Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE
DOI: 10.53555/87xt6v15

MICRONEEDLES AS A SMART APPROACH FOR TRANSDERMAL DRUG DELIVERY

Kiran Sharma[1], Dr. Shweta Paroha[2*], Dr. Pragnesh Patni[3]

[1*,2,3]Khyati College of Pharmacy, Palodia, Ahmedabad

***Corresponding Author**: Dr. Shweta Paroha
[*]Khyati College of Pharmacy, Palodia, Ahmedabad, Email: shwetatechno86@gmail.com

Abstract
Transdermal drug delivery systems (TDDS) have gained significant attention as an alternative to conventional routes of drug administration due to their ability to bypass first-pass metabolism, provide sustained release, and enhance patient compliance. However, the stratum corneum acts as a major barrier to effective drug permeation. Microneedle (MN) technology has emerged as a promising strategy to overcome this limitation by creating microscopic channels in the skin that facilitate drug transport without causing pain or significant tissue damage. This review highlights the fundamentals of microneedle technology, including its types—solid, coated, hollow, dissolving, and hydrogel-forming microneedles—along with the materials commonly employed for fabrication, such as silicon, metals, ceramics, and biodegradable polymers. The applications of MNs span diverse fields, ranging from vaccine delivery and insulin administration to cancer therapy and cosmetic treatments. Current trends in microneedle research emphasize advanced materials, smart drug delivery systems, and integration with nanotechnology and biosensors for personalized medicine. Advantages of MN-based systems include minimal invasiveness, improved patient compliance, enhanced bioavailability, and the potential for self-administration. Overall, microneedle technology represents a rapidly evolving platform with immense potential to revolutionize transdermal drug delivery and future therapeutic strategies.

Keywords: Microneedles technology, transdermal drug delivery, permeation enhancement, minimally invasive

1. Introduction

Transdermal drug delivery (TDD) involves administering medications via the skin for local or systemic therapeutic purposes[1]. TDD can constantly administer medications to maintain therapeutic concentration, reduce pain and infection risk, prevent gastrointestinal digestive enzyme metabolism and first-pass effects, and promote high patient compliance when compared to other drug-administration methods (oral, injectable, etc.)[2]. The topmost layer of skin, known as the stratum corneum (SC), is made up of dead keratinocyte-type cells. They are flat keratinocytes surrounded by a lipid matrix. More than 90% of the medications given topically may be blocked by this layer, which restricts their penetration and lowers the effectiveness of this delivery method.[3] Smaller molecules (< 500 Da) with moderate lipophilicity can easily permeate the skin, while macromolecular medicines are typically blocked by the SC barrier and have poor bioavailability. Transdermal medication delivery focuses on overcoming SC resistance and improving skin permeability[4]. As a result,

developing a transformational transdermal drug delivery system (TDDS) is critical for increasing treatment outcomes while also resolving current drug administration restrictions.

Microneedles (MNs) represent a significant development in treating TDDS, ushering in a new age in medical treatment. These needles, ranging in length from tens to thousands of micrometers, allow for direct medication administration to subcutaneous tissues, reducing side effects and increasing therapeutic efficacy[5,6]. Different needle materials can transport a variety of medicines, including small molecular weight pharmaceuticals, oligonucleotides, DNA, peptides, proteins, and inactivated viruses, via the skin. MN-based medication delivery can provide continuous or responsive release, meeting various therapy needs[7,8].

Microneedles (MNs) are a novel topical delivery method that has transformed transdermal drug delivery. Gerstel and Place originally proposed the use of MNs as medication delivery devices in a 1971 US patent[9]. In the late 1990s, Henry et al. successfully deployed silicon MNs to improve transdermal absorption of the model drug calcein in human skin. This was considered the first serious discussion and proof-of-concept for MNs[10]. MNs are typically intended to pierce the epidermis and avoid contact with blood vessels and nerve fibers located in the deep dermal layer. MNs provide a minimally invasive and painless approach to minimize bleeding from the application site[11]. Despite its many benefits, it also has certain drawbacks. Sensitive skin allergies or skin irritation are possible outcomes. Because the needle is so tiny and thin in comparison to the thickness of hair, microneedle tips may break, which could be problematic if they stay inside the skin. These restrictions are quite uncommon and can be addressed with sophisticated microneedle material selection[12].

