes evidence of mechanical integrity to ensure the needles reliably penetrate the skin without breaking, drug release profiles to confirm accurate and reproducible dosing, sterility to prevent infection, biocompatibility to avoid adverse tissue reactions, and clinical efficacy to demonstrate therapeutic benefit. The FDA may also require additional studies on stability, patient usability, and long-term safety depending on the drug or biologic being delivered [129]. Similarly, in Europe, MNs are regulated as medical devices under the Medical Device Regulation (MDR) overseen by the European Medicines Agency (EMA). Approval requires demonstration of device safety, consistent functional performance, and risk mitigation strategies to protect users. The EMA emphasizes a thorough risk–benefit assessment, particularly for combination products that deliver drugs or biologics [130]. Navigating these regulatory pathways requires early and ongoing engagement with agencies to define testing protocols, quality standards, and documentation requirements. This proactive collaboration helps ensure compliance, streamline approvals, and support the safe clinical translation of innovative microneedle technologies.

6.4. Market Adoption and User Acceptance

Even after receiving regulatory approval, the success of commercializing these products hinges on their acceptance by patients, healthcare providers, and institutions [100]. Patient preference is a significant factor, as the painless and self-administered nature of MN patches makes them particularly appealing for chronic diseases and vaccinations in children [131]. However, for these products to gain acceptance, healthcare providers need to provide training, demonstrate proven efficacy, and offer reassurance about safety. Additionally, economic factors play a crucial role. The cost-effectiveness of MN products, along with favorable reimbursement strategies and pricing models, will ultimately influence their adoption, especially in resource-limited regions [132]. Although the high manufacturing costs associated with early MN technologies may hinder widespread acceptance, ongoing research aims to develop a more affordable and efficient manufacturing process [133].

6.5. Case Studies of Marketed and Trial-Stage MN Products

Several MN platforms have progressed from laboratory research to advanced clinical trials and limited market entry, underscoring both the technological maturity and remaining translational challenges of this field. These case studies highlight key innovations, clinical outcomes, and development barriers such as mechanical reliability, drug stability, manufacturing scalability, regulatory classification, and cost management **(Table 3)** [134].

Table 3. Summary of representative MN products and their clinical development status.

MN Type	Product/Company	Therapeutic Area	Status/Outcome	Reference
Solid/coated	Vaxxas Micro-Needle Array Patch	Influenza vaccine	Phase II/III trials; strong immunogenicity, dose sparing	[100]
Dissolving	3M Microneedle Patch	Influenza, COVID-19 vaccines	Clinical trials; thermostable, self-administered	[135]

 doi:10.20944/preprints202512.0407.v1

Dissolving	Micron Biomedical MN Patch	Insulin	Preclinical & early human trials; sustained release demonstrated	[136]
Hollow	Zosano Pharma Qtrypta	Migraine (zolmitriptan)	FDA approved; commercial availability in select regions	[137]
Dissolving/hybrid	Teva/BD Microneedle Platform	Hormonal therapy	Early-stage clinical trials; ongoing safety evaluation	[138]

7. Future Perspectives

MN technologies have evolved from experimental concepts to highly promising platforms for transdermal and intradermal drug delivery with expanding therapeutic applications. Advances in smart and responsive materials enable MNs to respond to physiological stimuli, such as glucose, temperature, and pH, enabling precise, on-demand drug release. Integration with digital health technologies further enhances their function by supporting real-time monitoring and personalized treatment adjustments [9,126,132,139,140]. Hybrid MN systems that combine drug delivery with diagnostic capabilities are emerging, offering more comprehensive patient care. MNs also hold great potential for global health by facilitating needle-free, thermostable vaccine delivery suitable for resource-limited settings [25,141,142]. However, challenges remain in scalable manufacturing, regulatory standardization, biocompatibility, and patient education [134,143]. Ongoing research into biodegradable polymers, stimuli-responsive compounds, and collaborative efforts across academia, industry, and regulators will be crucial to overcoming these hurdles and accelerating clinical translation [144,145]. Overall, MN technologies represent a transformative approach toward personalized, minimally invasive, and patient-friendly healthcare solutions.

8. Conclusion

MN technologies have been revolutionary in drug delivery systems, as they are minimally invasive, support positive patient experiences, and offer potential for customization to individual therapeutic needs. Beyond improving adherence, MN systems provide remarkable clinical versatility, enabling transdermal delivery of a wide range of therapeutics, including vaccines, biologics, small molecules, and combination therapies. Their structural flexibility allows integration with advanced responsive materials and wearable biosensors, facilitating "on-demand" drug release and real-time physiological monitoring. On a global scale, MN technologies hold promises for portable, self-administered healthcare solutions, from chronic disease management to needle-free vaccination programs, particularly in resource-limited settings. Self-administered MN vaccines can reduce dosing frequency while improving therapeutic outcomes and adherence. However, the successful translation of MN systems into widespread clinical use will depend on overcoming key challenges, including scalable, reproducible manufacturing; long-term biocompatibility; regulatory harmonization across regions; and effective patient education. Addressing these hurdles will be critical to fully realizing the therapeutic and societal potential of microneedle technologies.

References

1. Jung, J.H.; Jin, S.G. Microneedle for transdermal drug delivery: current trends and fabrication. *J Pharm Investig* **2021**, *51*, 503-517, doi:10.1007/s40005-021-00512-4.
2. Chen, K.; Sun, X.; Liu, Y.; Li, S.; Meng, D. Advances in clinical applications of microneedle. *Front Pharmacol* **2025**, *16*, 1607210, doi:10.3389/fphar.2025.1607210.
3. Hulimane Shivaswamy, R.; Binulal, P.; Benoy, A.; Lakshmiramanan, K.; Bhaskar, N.; Pandya, H.J. Microneedles as a Promising Technology for Disease Monitoring and Drug Delivery: A Review. *ACS Mater Au* **2025**, *5*, 115-140, doi:10.1021/acsmaterialsau.4c00125.
4. Aldawood, F.K.; Andar, A.; Desai, S. A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications. *Polymers (Basel)* **2021**, *13*, doi:10.3390/polym13162815.

