Recent Developments in Microneedle Technology and Its Diverse Biomedical Applications

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Abstract

Microneedle (MN) technology has revolutionized transdermal drug delivery by bridging the gap between invasive injections and inefficient topical formulations. Traditional oral and parenteral routes often suffer from limitations such as poor bioavailability, first-pass metabolism, pain, and the need for skilled administration. Microneedles, by contrast, enable minimally invasive, painless, and precise delivery of therapeutic molecules, vaccines, and diagnostic agents directly through the skin. The development of microneedles has been propelled by advancements in polymer science, microfabrication, and nanotechnology. This review provides a comprehensive analysis of recent progress in microneedle design, materials, fabrication techniques, and their expanding biomedical applications, including drug delivery, vaccination, biosensing, and cancer therapy. It also discusses toxicity evaluations, regulatory challenges, and future prospects for clinical translation of MN-based systems.

Microneedle (MN) technology has emerged as a transformative platform in modern biomedical science, offering minimally invasive, painless, This review summarizes the latest developments in solid, coated, hollow, dissolving, and hydrogel-based microneedles, highlighting progress in microfabrication, biocompatible polymers, and smart responsive systems. Furthermore, we explore the broad and rapidly growing spectrum of biomedical applications, including transdermal drug delivery, vaccine administration, biosensing, cosmetic treatments, and regenerative medicine.

Keywords

Microneedles, Transdermal Drug Delivery, Microfabrication, Biocompatibility, Vaccine Delivery, Biosensors, Controlled Release, Biomedical Applications.

Introduction

Drug delivery remains a cornerstone of pharmaceutical innovation, aiming to maximize therapeutic efficacy while minimizing adverse effects. Oral administration has historically been the most preferred and convenient route for patients; however, it faces challenges such as limited absorption, enzymatic degradation, and first-pass metabolism, which collectively reduce the drug's bioavailability and therapeutic outcome **(1)**. To address these limitations, researchers explored alternative approaches, including parenteral, transdermal, and inhalation routes.

The skin, though accessible, acts as a formidable barrier due to its outermost layer—the stratum corneum—which restricts the passage of most therapeutic agents **(2)**. Historically, topical formulations were used for treating local disorders, yet deeper or systemic delivery through the skin remained ineffective. Syringes and hypodermic needles improved localized delivery but introduced issues like pain, infection risk, and the requirement for professional administration.

With the emergence of **microneedle (MN) technology**, scientists achieved a paradigm shift in transdermal delivery. Microneedles are miniature projections (25–2500 µm in height) that penetrate the stratum corneum without reaching pain nerves or blood vessels **(3,4)**. By forming transient microchannels, they enable the passage of drugs, proteins, vaccines, and nucleic acids into targeted skin layers while ensuring patient comfort and compliance.

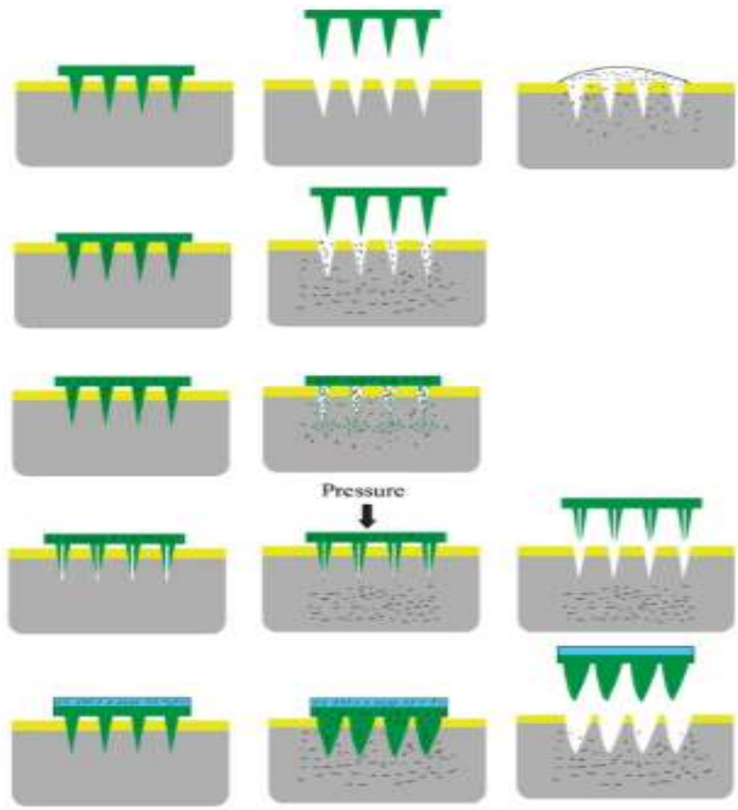
Microneedles can be fabricated in various forms—solid, hollow, coated, dissolving, or hydrogel-forming—each tailored to specific therapeutic needs **(5)**. They have proven particularly effective in delivering vaccines, hormones, peptides, and large biomolecules that otherwise cannot permeate intact skin. Modern research has expanded their application to continuous monitoring systems, smart responsive drug delivery, and minimally invasive diagnostics **(6,7)**.