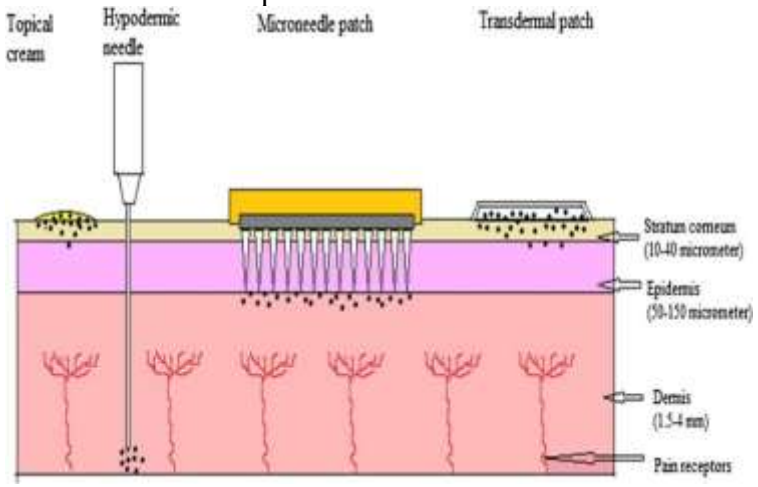

Fig. 1: Comparison of topical cream, hypodermic needle, microneedle patch and transdermal patch[12].

2. Classification

Solid, coated, dissolving, hollow, and hydrogel microneedles are among the various kinds of microneedles that have been created and studied for use in drug administration. Fig. shows several kinds of microneedles together with their distinct characteristics. Every kind of microneedle delivers the medication into the epidermis in a different way. Some are dissolvable, some are prefilled with the medication solution, some are precoated with the drug solution on their surface, and some are employed only to produce pores in the stratum corneum[13].

2.1 Solid microneedle

Solid microneedles, which can be applied as a skin pretreatment, were originally described in 1971[14]. Specifically, the medications are administered through the channels created when the solid microneedles are inserted into the skin. Solid microneedles have the benefit of a safe drug delivery method. Since the pathways the microneedles generate close once they are removed, infection or harmful substances can be avoided. Among other techniques, laser micromachining, lithography and etching, and micromolding are used to create the solid microneedle type, which includes silicon

microneedles, metal microneedles, stainless steel microneedle rollers, and certain polymer microneedles[15,16].

2.2 Coating microneedle

Coated microneedles, which are drug-coated at the tips via dipping, gas-jet drying, ink-jet printing, or spraying techniques. The drug delivery method of coated microneedles is known as the "coat and poke" strategy. Specifically, the medicine coated on the ends of the microneedles is released into the skin after the microneedle patch has been implanted[17]. The coating dissolves in the skin after the MNs are inserted, and then the MNs are extracted.

2.3 Hollow microneedle

Hollow MNs are similar to hypodermic injections but have a different micron size. They have a conduit in the middle of each protrusion. They are used for infusing liquid formulations into the skin or releasing drugs from a reservoir[18]. These microneedles are defined by their hollow form that serves as a route for distributing medications, cells, and other biological material[19].

2.4 Hydrogel microneedle

Hydrogel microneedles are a breakthrough in medical technology, made from crosslinked hydrogels like GelMA (Gelatin Methacrylate), hyaluronic acid methacrylate (HAMA), and PVA-dextran[20]. Precision techniques such as micromolding and 3D printing create microneedles that expand when inserted into the skin, delivering medications to specific regions[21].

2.5 Dissolving microneedle

Dissolving MNs have gained popularity due to their inexpensive production costs, superior biocompatibility, one-step application, and controllable drug release profiles. Dissolving MNs are often made from biocompatible polymers such as carbohydrates (e.g., hyaluronic acid, maltose, chitosan), proteins (e.g., silk fibrin, albumin), and aliphatic polyesters (e.g., PLGA, PLA)[22].

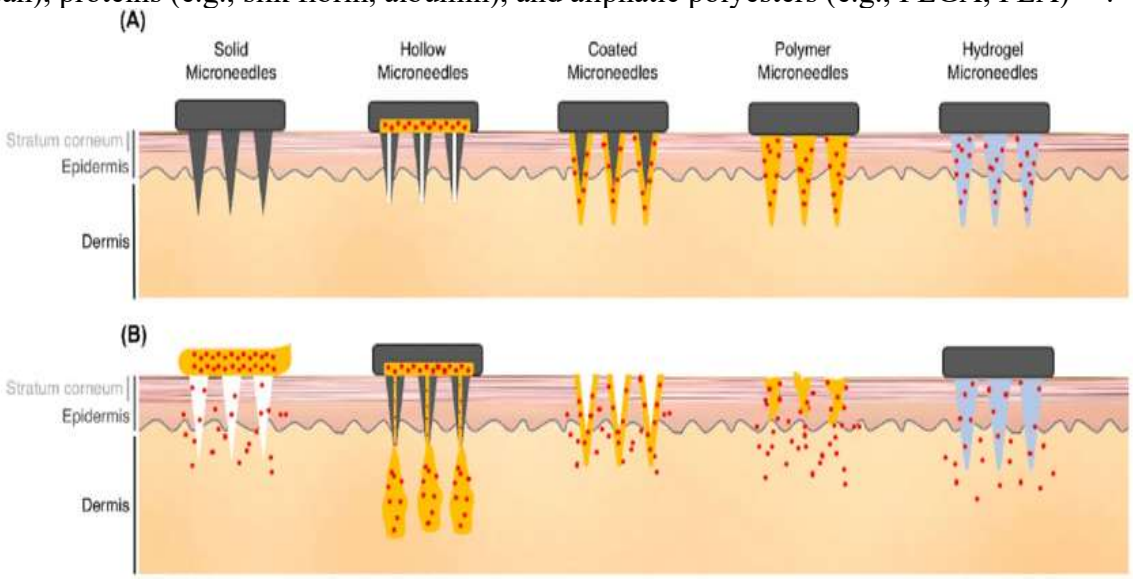

Fig. 2: Different types of microneedle[23]