 doi:10.20944/preprints202512.0407.v1

5. Kulkarni, D.; Damiri, F.; Rojekar, S.; Zehravi, M.; Ramproshad, S.; Dhoke, D.; Musale, S.; Mulani, A.A.; Modak, P.; Paradhi, R.; et al. Recent Advancements in Microneedle Technology for Multifaceted Biomedical Applications. *Pharmaceutics* **2022**, *14*, doi:10.3390/pharmaceutics14051097.
6. Vitore, J.G.; Pagar, S.; Singh, N.; Karunakaran, B.; Salve, S.; Hatvate, N.; Rojekar, S.; Benival, D. A comprehensive review of nanosuspension loaded microneedles: fabrication methods, applications, and recent developments. *J. Pharm. Investig.* **2023**, *53*, 475-504, doi:10.1007/s40005-023-00622-1.
7. Joshi, N.; Azizi Machekposhti, S.; Narayan, R.J. Evolution of Transdermal Drug Delivery Devices and Novel Microneedle Technologies: A Historical Perspective and Review. *JID Innov* **2023**, *3*, 100225, doi:10.1016/j.xjidi.2023.100225.
8. Wang, C.; Yang, Y.; Zhang, J.; Zhang, H.; Wang, Q.; Ma, S.; Zhao, P.; Li, Z.; Liu, Y. Microneedles at the Forefront of Next Generation Theranostics. *Adv Sci (Weinh)* **2025**, *12*, e2412140, doi:10.1002/advs.202412140.
9. 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*, 5161-5180, doi:10.1016/j.apsb.2024.08.013.
10. Zhang, X.; Gu, Q.; Sui, X.; Zhang, J.; Liu, J.; Zhou, R. Design and optimization of hollow microneedle spacing for three materials using finite element methods. *Sci Rep* **2025**, *15*, 652, doi:10.1038/s41598-024-82564-8.
11. Lyu, S.; Dong, Z.; Xu, X.; Bei, H.P.; Yuen, H.Y.; James Cheung, C.W.; Wong, M.S.; He, Y.; Zhao, X. Going below and beyond the surface: Microneedle structure, materials, drugs, fabrication, and applications for wound healing and tissue regeneration. *Bioact Mater* **2023**, *27*, 303-326, doi:10.1016/j.bioactmat.2023.04.003.
12. Tuan-Mahmood, T.M.; McCrudden, M.T.; Torrisi, B.M.; McAlister, E.; Garland, M.J.; Singh, T.R.; Donnelly, R.F. Microneedles for intradermal and transdermal drug delivery. *Eur J Pharm Sci* **2013**, *50*, 623-637, doi:10.1016/j.ejps.2013.05.005.
13. Shriky, B.; Babenko, M.; Whiteside, B.R. Dissolving and Swelling Hydrogel-Based Microneedles: An Overview of Their Materials, Fabrication, Characterization Methods, and Challenges. *Gels* **2023**, *9*, doi:10.3390/gels9100806.
14. Rojekar, S.; Parit, S.; Gholap, A.D.; Manchare, A.; Nangare, S.N.; Hatvate, N.; Sugandhi, V.V.; Paudel, K.R.; Ingle, R.G. Revolutionizing Eye Care: Exploring the Potential of Microneedle Drug Delivery. *Pharmaceutics* **2024**, *16*, 1398, doi:10.3390/pharmaceutics16111398.
15. Waghule, T.; Singhvi, G.; Dubey, S.K.; Pandey, M.M.; Gupta, G.; Singh, M.; Dua, K. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. *Biomed Pharmacother* **2019**, *109*, 1249-1258, doi:10.1016/j.biopha.2018.10.078.
16. Gupta, J.; Gill, H.S.; Andrews, S.N.; Prausnitz, M.R. Kinetics of skin resealing after insertion of microneedles in human subjects. *J Control Release* **2011**, *154*, 148-155, doi:10.1016/j.jconrel.2011.05.021.
17. Howells, O.; Blayney, G.J.; Gualeni, B.; Birchall, J.C.; Eng, P.F.; Ashraf, H.; Sharma, S.; Guy, O.J. Design, fabrication, and characterisation of a silicon microneedle array for transdermal therapeutic delivery using a single step wet etch process. *Eur J Pharm Biopharm* **2022**, *171*, 19-28, doi:10.1016/j.ejpb.2021.06.005.
18. Luo, X.; Yang, L.; Cui, Y. Microneedles: materials, fabrication, and biomedical applications. *Biomed Microdevices* **2023**, *25*, 20, doi:10.1007/s10544-023-00658-y.
19. Cormier, M.; Johnson, B.; Ameri, M.; Nyam, K.; Libiran, L.; Zhang, D.D.; Daddona, P. Transdermal delivery of desmopressin using a coated microneedle array patch system. *J Control Release* **2004**, *97*, 503-511, doi:10.1016/j.jconrel.2004.04.003.
20. Kim, Y.C.; Park, J.H.; Prausnitz, M.R. Microneedles for drug and vaccine delivery. *Adv Drug Deliv Rev* **2012**, *64*, 1547-1568, doi:10.1016/j.addr.2012.04.005.
21. Faraji Rad, Z.; Prewett, P.D.; Davies, G.J. An overview of microneedle applications, materials, and fabrication methods. *Beilstein J Nanotechnol* **2021**, *12*, 1034-1046, doi:10.3762/bjnano.12.77.
22. Ma, G.; Wu, C. Microneedle, bio-microneedle and bio-inspired microneedle: A review. *J Control Release* **2017**, *251*, 11-23, doi:10.1016/j.jconrel.2017.02.011.
23. Donnelly, R.F.; Raj Singh, T.R.; Woolfson, A.D. Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. *Drug Deliv* **2010**, *17*, 187-207, doi:10.3109/10717541003667798.