The evolution of MN systems is largely attributed to advancements in microelectromechanical systems (MEMS), polymer chemistry, and 3D printing technologies. These developments have enabled precise fabrication, improved mechanical strength, and versatile drug loading strategies, transforming microneedles into a promising frontier of biomedical innovation **(8,9)**.

In response to these challenges, researchers have explored multiple non-oral drug administration pathways-including parenteral, transdermal, intranasal, and inhalation routes each offering unique advantages for specific classes of drugs. Among these, the transdermal route is particularly attractive because the skin provides a readily accessible, large surface area for drug application, avoids first-pass metabolism, and allows for sustained release profiles. However, the skin itself poses substantial challenges. Its outermost layer, the stratum corneum, is a highly resistant biological barrier composed of densely packed corneocytes embedded in a lipid matrix, which prevents the permeation of most hydrophilic and macromolecular therapeutic agents (2). Although traditional topical formulations have been widely utilized for localized dermatological conditions, enabling systemic or deeper delivery through the intact skin has historically been ineffective. Conventional transdermal patches are limited to small, lipophilic molecules, while syringe-based injections, though effective, introduce drawbacks such as pain, tissue damage, needle-phobia, infection risk, and dependency

Table 1. Types of Microneedles and Their Mechanisms

Type of Microneedle	Mechanism	Common Materials	Advantages
Solid	Poke-and-patch	Metal, Silicon	Enhances permeability
Coated	Coat-and-poke	Metal, Polymer	Rapid release
Dissolving	Poke-and-release	PVA, PLA, PVP	No residue, biocompatible
Hollow	Poke-and-flow	Silicon, Glass	Precise liquid delivery
Hydrogel-forming	Swelling and diffusion	Cross-linked Polymers	Sustained release



Research Objectives (16)

Most of the medication are given by oral route. It is most prevalent and commonly preferred route of drug administration. The effectiveness of about 74% of medications, which are taken orally, is determined to be unsatisfactory.

- ➢ The primary objective of the proposed work is to develop a dosage form that would enhance the controlled release of a medicine, and a transdermal drug delivery system has been developed to achieve this.
- ➢ The ease of administration is a considerable benefit.
- ➢ To overcame some key limitations, such as poor bioavailability caused by hepatic metabolism (first pass) and the propensity to cause swift spikes in blood levels (both high and low), necessitating high and/or frequent doses, which may be both expensive and inconvenient.

In order to overcome these challenges, new drug delivery systems must be developed.

Merits & Demerits of TDDS (16)

Merits of TDDS

1. Reduced frequency of dose due to improved bioavailability and longer duration of action.
2. Consistent blood drug levels made possible by steady drug penetration over the skin; frequently an objective of therapy.
3. Lessened side effects, and additionally, toxicity from a medicine given transdermally could be mitigated by taking the patch off.
4. Topical patches are an easy, non-invasive approach to get drugs into your body.
5. This method of drug delivery is efficient for medications that are extensively destroyed by the liver, poorly absorbed from the gut, or broken down by the stomach acids.

6. For those who cannot or do not want to take drugs or vitamins orally, transdermal patches provide an alternative.
7. It is quite helpful for individuals who are queasy or unconscious.
8. Topical patches are practical and affordable; one aspect of particular note in some patches is that they only need to be applied once a week. Patient adherence to pharmacological therapy can be helped by such a straightforward dose schedule.

Transdermal patches have been effective in minimizing firstpass drug degradation effects and in creating novel therapeutic applications for currently available medications.

Demerits as well as limitations of TDDS

1. A lot of medications, especially those with hydrophilic components that penetrate the skin too slowly, might not work as intended.
2. Local erythema, itching, and oedema can be brought on by the medication, the adhesive, or any excipients in the patch formulation.
3. Ionic medicines cannot be delivered using TDDS.
4. TDDS is unable to achieve high drug concentrations in plasma or blood.
5. Drugs with large molecular sizes cannot be created using TDDS.
6. Pulsatile medication delivery is not possible with TDDS.
7. If a medicine or formulation irritates skin, TDDS cannot be established.
8. According to Latheeshjlal et al. (2011), the barrier function of the skin varies from one place to another on the same individual, from person to person, and also with age.