3. Fabrication of microneedle

Microneedles (MNs) are fabricated from a wide range of materials, each chosen for properties like mechanical strength, safety, and skin compatibility:

- Glass: Chemically inert, transparent, and inexpensive—but brittle and difficult to fabricate.
- Sugar (Carbohydrates): Includes materials like maltose, starch, trehalose. Biodegradable and biocompatible; fabricate well via micromolding and drawing lithography, but suffer from hygroscopicity and limited mechanical strength[24].

- Metals: Stainless steel, titanium, and nickel offer high mechanical strength and ease of manufacturing (e.g., via laser cutting), though cost, allergenicity, and non-biodegradable nature are potential drawbacks.
- Silicon: Enables precise fabrication via MEMS techniques (e.g., DRIE, photolithography), offering high biocompatibility but brittle and costly, with risk of tip fracture during skin insertion[25].
- Ceramics: Porous ceramics facilitate drug loading via interconnected pores and good chemical resistance; however, they are brittle and slow to manufacture.
- Polymers: Biodegradable and/or swellable materials like PLGA, PLA, PMMA, PVP, PVA, sodium CMC, as well as natural polymers like chitosan, hyaluronic acid. Widely used across all MN types—solid, coated, hollow, dissolving, swelling—due to high safety and versatility.
- Natural biopolymers: Carbohydrates (cellulose and derivatives, alginates, pullulan, chondroitin sulfate, chitin, xanthan gum) and protein polymers (gelatin, zein, collagen, silk fibroin) are particularly attractive because of minimal skin irritation and biodegradability[26].

3.1 Fabrication Methods:

- Additive Manufacturing (3D Printing & 4D Printing)

SLA, DLP, FDM, and two-photon polymerization (TPP) technologies enable customizable and rapid prototyping of MNs, including hollow and fine-featured structures. Hydrogel-based MNs with adjustable mechanical properties have been printed using light-curing processes. One innovation includes a hollow porous microneedle patch (HepMi-PCL) printed with methacrylated PCL for infection-responsive drug delivery and accelerated healing. Furthermore, 3D printing addresses diverse applications ranging from drug delivery and vaccine administration to diagnostics and AI-integrated design optimization. Emerging 4D-printed systems incorporate shape-changing materials such as shape-memory polymers and hydrogels to offer dynamic, stimuli-responsive MN behavior in tissue environments.

- Laser Cutting and Ablation

Lasers offer precision shaping of metallic substrates like stainless steel or titanium to form MN arrays. Techniques include excimer or femtosecond laser cutting, followed by electropolishing to refine tip geometry. These methods allow fast prototyping of sharp microneedles but require expensive equipment and careful thermal control.

- Subtractive Fabrication (Etching, DRIE, Micromilling)

Classical MEMS-based techniques such as DRIE and wet/dry etching enable micron-scale control in silicon MNs10. Micromilling can produce master molds from metals or PMMA. These methods offer great precision but are costly and require cleanroom infrastructure.

- Drawing Lithography

Also known as thermal drawing, this technique uses viscous polymer materials extended into MNs via pulling under external fields (thermal, magnetic, electrical, centrifugal). It provides simpler fabrication but may suffer from low reproducibility and uneven geometries.

- Microinjection Molding for Porous Metal MNs

Metal powders mixed with binders are injection molded and sintered to create porous metal MNs. These structures combine mechanical strength with fluid handling capabilities—ideal for sampling or controlled release[27].

3.2 Coating Techniques for MNs:

- Immersion/Dip-Coating: The simplest method—MNs are dipped into a drug solution. Coating parameters (e.g., viscosity, immersion duration) influence drug loading and uniformity.
- Layer-by-Layer Coating, Drop-Coating, Spray Coating: Facilitate finer control over loading and distribution, suitable for sequential or patterned drug layers(1).
- Electrohydrodynamic Atomization, Gas-Jet Drying, Piezoelectric Inkjet Printing: Provide advanced coating control—useful for precision dosing and multi-drug delivery systems[29].