 doi:10.20944/preprints202512.0407.v1

24. Ando, D.; Miyatsuji, M.; Sakoda, H.; Yamamoto, E.; Miyazaki, T.; Koide, T.; Sato, Y.; Izutsu, K.I. Mechanical Characterization of Dissolving Microneedles: Factors Affecting Physical Strength of Needles. *Pharmaceutics* **2024**, *16*, doi:10.3390/pharmaceutics16020200.
25. Yang, Y.; Sun, H.; Sun, X.; Wang, Y.; Xu, F.; Xia, W.; Chen, L.; Li, M.; Yang, T.; Qiao, Y.; et al. From mechanism to applications: Advanced microneedles for clinical medicine. *Bioact Mater* **2025**, *51*, 1-45, doi:10.1016/j.bioactmat.2025.04.025.
26. Razzaghi, M.; Akbari, M. 3D printed hollow microneedles: the latest innovation in drug delivery. *Expert Opin Drug Deliv* **2025**, *22*, 1487-1507, doi:10.1080/17425247.2025.2531062.
27. Mohite, P.; Puri, A.; Munde, S.; Ade, N.; Kumar, A.; Jantrawut, P.; Singh, S.; Chittasupho, C. Hydrogel-Forming Microneedles in the Management of Dermal Disorders Through a Non-Invasive Process: A Review. *Gels* **2024**, *10*, doi:10.3390/gels10110719.
28. Liu, L.; Wang, F.; Chen, X.; Liu, L.; Wang, Y.; Bei, J.; Lei, L.; Zhao, Z.; Tang, C. Designing Multifunctional Microneedles in Biomedical Engineering: Materials, Methods, and Applications. *Int J Nanomedicine* **2025**, *20*, 8693-8728, doi:10.2147/IJN.S531898.
29. Erikci, S.; van den Bergh, N.; Boehm, H. Kinetic and Mechanistic Release Studies on Hyaluronan Hydrogels for Their Potential Use as a pH-Responsive Drug Delivery Device. *Gels* **2024**, *10*, doi:10.3390/gels10110731.
30. Guan, S.; Wang, J.; Yang, Y.; Zhu, X.; Zhou, J.; Ye, D.; Chen, R.; Fan, Q.; Liao, Q. Microneedle-Based Biofuel Cell with MXene/CNT Hybrid Bioanode: Fundamental and Biomedical Application. *Adv Sci (Weinh)* **2025**, e16229, doi:10.1002/advs.202516229.
31. Sahu, B.; Maity, S.; Jain, A.; Banerjee, S. Next-generation stimuli-responsive polymers for a sustainable tomorrow. *Chem Commun (Camb)* **2025**, *61*, 12265-12282, doi:10.1039/d5cc02729b.
32. Thang, N.H.; Chien, T.B.; Cuong, D.X. Polymer-Based Hydrogels Applied in Drug Delivery: An Overview. *Gels* **2023**, *9*, doi:10.3390/gels9070523.
33. Li, A.D.R.; Putra, K.B.; Chen, L.; Montgomery, J.S.; Shih, A. Mosquito proboscis-inspired needle insertion to reduce tissue deformation and organ displacement. *Sci Rep* **2020**, *10*, 12248, doi:10.1038/s41598-020-68596-w.
34. Bedir, T.; Kadian, S.; Shukla, S.; Gunduz, O.; Narayan, R. Additive manufacturing of microneedles for sensing and drug delivery. *Expert Opin Drug Deliv* **2024**, *21*, 1053-1068, doi:10.1080/17425247.2024.2384696.
35. Ita, K. Dissolving microneedles for transdermal drug delivery: Advances and challenges. *Biomed Pharmacother* **2017**, *93*, 1116-1127, doi:10.1016/j.biopha.2017.07.019.
36. Kim, J.; Jeong, J.; Jo, J.K.; So, H. Hollow microneedles as a flexible dosing control solution for transdermal drug delivery. *Mater Today Bio* **2025**, *32*, 101754, doi:10.1016/j.mtbio.2025.101754.
37. Aroche, A.F.; Nissan, H.E.; Daniele, M.A. Hydrogel-Forming Microneedles and Applications in Interstitial Fluid Diagnostic Devices. *Adv Healthc Mater* **2025**, *14*, e2401782, doi:10.1002/adhm.202401782.
38. Peng, K.; Vora, L.K.; Dominguez-Robles, J.; Naser, Y.A.; Li, M.; Larraneta, E.; Donnelly, R.F. Hydrogel-forming microneedles for rapid and efficient skin deposition of controlled release tip-implants. *Mater Sci Eng C Mater Biol Appl* **2021**, *127*, 112226, doi:10.1016/j.msec.2021.112226.
39. Shi, H.; Huai, S.; Wei, H.; Xu, Y.; Lei, L.; Chen, H.; Li, X.; Ma, H. Dissolvable hybrid microneedle patch for efficient delivery of curcumin to reduce intraocular inflammation. *Int. J. Pharm* **2023**, *643*, 123205, doi:10.1016/j.ijpharm.2023.123205.
40. Liu, T.; Chen, M.; Fu, J.; Sun, Y.; Lu, C.; Quan, G.; Pan, X.; Wu, C. Recent advances in microneedles-mediated transdermal delivery of protein and peptide drugs. *Acta Pharm Sin B* **2021**, *11*, 2326-2343, doi:10.1016/j.apsb.2021.03.003.
41. Ahmed Saeed Al-Japairai, K.; Mahmood, S.; Hamed Almurisi, S.; Reddy Venugopal, J.; Rebhi Hilles, A.; Azmana, M.; Raman, S. Current trends in polymer microneedle for transdermal drug delivery. *Int J Pharm* **2020**, *587*, 119673, doi:10.1016/j.ijpharm.2020.119673.
42. Shi, S.; Wang, Y.; Mei, R.; Zhao, X.; Liu, X.; Chen, L. Revealing drug release and diffusion behavior in skin interstitial fluid by surface-enhanced Raman scattering microneedles. *J Mater Chem B* **2023**, *11*, 3097-3105, doi:10.1039/d2tb02600g.