Fabrication, Materials, and Mechanism of Microneedles

The design and fabrication of microneedles (MNs) play a pivotal role in determining their mechanical strength, biocompatibility, and efficiency in drug delivery. Each type of MN—solid, coated, dissolving, hollow, and hydrogel-forming—utilizes distinct fabrication methods and materials to achieve specific release profiles and therapeutic objectives **(10,11)**. Solid microneedles, for instance, are typically fabricated from metals, silicon, or robust polymers using micro-molding, etching, or laser-cutting methods, enabling them to create microchannels that enhance drug diffusion. Coated microneedles use similar base structures but employ additional techniques like dip coating, spray coating, or inkjet deposition to uniformly load therapeutic agents onto their surfaces.

Materials Used in Microneedle Fabrication

Microneedles are primarily categorized into **biodegradable** and **non-biodegradable** systems. Non-biodegradable MNs, made from materials such as silicon, glass, metals, and ceramics, provide structural rigidity and reusability, while biodegradable MNs—composed of polymers or sugars—offer the advantage of dissolving safely within the skin after drug release **(12)**.

Metals such as stainless steel, titanium, palladium, and nickel are widely used for solid and hollow MN fabrication due to their mechanical robustness and durability **(13)**. For instance, stainless-steel microneedle arrays have shown superior transdermal permeation compared to silicon or gold–titanium designs in atenolol delivery studies.
On the other hand, **polymeric materials** such as polylactic acid (PLA), poly(lactide-co-glycolide) (PLGA), polycaprolactone (PCL), hyaluronic acid (HA), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) have become the preferred choice for dissolving and hydrogel-forming MNs due to their biocompatibility, flexibility, and ease of fabrication **(14)**. Polymers enable controlled release, minimal invasiveness, and improved patient compliance.

Silicon, historically the first material used in MN fabrication, allows precise three-dimensional microstructures through microelectromechanical systems (MEMS). However, its brittleness and potential breakage risk have limited its clinical translation **(15)**. Consequently, research has shifted toward composite and hybrid MNs that combine polymer flexibility with metal strength.

Fabrication Techniques

Advancements in microengineering and nanotechnology have given rise to several fabrication techniques for microneedles. The choice of method depends on the material, desired geometry, and drug-loading mechanism. Advancements in microengineering, nanotechnology, and material science have led to the development of a wide array of sophisticated fabrication techniques for producing microneedles (MNs), each designed to meet specific structural, functional, and therapeutic requirements. The evolution of these technologies has enabled researchers to precisely manipulate microneedle dimensions, tip sharpness, mechanical strength, and drug-loading capacity at micro- and nanoscale levels. Fabrication strategies vary widely, ranging from traditional micro-molding and lithography-based approaches to more advanced techniques such as laser micromachining, photolithography, two-photon polymerization, and 3D printing. The choice of a specific method is largely dictated by the material being used-whether metals, silicon, ceramics, biodegradable polymers, or hydrogels-as well as the intended geometry of the microneedles, such as conical, pyramidal, cylindrical, or hollow internal structures. Additionally, the desired drug-loading mechanism plays a critical role in selecting the fabrication technique. For instance, dissolving MNs require polymer-casting processes that ensure uniform drug encapsulation, whereas coated MNs rely on surface deposition techniques like dip coating or spray coating to achieve precise loading on microneedle surfaces. Hollow microneedles demand highly controlled micro-drilling or lithographic fabrication to form internal channels for fluid transport. Thus, the integration of microengineering and nanotechnological advancements has not only expanded the design possibilities of microneedles but has also enhanced their efficiency, safety, and versatility across a broad spectrum of biomedical applications.

a. Micromolding

Micro molding remains the most widely employed and economical method for producing polymeric MNs. It involves casting polymer or drug–polymer mixtures into pre-designed molds—commonly made of polydimethylsiloxane (PDMS)—and solidifying them under controlled conditions. The technique allows high reproducibility and is particularly suitable for dissolving MNs loaded with vaccines, hormones, or peptides.

b. Photolithography

Adapted from semiconductor manufacturing, photolithography allows the fabrication of highly uniform MN arrays with nanoscale precision. Using light-sensitive photoresists on silicon wafers, complex shapes and sharp tips can be achieved after UV exposure and etching. This method is best suited for metallic or silicon-based MNs but is cost-intensive and requires sophisticated equipment.

c. Laser Micromachining and Etching

Laser ablation and etching enable the direct removal of material to form microneedle structures with fine geometrical control. Metals like stainless steel and titanium are often processed this way to produce durable MNs for drug and vaccine delivery. However, these methods involve high setup costs and are less suited for large-scale polymeric production.

d. 3D Printing (Additive Manufacturing)

Recent developments in 3D printing have significantly enhanced design flexibility in MN fabrication. Using computer-aided design (CAD) models, layer-by-layer polymer or resin deposition can create customized microneedle arrays with intricate internal channels. 3D printing is particularly valuable for rapid prototyping of personalized MN systems and hybrid structures combining solid and hollow components **(13,14)**.

e. Drawing Lithography

This thermal drawing approach forms tapered MNs by stretching polymer melts or viscous solutions under controlled conditions. It offers a low-cost and straightforward alternative to traditional microfabrication but lacks the precision and scalability required for industrial production.