Table 1: Comparison of different techniques

Method / Material	Key Advantages	Limitations
Micromolding / Casting	Scalable, low-cost, reproducible manufacture; supports multilayered formats	Mold fabrication complexity; limited fine-detail control
3D Printing (SLA, DLP, TPP)	High design flexibility; rapid prototyping; fine features	High cost; limited biocompatible material choices
Laser Cutting / Ablation	Sharp features; rapid prototyping	Equipment cost; thermal stress to materials
Etching / DRIE / Micromilling	High accuracy; custom geometries	Infrastructure intensive; expensive
Drawing Lithography	Simpler fabrication, solvent-free	Low reproducibility; geometry variability
Microinjection Molding (Metal)	Strong, porous structures; drug/fluid compatibility	Complex process; material shrinkage
Porous Polymeric MNs	High fluid/drug transport; large loading capacity	Mechanical strength trade-offs; pore control challenges

4. Advantages

Microneedle (MN) technology has emerged as a promising minimally invasive strategy that overcomes the major limitations associated with conventional transdermal patches and hypodermic injections. The unique design of microneedles—combining the pain-free nature of transdermal systems with the efficiency of injections—offers several clinical, pharmaceutical, and patient-centric advantages.

4.1 Minimally Invasive and Pain-Free Administration

Microneedles penetrate only the stratum corneum and upper dermis (typically < 1 mm), avoiding stimulation of deep dermal nerves and blood vessels.This makes the procedure virtually painless compared to conventional hypodermic needles, thereby improving patient compliance, especially in pediatrics, geriatrics, and needle-phobic populations.

4.2 Enhanced Drug Permeation

The stratum corneum is the primary barrier for transdermal drug delivery. MNs create transient microchannels that bypass this barrier.This enables efficient permeation of a wide variety of molecules—including hydrophilic drugs, peptides, proteins, and even vaccines—that otherwise show poor skin penetration.

4.3 Avoidance of Gastrointestinal (GI) Degradation and First-Pass Metabolism

Drugs delivered via microneedles bypass the harsh GI environment (acidic pH, enzymatic degradation) and hepatic first-pass metabolism.This enhances bioavailability of labile biomolecules such as insulin, growth hormones, and monoclonal antibodies.

4.4 Self-Administration and Improved Patient Compliance

MN patches are simple to apply and do not require trained healthcare professionals.This enables home-based self-administration, reducing the burden on healthcare systems and enhancing adherence to long-term therapies.

4.5 Reduced Risk of Infection and Cross-Contamination

Unlike conventional hypodermic needles, microneedles do not generate sharps waste. Dissolving and biodegradable microneedles completely dissolve within the skin, leaving no hazardous residues, thereby minimizing infection risk.

4.6 Controlled and Targeted Drug Release
MNs can be engineered to provide sustained, controlled, or pulsatile release. Materials such as biodegradable polymers (e.g., hyaluronic acid, PVP, PLGA) enable time-dependent dissolution, tailoring drug release kinetics to therapeutic needs.

4.7 Improved Stability of Sensitive Molecules
Unlike oral formulations, microneedle systems can stabilize fragile biomolecules by embedding them in a dry polymeric matrix.This reduces cold-chain dependency, particularly advantageous for vaccines in low-resource settings.

4.8 Enhanced Vaccination Strategies
MN patches enable intradermal delivery of vaccines, targeting the skin's abundant antigen-presenting cells (APCs), thereby eliciting strong immune responses. They require lower antigen doses compared to intramuscular injections, making vaccination cost-effective and dose-sparing.

4.9 Reduced Side Effects and Systemic Toxicity
MNs allow localized and controlled delivery, reducing systemic exposure. This minimizes side effects, particularly in potent drugs such as chemotherapeutics or corticosteroids[29,31].

5. Disadvantages
5.1 Limited Drug Loading Capacity
Due to their small dimensions, microneedles have restricted surface area and volume. This limits the drug loading capacity, making them unsuitable for therapies requiring large doses (e.g., antibiotics, high-dose analgesics). Particularly challenging for hollow MNs, as lumen volume is very small.

5.2 Suitability Restricted to Potent Drugs
Since only small amounts of drug can be delivered, MN technology is more appropriate for potent molecules (e.g., vaccines, hormones, peptides).Less effective for drugs that require gram-level dosing.

5.3 Mechanical Strength and Needle Fracture
Microneedles must be strong enough to penetrate the stratum corneum.Materials such as biodegradable polymers or sugar-based MNs may lack sufficient mechanical strength, leading to needle bending, incomplete insertion, or fracture inside the skin.Fractured residues may cause inflammation or infection.

5.4 Skin Variability and Penetration Issues
Human skin shows variability in thickness, hydration, elasticity, and anatomical site, which affects insertion depth.Incomplete insertion or variable penetration may lead to dose inconsistency. Patients with thick or calloused skin (e.g., soles, palms) may experience reduced MN effectiveness.

5.5 Drug Stability Issues
While some biomolecules are stabilized in solid-state MNs, others may undergo denaturation during fabrication processes (e.g., exposure to heat, UV curing, solvents). Maintaining the bioactivity of sensitive proteins, peptides, and vaccines remains a challenge.

5.6 Regulatory and Manufacturing Challenges
Large-scale, reproducible manufacturing of MNs with precise dimensions is technically demanding. Regulatory agencies (FDA, EMA) lack well-defined guidelines specific to MNs, leading to uncertainty in approval pathways. Sterility, packaging, and stability testing add to complexity.