 doi:10.20944/preprints202512.0407.v1

43. Damiri, F.; Kommineni, N.; Ebhodaghe, S.O.; Bulusu, R.; Jyothi, V.; Sayed, A.A.; Awaji, A.A.; Germoush, M.O.; Al-Malky, H.S.; Nasrullah, M.Z.; et al. Microneedle-Based Natural Polysaccharide for Drug Delivery Systems (DDS): Progress and Challenges. *Pharmaceuticals* **2022**, *15*, doi:10.3390/ph15020190.
44. Mao, Y.A.; Xu, S.; Shi, X.; Jin, Y.; Pan, Z.; Hao, T.; Li, G.; Chen, X.; Wang, H.; Wang, Y.; et al. Bioengineered microneedles and nanomedicine as therapeutic platform for tissue regeneration. *J Nanobiotechnology* **2025**, *23*, 573, doi:10.1186/s12951-025-03623-4.
45. Toews, P.; Bates, J. Influence of drug and polymer molecular weight on release kinetics from HEMA and HPMA hydrogels. *Sci Rep* **2023**, *13*, 16685, doi:10.1038/s41598-023-42923-3.
46. Moawad, F.; Pouliot, R.; Brambilla, D. Dissolving microneedles in transdermal drug delivery: A critical analysis of limitations and translation challenges. *J Control Release* **2025**, *383*, 113794, doi:10.1016/j.jconrel.2025.113794.
47. Abdullah, A.C.; Ahmadinejad, E.; Tasoglu, S. Optimizing Solid Microneedle Design: A Comprehensive ML-Augmented DOE Approach. *ACS Meas Sci Au* **2024**, *4*, 504-514, doi:10.1021/acsmeasuresciau.4c00021.
48. Donnelly, R.F.; Singh, T.R.; Garland, M.J.; Migalska, K.; Majithiya, R.; McCrudden, C.M.; Kole, P.L.; Mahmood, T.M.; McCarthy, H.O.; Woolfson, A.D. Hydrogel-Forming Microneedle Arrays for Enhanced Transdermal Drug Delivery. *Adv Funct Mater* **2012**, *22*, 4879-4890, doi:10.1002/adfm.201200864.
49. Fu, X.; Xian, H.; Xia, C.; Liu, Y.; Du, S.; Wang, B.; Xue, P.; Wang, B.; Kang, Y. Polymer homologue-mediated formation of hydrogel microneedles for controllable transdermal drug delivery. *Int J Pharm* **2024**, *666*, 124768, doi:10.1016/j.ijpharm.2024.124768.
50. Turner, J.G.; White, L.R.; Estrela, P.; Leese, H.S. Hydrogel-Forming Microneedles: Current Advancements and Future Trends. *Macromol Biosci* **2021**, *21*, e2000307, doi:10.1002/mabi.202000307.
51. Omidian, H.; Dey Chowdhury, S. Multifunctional Hydrogel Microneedles (HMNs) in Drug Delivery and Diagnostics. *Gels* **2025**, *11*, doi:10.3390/gels11030206.
52. Majumder, J.; Minko, T. Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic delivery. *Expert Opin Drug Deliv* **2021**, *18*, 205-227, doi:10.1080/17425247.2021.1828339.
53. Kumar, D.; Pandey, S.; Shiekmydeen, J.; Kumar, M.; Chopra, S.; Bhatia, A. Therapeutic Potential of Microneedle Assisted Drug Delivery for Wound Healing: Current State of the Art, Challenges, and Future Perspective. *AAPS PharmSciTech* **2025**, *26*, 25, doi:10.1208/s12249-024-03017-z.
54. Panda, P.; Mohanty, T.; Mohapatra, R. Advancements in Transdermal Drug Delivery Systems: Harnessing the Potential of Macromolecular Assisted Permeation Enhancement and Novel Techniques. *AAPS PharmSciTech* **2025**, *26*, 29, doi:10.1208/s12249-024-03029-9.
55. Hughes, K.J.; Ganesan, M.; Tenchov, R.; Iyer, K.A.; Ralhan, K.; Diaz, L.L.; Bird, R.E.; Ivanov, J.; Zhou, Q.A. Nanoscience in Action: Unveiling Emerging Trends in Materials and Applications. *ACS Omega* **2025**, *10*, 7530-7548, doi:10.1021/acsomega.4c10929.
56. Nair, A.; Chandrashekhar, H.R.; Day, C.M.; Garg, S.; Nayak, Y.; Shenoy, P.A.; Nayak, U.Y. Polymeric functionalization of mesoporous silica nanoparticles: Biomedical insights. *Int J Pharm* **2024**, *660*, 124314, doi:10.1016/j.ijpharm.2024.124314.
57. Li, Y.; Chen, Q.; Wang, T.; Ji, Z.; Regmi, S.; Tong, H.; Ju, J.; Wang, A. Advances in microneedle-based drug delivery system for metabolic diseases: structural considerations, design strategies, and future perspectives. *J Nanobiotechnology* **2025**, *23*, 350, doi:10.1186/s12951-025-03432-9.
58. Thomas, R.G.; Surendran, S.P.; Jeong, Y.Y. Tumor Microenvironment-Stimuli Responsive Nanoparticles for Anticancer Therapy. *Front Mol Biosci* **2020**, *7*, 610533, doi:10.3389/fmolb.2020.610533.
59. Chen, X.; Wu, D.; Chen, Z. Biomedical applications of stimuli-responsive nanomaterials. *MedComm (2020)* **2024**, *5*, e643, doi:10.1002/mco2.643.
60. Yi, B.; Yu, L.; Yang, Y.; Guimaraes, C.F.; Xu, R.; Thambi, T.; Zhou, B.; Zhou, Q.; Reis, R.L. Light-stimulated smart thermo-responsive constructs for enhanced wound healing: A streamlined command approach. *Asian J Pharm Sci* **2025**, *20*, 101057, doi:10.1016/j.ajps.2025.101057.
61. Liu, X.; Zhang, H.; Chen, L.; Zheng, Z.; Li, W.; Huang, C.; Zhou, H.; Chen, Y.; Jiang, Z.; Liang, J.; et al. Advanced wound healing with Stimuli-Responsive nanozymes: mechanisms, design and applications. *J Nanobiotechnology* **2025**, *23*, 479, doi:10.1186/s12951-025-03558-w.