Table 2. Comparison of Fabrication Techniques

Technique	Materials Used	Advantages	Limitations
Micromolding	Polymer	Low cost, scalable	Limited tip sharpness
Photolithography	Silicon/Metal	High precision	Complex and expensive
Laser Micromachining	Metal	Fast and accurate	High cost
3D Printing	Polymer/Resin	Customizable, flexible	Resolution limits
Drawing Lithography	Polymer	Simple, low-cost	Poor uniformity

Mechanism of Drug Delivery

The mechanism of transdermal drug delivery through microneedles (MNs) is fundamentally determined by their structural configuration, material composition, and mode of interaction with the skin barrier. Each class of MN operates through a distinct delivery pathway designed to maximize therapeutic efficiency while nimizing discomfort, tissue darnage, and variability in patient response (15,10).

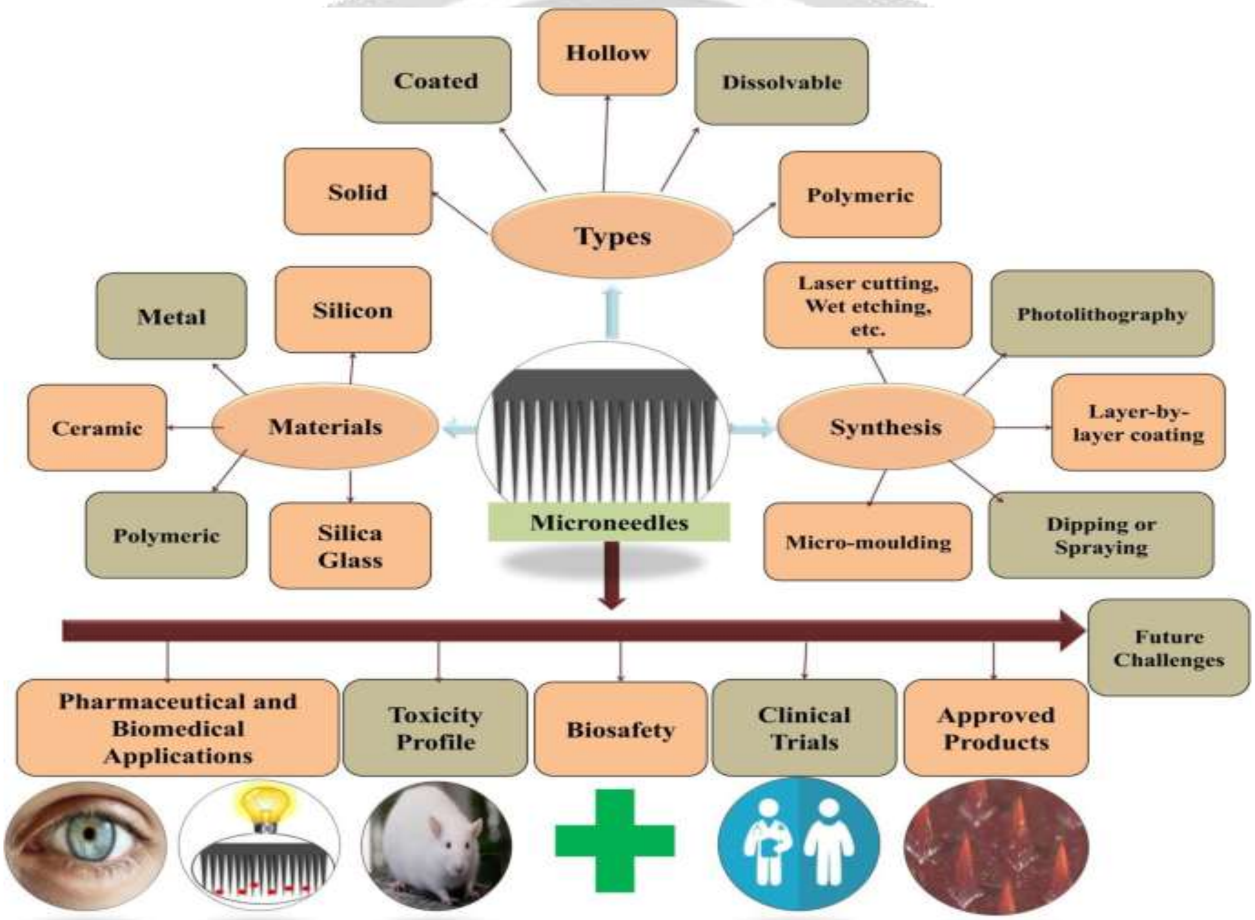
The mechanism of transdermal drug delivery through microneedles depends on their structural design:

- **Solid MNs** use a “poke-and-patch” mechanism, where microchannels are created in the skin followed by topical drug application. Solid microneedles function through a "poke-and-patch" mechanism, wherein the microneedles are first inserted into the skin to create transient microchannels across the stratum corneum, Once these microchannels are formed, the MNs are removed and a drug-loaded topical formulation such as a gel, cream, or patch-is applied over the treated site, allowing therapeutic molecules to permeate through the newly formed pathways. This method is particularly beneficial for enhancing the penetration of hydrophilic or macromolecular rugs that ordinarily exhibit poor transdermal permeation.
- **Coated MNs** employ a “coat-and-poke” mechanism, in which drugs coated on the MN surface dissolve rapidly upon insertion. Coated microneedles operate through a "coat-and-poke" mechanism in which the drug is uniformly deposited onto the surface of each microneedle using specialized techniques such as dip coating, spray coating, or layer-by-layer deposition. Upon insertion into the skin, the coated drug immediately dissolves in the interstitial fluid, enabling rapid release and absorption. This approach is especially suitable for vaccines, hormones, and small-molecule drugs that require precise dosing with minimal lag time
- **Dissolving MNs** rely on a “poke-and-release” mechanism—drugs are embedded within the microneedle matrix, which dissolves after insertion, releasing the encapsulated molecules. Dissolving microneedles follow a "poke-and-release" mechanism, wherein therapeutic agents are encapsulated within a biodegradable or water-soluble polymer matrix that dissolves upon insertions the microneedles disintegrate within the skin, they release their drug payload in a controlled manner, eliminating the risk of sharp waste and enhancing safety, particularly for self-administered applications.
- **Hollow MNs** utilize a “poke-and-flow” approach, where drugs are actively pumped through hollow bores under controlled pressure, enabling precise and rapid administration. Hollow microneedles utilize a more active mechanism known as "poke-and-flow," in which the microneedles contain hollow internal bores that serve as conduits for liquid drug formulations. These drugs can be delivered by applying external pressure-using pumps, syringes, or microfluidic actuation-allowing precise control over infusion rate, dosage, and

depth of delivery. This makes hollow MNs highly suitable for administering large volumes or viscous formulations that cannot be efficiently delivered through solid or dissolving systems. Hydrogel-forming microneedles employ a unique mechanism wherein the polymeric microneedle tips absorb interstitial fluid upon insertion and subsequently swell to form continuous aqueous channels.

Collectively, these mechanisms overcome the stratum corneum barrier, offering pain-free and effective systemic or localized drug delivery. Integration with **microelectronic sensors** and **smart drug-responsive systems** has further expanded their potential for controlled, patient-specific therapies. Moreover, recent advances in biodegradable microneedle materials have enhanced safety by eliminating the need for device removal after application.

These innovations also support sustained drug release, enabling long-term therapeutic effects with minimal patient intervention. Additionally, clinical evaluations have demonstrated high patient compliance, highlighting their practicality for real-world medical use. Overall, the rapid progress in microneedle engineering continues to push the boundaries of non-invasive drug delivery systems.



Biomedical Applications of Microneedles

Microneedle (MN) technology has evolved from a niche research idea into a cornerstone of modern transdermal drug delivery. Their unique ability to pierce the stratum corneum painlessly while maintaining the skin's integrity enables a vast range of medical, pharmaceutical, and cosmetic applications. From drug and vaccine delivery to diagnostics and biosensing, MNs combine precision, comfort, and versatility unmatched by conventional administration routes **(10–15)**.

Transdermal Drug Delivery

Traditional transdermal patches are restricted to lipophilic, low-molecular-weight compounds due to the skin's natural barrier. MNs overcome this by creating transient micropores through which macromolecules, hydrophilic drugs, and nanoparticles can pass. The method ensures **bypass of hepatic first-pass metabolism**, enhanced **bioavailability**, and sustained release over time.

MNs have been successfully employed to deliver drugs such as **insulin, lidocaine, ketoprofen, and diclofenac**, achieving therapeutic plasma concentrations without the pain associated with injections. Moreover, their minimally invasive nature improves patient compliance in chronic therapies such as pain management and hormone replacement.