5.7 Cost of Production
Compared to traditional oral tablets or patches, MNs involve sophisticated fabrication techniques (e.g., micro-molding, lithography, 3D printing). This increases production costs, making them less affordable in low-resource settings.

5.8 Skin Irritation and Safety Concerns
Repeated application of MN patches may cause erythema, irritation, or localized inflammation. Risk of infection exists if MN insertion creates microchannels that are exposed to contaminants. Long-term safety data on chronic MN use is still limited.

5.9 Patient-Related Limitations
Though minimally invasive, some patients may still feel discomfort, especially with hollow MNs. Needle phobia may persist in sensitive populations despite reduced pain. Incorrect self-application can lead to ineffective drug delivery[32,33].

6. Appplications
6.1 Vaccine delivery
MNDs have made vaccination delivery more efficient and pain-free. They boost the immune response by focusing on antigen-presenting cells in the skin's dermal layer. MNDs patches for vaccinations including influenza, measles, and COVID-19 have showed encouraging outcomes in both preclinical and clinical trials. These patches simplify logistics, increase patient compliance, and decrease the requirement for skilled healthcare staff[34].

6.2 Pain management
They provide analgesics in a targeted and regulated manner, resulting in excellent pain relief with minimal systemic adverse effects. This is especially effective for chronic pain problems that require continuous drug supply. MNDs can administer nonsteroidal anti-inflammatory medicines (NSAIDs), local anesthetics, and other pain treatment medications directly to the target area[35].

6.3 Hormone delivery
Microneedle technology helps provide hormone therapy like insulin for diabetes and endocrine diseases. MNDs provide painless and accurate insulin administration, enhancing patient adherence to treatment regimens. They allow for regulated release of other hormones, resulting in a consistent therapeutic effect and less frequent administration[36].

6.4 Biologics
Delivering big biologics, such proteins and monoclonal antibodies, is problematic due to their size and sensitivity. MNDs enable the direct administration of these macromolecules into the skin, retaining their function and increasing bioavailability[37].

6.5 Skin diseases
Microneedles are widely applied in treating skin diseases due to their ability to enhance drug penetration and provide localized, painless therapy. They are effective in psoriasis, eczema, acne, vitiligo, and skin cancers by delivering drugs like methotrexate, corticosteroids, retinoids, and immunotherapies directly into the skin. MNs are also useful for fungal/viral infections, scar management, and wound healing. Overall, they improve treatment efficacy while minimizing systemic side effects[38].

6.6 Superficial cancer
In superficial skin cancers (such as basal cell carcinoma, squamous cell carcinoma, and early-stage melanoma), microneedles are highly beneficial as they can directly deliver chemotherapeutic agents (5-fluorouracil, doxorubicin), immune modulators, and cancer vaccines into the tumor site with

minimal invasiveness. This localized delivery enhances drug concentration at the lesion, reduces systemic toxicity, and can be combined with photothermal or immunotherapy for improved outcomes. Thus, MNs provide a promising, patient-friendly approach for managing superficial cancers[39].

6.7 Ocular delivery

Targeted medication administration can effectively treat several posterior segment indications. Iontophoresis was employed to transport nanoparticles over the suprachoroidal space. Without iontophoresis, the particles were observed to be concentrated at the injection location. When coupled with microneedles, over 30% of nanoparticles were transported to the posterior segment of the eye[40].

7. Factors Affecting Microneedle Technology

The successful design and performance of microneedle-based drug delivery systems depend on multiple formulation, fabrication, biological, and patient-related factors. These can be broadly classified as follows:

7.1 Microneedle Geometry and Dimensions

Length, tip angle, and base width strongly influence skin penetration efficiency and pain perception. Short MNs (<200 μm) may not reach viable epidermis, while excessively long MNs (>1000 μm) risk stimulating dermal nerves and causing pain. Optimal tip sharpness ensures easy insertion and reduced insertion force[41,42].

7.2 Material of Construction

MNs are fabricated from metals (stainless steel, titanium), polymers (PVP, PVA, PLGA), silicon, and sugars. Mechanical strength and biocompatibility of the material determine insertion reliability and drug release mechanism (dissolving vs hydrogel-forming). Biodegradable polymers enhance safety by avoiding sharp waste[43-45].

7.3 Drug Properties

Molecular weight, solubility, and stability affect loading and release. Hydrophilic drugs are more suitable for dissolving MNs, while poorly soluble molecules may require encapsulation in nanoparticles or hydrogels. Protein/peptide drugs are sensitive to heat and solvent exposure during fabrication[46].

7.4 Fabrication Method

Techniques like molding, lithography, 3D printing, laser cutting, and two-photon polymerization influence MN sharpness, reproducibility, and cost. Fabrication conditions (temperature, solvents, curing agents) affect drug stability and device scalability[46].

7.5 Skin Characteristics

Thickness of stratum corneum, hydration, elasticity, and anatomical site of application impact penetration depth.Variations between individuals (age, disease, ethnicity) also affect performance. Presence of hair follicles and sweat glands can alter drug diffusion.