 doi:10.20944/preprints202512.0407.v1

62. Wei, Y.; You, W.; Li, H.; Chen, J.; Tang, Z.; Luo, Y.; Xiao, W.; Yang, Q.; Feng, M.; Li, L.; et al. Stimuli-responsive nanozymes for wound healing: From design strategies to therapeutic advances. *Mater Today Bio* **2025**, *33*, 102046, doi:10.1016/j.mtbio.2025.102046.
63. Venturini, J.; Chakraborty, A.; Baysal, M.A.; Tsimberidou, A.M. Developments in nanotechnology approaches for the treatment of solid tumors. *Exp Hematol Oncol* **2025**, *14*, 76, doi:10.1186/s40164-025-00656-1.
64. Yang, W.; Mixich, L.; Boonstra, E.; Cabral, H. Polymer-Based mRNA Delivery Strategies for Advanced Therapies. *Adv Healthc Mater* **2023**, *12*, e2202688, doi:10.1002/adhm.202202688.
65. Harun-Or-Rashid, M.; Aktar, M.N.; Hossain, M.S.; Sarkar, N.; Islam, M.R.; Arafat, M.E.; Bhowmik, S.; Yusa, S.I. Recent Advances in Micro- and Nano-Drug Delivery Systems Based on Natural and Synthetic Biomaterials. *Polymers (Basel)* **2023**, *15*, doi:10.3390/polym15234563.
66. Cha, S.; Choi, M.Y.; Kim, M.J.; Sim, S.B.; Haizan, I.; Choi, J.H. Electrochemical Microneedles for Real-Time Monitoring in Interstitial Fluid: Emerging Technologies and Future Directions. *Biosensors (Basel)* **2025**, *15*, doi:10.3390/bios15060380.
67. Zhao, P.; Zhou, Z.; Wolter, T.; Womelsdorf, J.; Somers, A.; Feng, Y.; Nuutila, K.; Tian, Z.; Chen, J.; Tamayol, A.; et al. Engineering microneedles for biosensing and drug delivery. *Bioact Mater* **2025**, *52*, 36-59, doi:10.1016/j.bioactmat.2025.05.027.
68. Naghib, S.M.; Ahmadi, B.; Mikaeeli Kangarshahi, B.; Mozafari, M.R. Chitosan-based smart stimuli-responsive nanoparticles for gene delivery and gene therapy: Recent progresses on cancer therapy. *Int J Biol Macromol* **2024**, *278*, 134542, doi:10.1016/j.ijbiomac.2024.134542.
69. Zhu, Y.; Guo, S.; Ravichandran, D.; Ramanathan, A.; Sobczak, M.T.; Sacco, A.F.; Patil, D.; Thummalapalli, S.V.; Pulido, T.V.; Lancaster, J.N.; et al. 3D-Printed Polymeric Biomaterials for Health Applications. *Adv Healthc Mater* **2025**, *14*, e2402571, doi:10.1002/adhm.202402571.
70. Sirbubalo, M.; Tucak, A.; Muhamedagic, K.; Hindija, L.; Rahic, O.; Hadziabdic, J.; Cekic, A.; Begic-Hajdarevic, D.; Cohodar Husic, M.; Dervisevic, A.; et al. 3D Printing-A "Touch-Button" Approach to Manufacture Microneedles for Transdermal Drug Delivery. *Pharmaceutics* **2021**, *13*, doi:10.3390/pharmaceutics13070924.
71. 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. *Mol Pharm* **2022**, *19*, 3314-3322, doi:10.1021/acs.molpharmaceut.2c00466.
72. Al-Nimry, S.S.; Daghmash, R.M. Three Dimensional Printing and Its Applications Focusing on Microneedles for Drug Delivery. *Pharmaceutics* **2023**, *15*, doi:10.3390/pharmaceutics15061597.
73. McLoughlin, C.D.; Nevins, S.; Stein, J.B.; Khakbiz, M.; Lee, K.B. Overcoming the Blood-Brain Barrier: Multifunctional Nanomaterial-Based Strategies for Targeted Drug Delivery in Neurological Disorders. *Small Sci* **2024**, *4*, 2400232, doi:10.1002/smsc.202400232.
74. Meng, F.; Hasan, A.; Mahdi Nejadi Babadaei, M.; Hashemi Kani, P.; Jouya Talaei, A.; Sharifi, M.; Cai, T.; Falahati, M.; Cai, Y. Polymeric-based microneedle arrays as potential platforms in the development of drugs delivery systems. *J Adv Res* **2020**, *26*, 137-147, doi:10.1016/j.jare.2020.07.017.
75. Ban, G.; Hou, Y.; Shen, Z.; Jia, J.; Chai, L.; Ma, C. Potential Biomedical Limitations of Graphene Nanomaterials. *Int J Nanomedicine* **2023**, *18*, 1695-1708, doi:10.2147/IJN.S402954.
76. Shim, K.W. Medical Applications of 3D Printing and Standardization Issues. *Brain Tumor Res Treat* **2023**, *11*, 159-165, doi:10.14791/btrt.2023.0001.
77. Parrilla, M.; Detamornrat, U.; Dominguez-Robles, J.; Tunca, S.; Donnelly, R.F.; De Wael, K. Wearable Microneedle-Based Array Patches for Continuous Electrochemical Monitoring and Drug Delivery: Toward a Closed-Loop System for Methotrexate Treatment. *ACS Sens* **2023**, *8*, 4161-4170, doi:10.1021/acssensors.3c01381.
78. Duan, H.; Peng, S.; He, S.; Tang, S.Y.; Goda, K.; Wang, C.H.; Li, M. Wearable Electrochemical Biosensors for Advanced Healthcare Monitoring. *Adv Sci (Weinh)* **2025**, *12*, e2411433, doi:10.1002/advs.202411433.
79. Bakhshandeh, F.; Zheng, H.; Barra, N.G.; Sadeghzadeh, S.; Ausri, I.; Sen, P.; Keyvani, F.; Rahman, F.; Quadrilatero, J.; Liu, J.; et al. Wearable Aptalyzer Integrates Microneedle and Electrochemical Sensing for

 doi:10.20944/preprints202512.0407.v1

In Vivo Monitoring of Glucose and Lactate in Live Animals. *Adv Mater* **2024**, *36*, e2313743, doi:10.1002/adma.202313743.