Vaccine Delivery

Among all applications, **vaccine administration** via microneedles has received the most global attention. Conventional vaccination involves hypodermic injections that require trained personnel, generate medical waste, and often cause needle phobia. MNs eliminate these drawbacks by delivering vaccines directly into the epidermal and dermal layers, which are rich in antigen-presenting cells such as **Langerhans and dendritic cells**, resulting in robust immune activation even with lower doses **(10)**.

Diabetes Management: Insulin Delivery and Glucose Monitoring

Diabetes mellitus remains one of the most widespread chronic diseases globally, and its management heavily depends on frequent glucose monitoring and regular insulin administration. Traditionally, diabetic patients rely on multiple daily subcutaneous injections or insulin pens, both of which can cause pain, needle anxiety, skin irritation, and poor adherence. These limitations have accelerated the search for patient-friendly alternatives, positioning microneedle (MN) technology as a transformative advancement in diabetes care (11).

For millions of diabetic patients, daily insulin injections are painful and inconvenient. Microneedle patches offer a revolutionary alternative through **painless, controlled, and self-administrable** insulin delivery.
Dissolving MNs composed of biocompatible polymers such as **PVA or CMC** gradually release insulin after insertion, maintaining stable glucose levels for extended periods. Recent advancements include **smart glucose-responsive MNs**, which automatically release insulin in response to blood glucose concentration—reducing the risk of hypoglycemia and improving patient comfort. These advanced systems incorporate glucose-sensitive polymers, phenylboronic acid derivatives, or enzyme-based sensing elements such as glucose oxidase. When blood glucose levels rise, these components trigger the release of insulin loaded within the MNs, creating a closed-loop delivery mechanism. **(11)**.

In addition to drug delivery, MNs have been incorporated into **continuous glucose monitoring (CGM)** systems. These biosensing patches extract interstitial fluid or directly measure glucose via enzyme-embedded MNs, enabling non-invasive, real-time monitoring—eliminating the need for finger pricks.

Cancer Therapy

MNs present a novel approach to **localized chemotherapy**, minimizing systemic toxicity while maintaining therapeutic efficacy. By delivering anticancer agents such as **doxorubicin, cisplatin, and 5-fluorouracil** directly into tumor tissues, MNs ensure high local concentrations with reduced side effects.

Polymeric dissolving MNs have been tested for **melanoma treatment**, where drug-loaded nanoparticles penetrate deeply into tumor sites, inducing apoptosis. Other designs integrate **immunotherapy or photothermal therapy**, where MNs deliver immune checkpoint inhibitors or gold nanomaterials activated by near-infrared light to enhance tumor destruction **(12)**.

This approach represents a promising alternative for managing skin and subcutaneous cancers with fewer complications compared to systemic chemotherapy.

Cosmetic and Dermatological Applications

In cosmetic dermatology, microneedles have become a popular non-surgical tool for **skin rejuvenation, pigmentation control, and scar treatment**.
By stimulating **collagen remodeling and neovascularization**, MNs improve skin elasticity, reduce wrinkles, and enhance the absorption of active cosmetic agents such as **vitamin C, retinol, peptides, and hyaluronic acid**.

Derma rollers and **microneedle patches** containing growth factors or hyaluronic acid are now commercially available for at-home or clinical use. MN-assisted drug delivery also enhances the efficacy of topical treatments for acne, melasma, and alopecia.

The controlled micro-injury caused by MN insertion triggers natural skin repair mechanisms, making this technology highly valued in anti-aging therapies **(13)**.

Pain Management

MNs have demonstrated success in delivering analgesics and local anesthetics such as **lidocaine, fentanyl, and diclofenac**.
Coated and dissolving MN patches enable rapid drug diffusion for immediate relief during dental or dermatological procedures.
They also allow **controlled release of opioids**, reducing overdose risks in chronic pain patients **(14)**.

Gene and Nucleic Acid Delivery

Delivering genetic materials like **DNA, RNA, siRNA, and plasmids** across biological membranes has always been challenging due to their instability and size. MNs overcome these barriers by introducing nucleic acids directly into epidermal cells, enabling **localized gene expression** or **gene silencing (15)**.

Dissolving MNs loaded with DNA vaccines have shown potent immune responses compared to traditional injections. Similarly, **siRNA-loaded MN arrays** have achieved successful tumor suppression in melanoma models. These findings open new possibilities for **gene therapy and personalized medicine**.

Diagnostic and Biosensing Applications

MNs are also revolutionizing **point-of-care diagnostics**.
Sampling MNs extract interstitial fluid for biochemical analysis, while **sensing MNs** incorporate microelectrodes or fluorescent dyes for real-time detection of biomarkers.
They have been used for monitoring **glucose, lactate, cholesterol, and electrolytes**, as well as for detecting cancer biomarkers and cytokines in skin interstitial fluid.