7.6 Application Force and Device Design

Manual vs applicator-assisted insertion changes reproducibility. Spring-loaded, piston, or patch-based applicators ensure uniform force and complete penetration compared to finger pressure[47].

7.7 Drug Loading and Release Kinetics

The amount of drug incorporated depends on MN volume, surface coating uniformity, and polymer matrix properties. Release can be immediate (coated MNs), sustained (hydrogel or polymer MNs), or controlled (responsive MNs)[48].

7.8 Patient Safety and Comfort

Pain perception, risk of infection, and local irritation must be minimal. Biocompatible and biodegradable materials improve patient compliance. Safety considerations include dose reproducibility, sterility, and elimination of sharp waste[49-51].

8. Conclusion

Microneedle technology has emerged as a versatile and clinically promising platform for transdermal drug delivery, bridging the gap between non-invasive topical systems and invasive injections. Across the diverse types—solid, coated, dissolving, hollow, and hydrogel-forming—microneedles enable controlled, targeted, and often pain-free administration of small molecules, biologics, vaccines, and diagnostic agents. Advances in materials and fabrication (from silicon and metals to biodegradable polymers and 3D printing) have expanded the design space, allowing tunable mechanical strength, drug loading, release kinetics, and patient-friendly formats.

Despite clear advantages such as improved patient compliance, enhanced bioavailability, reduced needle-phobia, and the potential for self-administration, important challenges remain. Mechanical robustness, scale-up manufacturing, sterility, dose limitations, skin variability, and regulatory pathways are nontrivial hurdles for broad clinical translation. Safety considerations—local irritation, infection risk with repeated use, and long-term skin effects—require standardized testing and long-term data to build clinician and regulator confidence.

Looking forward, the most impactful progress will come from integrating smart materials, precision microfabrication, and rigorous clinical validation. Combination approaches (e.g., microneedles with nanoparticles or responsive hydrogels), wearable microneedle patches for sustained or on-demand dosing, and point-of-care diagnostic/theranostic devices are especially promising. To realize their full potential, collaborative efforts across materials science, pharmaceutical formulation, engineering, and regulatory science are essential. In sum, microneedles stand at the cusp of transforming transdermal therapy—from experimental innovation to practical, widely used medical technology—provided remaining technical and regulatory challenges are systematically addressed.

9. Reference

1. Marwah H., Garg T., Goyal A. K., & Rath G, “Permeation enhancer strategies in transdermal drug delivery.” *Drug Deliv.*,2014, *23*(2), 564–578. https://doi.org/10.3109/10717544.2014.935532
2. M Chen, G Quan, Y Sun, D Yang, X Pan, C Wu, “Nanoparticles-encapsulated polymeric microneedles for transdermal drug delivery.” *J. Contr. Release*, 2020,325, 163-175.
3. Dharadhara S, Majumdara A, Dhobleb S, Patravaleb V, “Microneedles for transdermal drug delivery: a systematic review.” *Drug Dev. Ind. Pharm.*, 2019, 45(2), 188-201, DOI: 10.1080/03639045.2018.1539497
4. D. Yang, M. Chen, Y. Sun et al., “Microneedle-mediated transdermal drug delivery for treating diverse skin diseases.” *Acta Biomater.*, 2020, 9(13), 1-15. https://doi.org/10.1016/j.actbio.2020.12.004
5. Zhang X, Chen G, Yu Y, Sun L, Zhao Y., “Bioinspired adhesive and antibacterial microneedles for versatile transdermal drug delivery”. *Research* 2020, 2020(3672120).
6. Yang L, Liu Q, Wang X, Gao N, Li X, Chen H, et al., “Actively separated microneedle patch for sustained-release of growth hormone to treat growth hormone deficiency.” *Acta Pharm Sin B* 2023, 13(344e58).
7. Yu J, Wang J, Zhang Y, Chen G, Mao W, Ye Y, et al. “Glucose-responsive insulin patch for the regulation of blood glucose in mice and minipigs.” *Nat Biomed Eng*., 2020, 4, 499-506.
8. Chen Z, He J, Qi J, Zhu Q, Wu W, Lu Y, “Long-acting microneedles: a progress report of the state-of-the-art techniques.” *Drug Discov Today*, 2020;,25, 1462-8.
9. M.S. Gerstel, V.A. Place, Drug delivery device, US, 1976.
10. Henry, D.V. McAllister, M.G. Allen, M.R. Prausnitz, “Microfabricated microneedles: a novel approach to transdermal drug delivery.” 1998, 88(9), 948.