80. Hu, Y.; Pan, Z.; De Bock, M.; Tan, T.X.; Wang, Y.; Shi, Y.; Yan, N.; Yetisen, A.K. A wearable microneedle patch incorporating reversible FRET-based hydrogel sensors for continuous glucose monitoring. *Biosens Bioelectron* **2024**, *262*, 116542, doi:10.1016/j.bios.2024.116542.
81. Yoo, J.H.; Kim, J.H. Advances in Continuous Glucose Monitoring and Integrated Devices for Management of Diabetes with Insulin-Based Therapy: Improvement in Glycemic Control. *Diabetes Metab J* **2023**, *47*, 27-41, doi:10.4093/dmj.2022.0271.
82. Guan, Z.; Li, H.; Liu, R.; Cai, C.; Liu, Y.; Li, J.; Wang, X.; Huang, S.; Wu, L.; Liu, D.; et al. Artificial intelligence in diabetes management: Advancements, opportunities, and challenges. *Cell Rep Med* **2023**, *4*, 101213, doi:10.1016/j.xcrm.2023.101213.
83. Sachdeva, S.; Bhatia, S.; Al Harrasi, A.; Shah, Y.A.; Anwer, K.; Philip, A.K.; Shah, S.F.A.; Khan, A.; Ahsan Halim, S. Unraveling the role of cloud computing in health care system and biomedical sciences. *Heliyon* **2024**, *10*, e29044, doi:10.1016/j.heliyon.2024.e29044.
84. Elendu, C.; Elendu, T.C.; Elendu, I.D. 5G-enabled smart hospitals: Innovations in patient care and facility management. *Medicine (Baltimore)* **2024**, *103*, e38239, doi:10.1097/MD.0000000000038239.
85. Zorlutuna, P.; Annabi, N.; Camci-Unal, G.; Nikkhah, M.; Cha, J.M.; Nichol, J.W.; Manbachi, A.; Bae, H.; Chen, S.; Khademhosseini, A. Microfabricated biomaterials for engineering 3D tissues. *Adv Mater* **2012**, *24*, 1782-1804, doi:10.1002/adma.201104631.
86. Omidian, H.; Dey Chowdhury, S. Swellable Microneedles in Drug Delivery and Diagnostics. *Pharmaceuticals (Basel)* **2024**, *17*, doi:10.3390/ph17060791.
87. Dixon, A.R.; Vondra, I. Biting Innovations of Mosquito-Based Biomaterials and Medical Devices. *Materials (Basel)* **2022**, *15*, doi:10.3390/ma15134587.
88. Mbituyimana, B.; Adhikari, M.; Qi, F.; Shi, Z.; Fu, L.; Yang, G. Microneedle-based cell delivery and cell sampling for biomedical applications. *J Control Release* **2023**, *362*, 692-714, doi:10.1016/j.jconrel.2023.09.013.
89. Baker-Sediako, R.D.; Richter, B.; Blaicher, M.; Thiel, M.; Hermatschweiler, M. Industrial perspectives for personalized microneedles. *Beilstein J Nanotechnol* **2023**, *14*, 857-864, doi:10.3762/bjnano.14.70.
90. Makvandi, P.; Jamaledin, R.; Chen, G.; Baghbantaraghdari, Z.; Zare, E.N.; Di Natale, C.; Onesto, V.; Vecchione, R.; Lee, J.; Tay, F.R.; et al. Stimuli-responsive transdermal microneedle patches. *Mater Today (Kidlington)* **2021**, *47*, 206-222, doi:10.1016/j.mattod.2021.03.012.
91. Yusuf, A.; Almotairy, A.R.Z.; Henidi, H.; Alshehri, O.Y.; Aldughaim, M.S. Nanoparticles as Drug Delivery Systems: A Review of the Implication of Nanoparticles' Physicochemical Properties on Responses in Biological Systems. *Polymers (Basel)* **2023**, *15*, doi:10.3390/polym15071596.
92. Loh, J.M.; Lim, Y.J.L.; Tay, J.T.; Cheng, H.M.; Tey, H.L.; Liang, K. Design and fabrication of customizable microneedles enabled by 3D printing for biomedical applications. *Bioact Mater* **2024**, *32*, 222-241, doi:10.1016/j.bioactmat.2023.09.022.
93. Shahzad, S.; Iftikhar, F.J.; Shah, A.; Rehman, H.A.; Iwuoha, E. Novel interfaces for internet of wearable electrochemical sensors. *RSC Adv* **2024**, *14*, 36713-36732, doi:10.1039/d4ra07165d.
94. Che, Q.T.; Seo, J.W.; Charoensri, K.; Nguyen, M.H.; Park, H.J.; Bae, H. 4D-printed microneedles from dual-sensitive chitosan for non-transdermal drug delivery. *Int J Biol Macromol* **2024**, *261*, 129638, doi:10.1016/j.ijbiomac.2024.129638.
95. Correia, A.; Agostinho Cordeiro, M.; Mendes, M.; Marques Ribeiro, M.; Mascarenhas-Melo, F.; Vitorino, C. Additive manufacturing of microneedles: a quality by design approach to clinical translation. *Int J Pharm* **2025**, *687*, 126399, doi:10.1016/j.ijpharm.2025.126399.
96. Maia, R.F.; Machado, P.; Rodrigues, R.O.; Faustino, V.; Schutte, H.; Gassmann, S.; Lima, R.A.; Minas, G. Recent advances and perspectives of MicroNeedles for biomedical applications. *Biophys Rev* **2025**, *17*, 909-928, doi:10.1007/s12551-025-01317-7.
97. Montero, D.A.; Vidal, R.M.; Velasco, J.; Carreno, L.J.; Torres, J.P.; Benachi, O.M.; Tovar-Rosero, Y.Y.; Onate, A.A.; O'Ryan, M. Two centuries of vaccination: historical and conceptual approach and future perspectives. *Front Public Health* **2023**, *11*, 1326154, doi:10.3389/fpubh.2023.1326154.