This minimally invasive approach eliminates the need for venipuncture and facilitates continuous monitoring through wearable devices, representing the future of **digital health integration**.

Hormone and Peptide Delivery

Microneedles provide a highly efficient method for delivering **fragile macromolecules** such as **human growth hormone (hGH), oxytocin, parathyroid hormone (PTH), and leuprolide acetate**.
Unlike oral routes that degrade these molecules enzymatically, MNs enable **sustained and protected release** through the skin.
Studies show that hGH administered via MN patches exhibits bioavailability equivalent to subcutaneous injection **(14)**.

Emerging and Miscellaneous Applications

Beyond conventional medicine, MNs are now being explored for specialized fields such as **ocular drug delivery**, targeting diseases like **glaucoma and macular degeneration** using fenestrated MNs **(15)**.
Research has also indicated the potential for **neurotherapeutic delivery**, where MNs bypass the blood–brain barrier to deliver drugs directly to neural tissues.
In **veterinary medicine**, MN patches simplify mass vaccination in livestock and eliminate the risk of accidental needle-stick injuries to workers.

Table 3. Biomedical Applications of Microneedles

Application Area	Purpose	Example
Drug Delivery	Transdermal delivery of drugs	Insulin, Ketoprofen
Vaccine Delivery	Painless immunization	Influenza, Hepatitis B
Cancer Therapy	Localized drug delivery	Doxorubicin patches
Diabetes Monitoring	Continuous glucose sensing	Glucose MN biosensors
Cosmetic Dermatology	Skin rejuvenation	HA or peptide MN patches

Toxicity, Biocompatibility, and Regulatory Aspects

While microneedles (MNs) have demonstrated immense therapeutic and diagnostic potential, ensuring their **safety and biocompatibility** remains essential for successful clinical translation. Toxicity testing determines whether MNs, their materials, or degradation by-products induce harmful local or systemic effects **(10–15)**.

These evaluations are generally conducted at three levels — *in vitro*, *ex vivo*, and *in vivo* — to provide comprehensive safety assurance before human use.

In Vitro Toxicity Evaluation

In vitro studies form the first line of toxicity screening. Using cultured human or animal cell lines such as **HaCaT keratinocytes and fibroblasts**, researchers can assess cytotoxicity, genotoxicity, and hemocompatibility of MN materials or their drug formulations.

a. Cytotoxicity Assays

Common assays include:

- **MTT assay:** Measures mitochondrial enzyme activity by converting MTT to purple formazan crystals. A cell viability above 80% indicates non-toxicity.
- **Neutral Red Uptake (NRU) test:** Evaluates lysosomal integrity in viable cells.
- **Lactate Dehydrogenase (LDH) release assay:** Detects plasma membrane damage by measuring extracellular LDH levels.
- **Trypan Blue Exclusion test:** Determines membrane integrity by identifying dead cells stained blue.

b. Hemocompatibility Tests

Since MNs often interact with blood components during insertion, hemolysis and coagulation studies are crucial.

- **Hemolysis test:** Determines whether red blood cells (RBCs) are lysed after exposure to the MN extract. Less than 5% hemolysis is considered safe.
- **Coagulation assays:** Evaluate parameters like *prothrombin time (PT)* and *activated partial thromboplastin time (aPTT)* to ensure no interference with clotting mechanisms.

c. Genotoxicity and Mutagenicity Tests

- **Ames test:** Detects mutagenic potential using *Salmonella typhimurium* strains.
- **Comet assay:** Measures DNA strand breaks in individual cells.
- **Micronucleus test:** Identifies chromosomal fragments excluded from nuclei, indicating genotoxic stress.

These assays collectively confirm that MN formulations do not damage genetic material or interfere with cellular functions **(11)**.

Ex Vivo Toxicity Studies

Ex vivo experiments use freshly excised animal or human skin samples to evaluate local tissue effects such as irritation, erythema, and microstructural damage.

a. Skin Irritation and Erythema Assessment

After MN insertion, skin samples are visually examined and analyzed histopathologically (H&E staining) for epidermal disruption or inflammatory infiltration. Minimal redness or inflammation signifies acceptable biocompatibility.

b. Skin Permeation and Barrier Recovery Tests

These studies measure **transepidermal water loss (TEWL)** before and after MN application. A quick recovery within 24 hours confirms that MN-induced pores are transient and reversible, supporting safe clinical use.