11. S.M. Bal, J. Caussin, S. Pavel, J.A. Bouwstra, "In vivo assessment of safety of microneedle arrays in human skin." *Eur. J. Pharm Sci*. 2008, 35(3), 193–202.
12. Waghulea T. et al., "Microneedles: A smart approach and increasing potential for transdermal drug delivery system" *Biomedicine & Pharmacotherapy*, 2019, 1249–1258.
13. J. Li, M. Zeng, H. Shan, C. Tong, "Microneedle patches as drug and vaccine delivery platform." *Curr. Med. Chem*. 2017, 24(22), 2413–2422.
14. M. S. Gerstel and V. A. Place, Drug delivery device. US Patent 3, 482, 1976.
15. M. T. Hoang, K. B. Ita, and D. A. Bair, "Solid microneedles for transdermal delivery of amantadine hydrochloride and pramipexole dihydrochloride." *Pharmaceutics*, 2015,7(4), 379-396. doi:10.3390/pharmaceutics7040379
16. U. Andar, et al., "Microneedle-assisted skin permeation by nontoxic bioengineerable gas vesicle nanoparticles." *Mol. Pharm*., 2017, 14(3), 953-958. doi:10.1021/acs.molpharmaceut.6b00859
17. Haj-Ahmad R, et al. "Microneedle Coating Techniques for Transdermal Drug Delivery." *Pharmaceutics*. 2015, 7(4), 486-502.doi:10.3390/pharmaceutics7040486
18. Mansoor I, Liu Y, Häfeli UO, Stoeber B, "Arrays of hollow out-of-plane microneedles made by metal electrodeposition onto solvent cast conductive polymer structures." *Journal of Micromechanics and Microengineering*. 2013, 23(8):085011. doi:10.1088/0960-1317/23/8/085011
19. Vora LK, et al., "Long-acting microneedle formulations." *Advanced Drug Delivery Reviews*. 2023,14(12), 5161-5180 doi:10.1016/j.addr.2023.115055
20. Filho D, Guerrero M, Pariguana M, Marican A, Durán-Lara EF, "Hydrogel-Based Microneedle as a Drug Delivery System." *Pharmaceutics*. 2023, 15(10), 2444. https://doi.org/10.3390/pharmaceutics15102444
21. Yao W, Li D, Zhao Y, Zhan Z, Jin G, Liang H, Yang R, "3D Printed Multi-Functional Hydrogel Microneedles Based on High-Precision Digital Light Processing." *Micromachines*. 2020, 11(1), 17. https://doi.org/10.3390/mi11010017
22. Wu X, Chen Y, Gui S, et al. "Sinomenine hydrochloride-loaded dissolving microneedles enhanced its absorption in rabbits." *Pharm Dev Technol*. 2016, 21(7), 787-793. doi:10.3109/10837450.2015.1055766
23. Wang FY, Chen Y, Huang YY, Cheng CM, "Transdermal drug delivery systems for fighting common viral infectious diseases." *Drug Delivery and Translational Research*. 2021, 11(4), 1498-1508.
24. doi:10.1007/s13346-021-01004-6
25. Gupta J, Felner EI, Prausnitz MR, "Minimally Invasive Insulin Delivery in Subjects with Type 1 Diabetes Using Hollow Microneedles." *Diabetes Technology & Therapeutics*. 2009, 11(6), 329-337. doi:10.1089/dia.2008.0103
26. Li WZ, Huo MR, Zhou JP, et al., "Super-short solid silicon microneedles for transdermal drug delivery applications." *Int J Pharm*. 2010, 389(1-2), 122-129. doi:10.1016/j.ijpharm.2010.01.024
27. McGrath MG, Vucen S, Vrdoljak A, et al., "Production of dissolvable microneedles using an atomised spray process: effect of microneedle composition on skin penetration." *Eur J Pharm Biopharm*. 2014, 86(2), 200-211. doi:10.1016/j.ejpb.2013.04.023
28. Wang QL, Zhang XP, Chen BZ, Guo XD, "Dissolvable layered microneedles with core-shell structures for transdermal drug delivery." *Mater Sci Eng C Mater Biol Appl*. 2018, 83, 143-147. doi:10.1016/j.msec.2017.11.009
29. Duong HTT, Kim NW, Thambi T, et al., "Microneedle arrays coated with charge reversal pH-sensitive copolymers improve antigen presenting cells-homing DNA vaccine delivery and immune responses." *J Control Release*. 2018, 269, 225-234. doi:10.1016/j.jconrel.2017.11.025
30. Lin Z, Zheng K, Zhong J, Zheng X., "Advances in microneedle-based therapy for bone disorders." *Biomedicine and Pharmacother*apy, 2023, 165(115013). doi:10.1016/j.biopha.2023.115013