98. Menon, I.; Bagwe, P.; Gomes, K.B.; Bajaj, L.; Gala, R.; Uddin, M.N.; D'Souza, M.J.; Zughaier, S.M. Microneedles: A New Generation Vaccine Delivery System. *Micromachines (Basel)* **2021**, *12*, doi:10.3390/mi12040435.
99. Jia, H.; Liu, J.; Shi, M.; Abbas, M.; Xing, R.; Yan, X. Microneedle delivery systems for vaccines and immunotherapy. *Smart Mol* **2025**, *3*, e20240067, doi:10.1002/smo.20240067.
100. Nguyen, H.X. Beyond the Needle: Innovative Microneedle-Based Transdermal Vaccination. *Medicines (Basel)* **2025**, *12*, doi:10.3390/medicines12010004.
101. Taddio, A.; Appleton, M.; Bortolussi, R.; Chambers, C.; Dubey, V.; Halperin, S.; Hanrahan, A.; Ipp, M.; Lockett, D.; MacDonald, N.; et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline. *CMAJ* **2010**, *182*, E843-855, doi:10.1503/cmaj.101720.
102. Campa, C.; Pronce, T.; Paludi, M.; Weusten, J.; Conway, L.; Savery, J.; Richards, C.; Clenet, D. Use of Stability Modeling to Support Accelerated Vaccine Development and Supply. *Vaccines (Basel)* **2021**, *9*, doi:10.3390/vaccines9101114.
103. Ostrowsky, J.T.; Vestin, N.C.; Mehr, A.J.; Ulrich, A.K.; Bigalke, L.; Bresee, J.S.; Friede, M.H.; Gellin, B.G.; Klugman, K.P.; Nakakana, U.N.; et al. Accomplishments and challenges in developing improved influenza vaccines: An evaluation of three years of progress toward the milestones of the influenza vaccines research and development roadmap. *Vaccine* **2025**, *61*, 127431, doi:10.1016/j.vaccine.2025.127431.
104. Liu, X.; Song, H.; Sun, T.; Wang, H. Responsive Microneedles as a New Platform for Precision Immunotherapy. *Pharmaceutics* **2023**, *15*, doi:10.3390/pharmaceutics15051407.
105. Moonla, C.; Reynoso, M.; Chang, A.Y.; Saha, T.; Surace, S.; Wang, J. Microneedle-Based Multiplexed Monitoring of Diabetes Biomarkers: Capabilities Beyond Glucose Toward Closed-Loop Theranostic Systems. *ACS Sens* **2025**, *10*, 5363-5379, doi:10.1021/acssensors.5c00652.
106. Olukorode, J.O.; Orimoloye, D.A.; Nwachukwu, N.O.; Onwuzo, C.N.; Oloyede, P.O.; Fayemi, T.; Odunaike, O.S.; Ayobami-Ojo, P.S.; Divine, N.; Alo, D.J.; et al. Recent Advances and Therapeutic Benefits of Glucagon-Like Peptide-1 (GLP-1) Agonists in the Management of Type 2 Diabetes and Associated Metabolic Disorders. *Cureus* **2024**, *16*, e72080, doi:10.7759/cureus.72080.
107. Woodring, R.N.; Gurysh, E.G.; Bachelder, E.M.; Ainslie, K.M. Drug Delivery Systems for Localized Cancer Combination Therapy. *ACS Appl Bio Mater* **2023**, *6*, 934-950, doi:10.1021/acsabm.2c00973.
108. Santangelo, G. [Principles of general diagnosis in blood platelet deficiency syndromes]. *Minerva Pediatr* **1972**, *24*, 1291-1299.
109. Sareen, G.; Mohan, M.; Mannan, A.; Dua, K.; Singh, T.G. A new era of cancer immunotherapy: vaccines and miRNAs. *Cancer Immunol Immunother* **2025**, *74*, 163, doi:10.1007/s00262-025-04011-5.
110. Yoon, M.S.; Lee, J.M.; Jo, M.J.; Kang, S.J.; Yoo, M.K.; Park, S.Y.; Bong, S.; Park, C.S.; Park, C.W.; Kim, J.S.; et al. Dual-Drug Delivery Systems Using Hydrogel-Nanoparticle Composites: Recent Advances and Key Applications. *Gels* **2025**, *11*, doi:10.3390/gels11070520.
111. Li, W.; Chen, J.Y.; Terry, R.N.; Tang, J.; Romanyuk, A.; Schwendeman, S.P.; Prausnitz, M.R. Core-shell microneedle patch for six-month controlled-release contraceptive delivery. *J Control Release* **2022**, *347*, 489-499, doi:10.1016/j.jconrel.2022.04.051.
112. Garcia-Perez, L.E.; Alvarez, M.; Dilla, T.; Gil-Guillen, V.; Orozco-Beltran, D. Adherence to therapies in patients with type 2 diabetes. *Diabetes Ther* **2013**, *4*, 175-194, doi:10.1007/s13300-013-0034-y.
113. Chen, W.; Jian, X.; Yu, B. Review of Applications of Microneedling in Melasma. *J Cosmet Dermatol* **2025**, *24*, e16707, doi:10.1111/jocd.16707.
114. Yang, Y.; Zhang, T.; Niu, B.; Wang, X.; Liu, L.; Zhu, P.; Meng, F. Research progress of dissolving microneedles in the field of component administration of traditional Chinese medicine. *Front Pharmacol* **2025**, *16*, 1623476, doi:10.3389/fphar.2025.1623476.
115. Wei, H.H.; Zheng, L.; Wang, Z. mRNA therapeutics: New vaccination and beyond. *Fundam Res* **2023**, *3*, 749-759, doi:10.1016/j.fmre.2023.02.022.
116. Bilal, M.; Mehmood, S.; Raza, A.; Hayat, U.; Rasheed, T.; Iqbal, H.M.N. Microneedles in Smart Drug Delivery. *Adv Wound Care (New Rochelle)* **2021**, *10*, 204-219, doi:10.1089/wound.2019.1122.

 doi:10.20944/preprints202512.0407.v1

117. Rojekar, S.; Vora, L.K.; Tekko, I.A.; Volpe-Zanutto, F.; McCarthy, H.O.; Vavia, P.R.; Donnelly, R.F. Etravirine-loaded dissolving microneedle arrays for long-acting delivery. *Eur J Pharm Biopharm* **2021**, *165*, 41-51, doi:10.1016/j.ejpb.2021.04.024.
118. Mc Crudden, M.T.C.; Larrañeta, E.; Clark, A.; Jarrahian, C.; Rein-Weston, A.; Lachau-Durand, S.; Niemeijer, N.; Williams, P.; Haeck, C.; McCarthy, H.O.; et al. Design, formulation and evaluation of novel dissolving microarray patches containing a long-acting rilpivirine nanosuspension. *J Control Release* **2018**, *292*, 119-129, doi:10.1016/j.jconrel.2018.11.002.
119. Moffatt, K.; Tekko, I.A.; Vora, L.; Volpe-Zanutto, F.; Hutton, A.R.J.; Mistilis, J.; Jarrahian, C.; Akhavein, N.; Weber, A.D.; McCarthy, H.O.; et al. Development and Evaluation of Dissolving Microarray Patches for Co-administered and Repeated Intradermal Delivery of Long-acting Rilpivirine and Cabotegravir Nanosuspensions for Paediatric HIV Antiretroviral Therapy. *Pharm. Res.* **2023**, *40*, 1673-1696, doi:10.1007/s11095-022-03408-6.
120. Zhang, C.; Wu, Y.; Hutton, A.R.J.; Hidayat Bin Sabri, A.; Hobson, J.J.; Savage, A.C.; McCarthy, H.O.; Paredes, A.J.; Owen, A.; Rannard, S.P.; et al. Systemic delivery of bictegravir and tenofovir alafenamide using dissolving microneedles for HIV preexposure prophylaxis. *Int. J. Pharm* **2024**, *660*, 124317, doi:10.1016/j.ijpharm.2024.124317.
121. Yang, J.; Liu, X.; Fu, Y.; Song, Y. Recent advances of microneedles for biomedical applications: drug delivery and beyond. *Acta Pharm Sin B* **2019**, *9*, 469-483, doi:10.1016/j.apsb.2019.03.007.
122. Bi, Y.; Xie, S.; Li, Z.; Dong, S.; Teng, L. Precise nanoscale fabrication technologies, the "last mile" of medicinal development. *Acta Pharm Sin B* **2025**, *15*, 2372-2401, doi:10.1016/j.apsb.2025.03.040.
123. Sartawi, Z.; Blackshields, C.; Faisal, W. Dissolving microneedles: Applications and growing therapeutic potential. *J Control Release* **2022**, *348*, 186-205, doi:10.1016/j.jconrel.2022.05.045.
124. Alonso, J.M.; Andrade Del Olmo, J.; Perez Gonzalez, R.; Saez-Martinez, V. Injectable Hydrogels: From Laboratory to Industrialization. *Polymers (Basel)* **2021**, *13*, doi:10.3390/polym13040650.
125. Sati, A.; Mali, S.N.; Samdani, N.; Annadurai, S.; Dongre, R.; Satpute, N.; Ranade, T.N.; Pratap, A.P. From Past to Present: Gold Nanoparticles (AuNPs) in Daily Life • Synthesis Mechanisms, Influencing Factors, Characterization, Toxicity, and Emerging Applications in Biomedicine, Nanoelectronics, and Materials Science. *ACS Omega* **2025**, *10*, 33999-34087, doi:10.1021/acsomega.5c03162.
126. Zhao, J.; Xu, G.; Yao, X.; Zhou, H.; Lyu, B.; Pei, S.; Wen, P. Microneedle-based insulin transdermal delivery system: current status and translation challenges. *Drug Deliv Transl Res* **2022**, *12*, 2403-2427, doi:10.1007/s13346-021-01077-3.
127. Trombetta, C.M.; Gianchecchi, E.; Montomoli, E. Influenza vaccines: Evaluation of the safety profile. *Hum Vaccin Immunother* **2018**, *14*, 657-670, doi:10.1080/21645515.2017.1423153.
128. Reis, M.E.; Bettencourt, A.; Ribeiro, H.M. The regulatory challenges of innovative customized combination products. *Front Med (Lausanne)* **2022**, *9*, 821094, doi:10.3389/fmed.2022.821094.
129. Van Norman, G.A. Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs. *JACC Basic Transl Sci* **2016**, *1*, 170-179, doi:10.1016/j.jacbts.2016.03.002.
130. Franco, P.; Jain, R.; Rosenkrands-Lange, E.; Hey, C.; Koban, M.U. Regulatory Pathways Supporting Expedited Drug Development and Approval in ICH Member Countries. *Ther Innov Regul Sci* **2023**, *57*, 484-514, doi:10.1007/s43441-022-00480-3.
131. Baryakova, T.H.; Pogostin, B.H.; Langer, R.; McHugh, K.J. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. *Nat Rev Drug Discov* **2023**, *22*, 387-409, doi:10.1038/s41573-023-00670-0.
132. Cammarano, A.; Dello Iacono, S.; Battisti, M.; De Stefano, L.; Meglio, C.; Nicolais, L. A systematic review of microneedles technology in drug delivery through a bibliometric and patent overview. *Heliyon* **2024**, *10*, e40658, doi:10.1016/j.heliyon.2024.e40658.
133. Saghafian, M.; Laumann, K.; Skogstad, M.R. Stagewise Overview of Issues Influencing Organizational Technology Adoption and Use. *Front Psychol* **2021**, *12*, 630145, doi:10.3389/fpsyg.2021.630145.
134. Nguyen, H.X.; Nguyen, C.N. Microneedle-Mediated Transdermal Delivery of Biopharmaceuticals. *Pharmaceutics* **2023**, *15*, doi:10.3390/pharmaceutics15010277.