In Vivo Toxicity Studies

In vivo evaluations offer the most realistic assessment of MN safety, accounting for both **local** and **systemic effects**. Studies are performed following **OECD** and **CPCSEA** guidelines to ensure ethical compliance.

a. Acute Toxicity

Conducted in rodents, this test identifies immediate toxic effects following single-dose administration. Parameters include mortality rate, behavioral changes, body weight, and clinical signs. Post-study histopathology of organs (liver, kidney, skin, heart) helps detect tissue-specific toxicity.

b. Sub-Acute and Chronic Toxicity

These long-term studies (28–90 days) evaluate repeated exposure effects. Hematological parameters (RBC, WBC, Hb), serum markers (ALT, AST, creatinine, urea), and organ histology are analyzed. The **No-Observed-Adverse-Effect Level (NOAEL)** is determined to establish safety margins for human trials **(12)**.

c. Skin Sensitization and Allergy Tests

- **Local Lymph Node Assay (LLNA):** Measures lymphocyte proliferation near MN application sites to assess allergenic potential.
- **Guinea Pig Maximization Test (GPMT):** Detects hypersensitivity reactions after repeated exposures. A stimulation index (SI) below 3 indicates non-sensitizing materials.

d. Histopathological Examination

Post-treatment, skin tissues are fixed, sectioned, and stained for microscopic observation. The absence of necrosis, edema, or inflammatory infiltration confirms good tissue compatibility.

Hematological and Biochemical Analyses

These evaluations further establish systemic safety.
Blood parameters (RBC count, WBC count, platelet count) and biochemical indicators such as **ALT, AST, creatinine, and urea** are measured. No significant deviation from control values validates the non-toxic behavior of the MN system **(13)**.

Biocompatibility Standards

Biocompatibility assessments follow **ISO 10993 guidelines** for medical devices:

- **ISO 10993-5:** Cytotoxicity
- **ISO 10993-10:** Irritation and Sensitization
- **ISO 10993-11:** Systemic Toxicity

If microneedles show negligible cytotoxicity, no inflammatory response, and no organ damage, they are considered biocompatible and ready for clinical translation **(14)**.

Ethical and Regulatory Considerations

Before clinical application, all MN-based formulations must comply with ethical and safety regulations:

- Approval from **Institutional Animal Ethics Committees (IAEC)** is mandatory for animal studies.
- Human clinical trials must align with **Good Clinical Practice (GCP)** and **ICH** guidelines.
- Regulatory bodies like the **U.S. FDA**, **EMA**, and **CDSCO (India)** classify microneedles as **Class II medical devices**, requiring biocompatibility and sterility validation prior to approval.

Safety Summary

The cumulative findings from in vitro, ex vivo, and in vivo studies demonstrate that most polymeric and metallic microneedles are **non-toxic, biocompatible, and safe** when fabricated and sterilized under standard conditions. Minimal irritation, quick skin recovery, and negligible systemic effects establish MNs as a patient-friendly, clinically viable platform for future transdermal therapeutics.

Research consistently shows that microneedles cause only minimal irritation to the skin and allow rapid recovery of the microchannels created during application. Since the penetration depth is limited to the upper skin layers, systemic exposure is extremely low, resulting in negligible side effects compared to conventional hypodermic needles.

Overall, these safety outcomes establish microneedles as a patient-friendly, clinically reliable, and highly promising platform for future transdermal therapeutics

Conclusion

Microneedle (MN) technology represents a revolutionary leap in the field of transdermal and targeted drug delivery. By overcoming the limitations of oral, parenteral, and conventional transdermal routes, MNs have opened new horizons for the painless, efficient, and patient-friendly administration of a wide variety of therapeutic and diagnostic agents.

Over the years, significant advancements in **microfabrication, polymer science, and nanotechnology** have led to the development of diverse MN designs—solid, coated, dissolving, hollow, and hydrogel-forming—each capable of addressing specific biomedical needs **(10–15)**. The adaptability of materials such as **biodegradable polymers** and **biocompatible metals** has made it possible to fine-tune drug release kinetics, mechanical strength, and safety profiles for various clinical applications.

The applications of MNs now span across **drug and vaccine delivery, diabetes management, cancer therapy, pain control, cosmetic dermatology, gene transfer, and biosensing**. Their high precision, minimal invasiveness, and potential for self-administration make them ideal for chronic conditions and large-scale public health programs such as vaccination drives.

Equally important are the **toxicity and biocompatibility evaluations**, which ensure the clinical safety of MNs. Studies consistently show that most MN systems are **non-toxic, non-irritant, and biocompatible**, adhering to international safety standards such as **ISO 10993**. This robust safety record, combined with the rapid progress of 3D printing and MEMS-based manufacturing, positions MNs as a next-generation platform capable of transforming global healthcare accessibility.

Looking forward, integration with **smart sensors, responsive polymers, and wearable electronics** will further enhance MN systems, enabling personalized, data-driven medicine. The ongoing translation of MN-based systems from laboratory research to regulatory approval.

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