31. Gholami S, Mohebi MM, Hajizadeh Saffar E, Ghanian MH, Zarkesh I, Baharvand H., "Fabrication of microporous inorganic microneedles by centrifugal casting method for transdermal extraction and delivery." *Int J Pharm*. 2019, 558, 299-310. doi: 10.1016/j.ijpharm.2018.12.089
32. Jiang X, Chen P, Niu W, Fang R, Chen H, An Y, "Preparation and evaluation of dissolving tofacitinib microneedles for effective management of rheumatoid arthritis." *Eur J Pharm Sci*. 2023, 188(106518). doi: 10.1016/j.ejps.2023.106518
33. Koyani RD, "Synthetic polymers for microneedle synthesis: from then to now." *J Drug Deliv Sci Technol*. 2020, 60(102071). doi: 10.1016/j.jddst.2020.102071.
34. Azmana M, Mahmood S, Hilles AR, Mandal UK, Saeed Al Japairai KA, Raman S, "Transdermal drug delivery system through polymeric microneedle: a recent update." *J Drug Deliv Sci Technol*. 2020, 60(101877). doi: 10.1016/j.jddst.2020.101877
35. Mulkutkar M, Damani M, Sawarkar S, "Polymeric microneedles for the eye: An overview of advances and ocular applications for minimally invasive drug delivery." *European Journal of Pharmaceutics and Biopharmaceutics*. 2024, 197:114209. doi:10.1016/j.ejpb.2024.114209
36. Sil D, Bhowmik S, Patel P, Kurmi BD, "Promising role of microneedles in therapeutic and biomedical applications." *Journal of Drug Delivery Science and Technology*. 2023, 91(105273). doi:10.1016/j.jddst.2023.105273
37. Ronnander P, Simon L, Spilgies H, Koch A, "Modelling the in-vitro dissolution and release of sumatriptan succinate from polyvinylpyrrolidone-based microneedles." *European Journal of Pharmaceutical Sciences*. 2018, 125, 54-63. doi:10.1016/j.ejps.2018.09.010
38. Tomono T., "A new way to control the internal structure of microneedles: a case of chitosan lactate." *Materials Today Chemistry*. 2019,13, 79-87. doi:10.1016/j.mtchem.2019.04.009
39. Wu C, Yu Q, Huang C, Li F, Zhang L, Zhu D, "Microneedles as transdermal drug delivery system for enhancing skin disease treatment." *Acta Pharm Sin B*. 2024, 14(12), 5161-5180. doi:10.1016/j.apsb.2024.08.013
40. Sadeq MA, Ashry MH, Ghorab RMF, Afify AY, "Causes of death among patients with cutaneous melanoma: a US population-based study." *Sci Rep*. 2023,13(1),10257. doi:10.1038/s41598-023-37333-4
41. Jung JH, Chiang B, Grossniklaus HE, Prausnitz MR. "Ocular drug delivery targeted by iontophoresis in the suprachoroidal space using a microneedle." *J Control Release*. 2018, 277, 14-22. doi:10.1016/j.jconrel.2018.03.001
42. Donnelly RF, Raj Singh TR, Woolfson AD. "Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety." *Drug Deliv*. 2010, 17(4), 187-207. doi:10.3109/10717541003667798
43. Prausnitz MR, Langer R. "Transdermal drug delivery. "*Nat Biotechnol*. 2008, 26(11), 1261-1268. doi:10.1038/nbt.1504
44. Ita K. "Transdermal Delivery of Drugs with Microneedles-Potential and Challenges.: *Pharmaceutics*. 2015, 7(3), 90-105. doi:10.3390/pharmaceutics7030090
45. Makvandi P, Kirkby M, Hutton ARJ, et al. "Engineering Microneedle Patches for Improved Penetration: Analysis, Skin Models and Factors Affecting Needle Insertion." *Nanomicro Lett*. 2021, 13(1), 93. doi:10.1007/s40820-021-00611-9
46. Aggarwal P, Johnston CR. "Geometrical effects in mechanical characterizing of microneedle for biomedical applications." *Sens. Actuat. B: Chem*. 2004, 102, 226–234. doi: 10.1016/ j.snb.2004.04.024
47. Al-Qallaf B, Das DB, Davidson A. "Transdermal drug delivery by coated microneedles: geometry effects on drug concentration in blood." *Asia-Pacific J. Chem. Eng*. 2009, 4, 845–857. doi: 10.1002/apj.353
48. Zoudani, E.L.; Soltani, M. "A new computational method of modeling and evaluation of dissolving microneedle for drug delivery applications: Extension to theoretical modeling of a novel design of microneedle (array in array) for efficient drug delivery." *Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci.* 2020, 150, 105339

49. O'Mahony, C. "Structural characterization and in-vivo reliability evaluation of silicon microneedles." *Biomed. Microdevices* 2014, 16, 333–343.
50. Zhu,D.D., Zhang, X.P., Zhang, B.L., Hao, Y.Y., Guo, X.D. "Safety Assessment of Microneedle Technology for Transdermal Drug Delivery: A Review." *Adv. Ther*. 2020, 3, 2000033.
51. Permana, A.D.; Nainu, F.; Moffatt, K.; Larrañeta, E.; Donnelly, R.F, "Recent advances in combination of microneedles and nanomedicines for lymphatic targeted drug delivery." *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnology* 2021, 13, e1690.
52. Avcil M, Çelik A., "Microneedles in Drug Delivery: Progress and Challenges." *Micromachines (Basel)*. 2021, 12(11), 1321. doi:10.3390/mi12111321