 doi:10.20944/preprints202512.0407.v1

135. Hassan, J.; Haigh, C.; Ahmed, T.; Uddin, M.J.; Das, D.B. Potential of Microneedle Systems for COVID-19 Vaccination: Current Trends and Challenges. *Pharmaceutics* **2022**, *14*, doi:10.3390/pharmaceutics14051066.
136. Brahmam, B.; Salwa; Yarlagadda, D.L.; Gurram, P.C.; Kumar, L.; Shenoy, R.R.; Lewis, S.A. Dissolving Microneedle Patch Incorporated with Insulin Nanoparticles for The Management of Type-I Diabetes Mellitus: Formulation Development and in Vivo Monitoring. *Adv Pharm Bull* **2025**, *15*, 359-370, doi:10.34172/apb.025.42583.
137. Rapoport, A.M.; Ameri, M.; Lewis, H.; Kellerman, D.J. Development of a novel zolmitriptan intracutaneous microneedle system (Qtrypta) for the acute treatment of migraine. *Pain Manag* **2020**, *10*, 359-366, doi:10.2217/pmt-2020-0041.
138. Shin, J.Y.; Han, D.; Yoon, K.Y.; Jeong, D.H.; Park, Y.I. Clinical Safety and Efficacy Evaluation of a Dissolving Microneedle Patch Having Dual Anti-Wrinkle Effects With Safe and Long-Term Activities. *Ann Dermatol* **2024**, *36*, 215-224, doi:10.5021/ad.23.136.
139. Chen, G.; Yu, J.; Gu, Z. Glucose-Responsive Microneedle Patches for Diabetes Treatment. *J Diabetes Sci Technol* **2019**, *13*, 41-48, doi:10.1177/1932296818778607.
140. Thacharodi, A.; Singh, P.; Meenatchi, R.; Tawfeeq Ahmed, Z.H.; Kumar, R.R.S.; V, N.; Kavish, S.; Maqbool, M.; Hassan, S. Revolutionizing healthcare and medicine: The impact of modern technologies for a healthier future-A comprehensive review. *Health Care Sci* **2024**, *3*, 329-349, doi:10.1002/hcs2.115.
141. Choi, J.; Jang, S.; Yu, S.; Ahn, Y.R.; Kim, M.; Lee, H.; Kim, H.O. Microneedle-nanoparticle hybrid platforms for metabolic syndrome: advances in point-of-care diagnostics and transdermal therapeutics. *Discov Nano* **2025**, *20*, 193, doi:10.1186/s11671-025-04376-7.
142. Joyce, J.C.; Collins, M.L.; Rota, P.A.; Prausnitz, M.R. Thermostability of Measles and Rubella Vaccines in a Microneedle Patch. *Adv Ther (Weinh)* **2021**, *4*, doi:10.1002/adtp.202100095.
143. Avcil, M.; Celik, A. Microneedles in Drug Delivery: Progress and Challenges. *Micromachines (Basel)* **2021**, *12*, doi:10.3390/mi12111321.
144. Prasad, R.; Ghosh, A.; Patel, V.; Peng, B.; Mendes, B.B.; Win, E.H.A.; Delogu, L.G.; Wong, J.Y.; Pischel, K.J.; Bellare, J.R.; et al. Voices of Nanomedicine: Blueprint Guidelines for Collaboration in Addressing Global Unmet Medical Needs. *ACS Nano* **2025**, *19*, 2979-2991, doi:10.1021/acsnano.4c13513.
145. Tanaka, M.L.; Lopez, O. Outlook on Industry-Academia-Government Collaborations Impacting Medical Device Innovation. *J Eng Sci Med Diagn Ther* **2024**, *7*, 025001, doi:10.1115/1.4063464.