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BREAKING BARRIERS, NOT SKIN: MICRONEEDLE PATCHES FOR A PAIN-FREE FUTURE IN MEDICINE

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Abstract

Microneedle (MN) patches have emerged as a groundbreaking advancement in transdermal drug delivery, offering a minimally invasive, painless, and efficient alternative to conventional hypodermic injections. These patches consist of micron-scale needles that penetrate the outermost layer of the skin to facilitate drug absorption while avoiding deeper tissues, thus reducing pain and needle-associated risks. Microneedle patches have shown significant promise in vaccine delivery, transdermal drug administration, and cosmetic applications due to their ability to enhance patient compliance, eliminate the need for trained medical personnel, and minimize biohazardous waste.

Different types of microneedles, including solid, coated, dissolving, and hydrogel-forming microneedles, have been developed to optimize drug delivery efficiency. These innovations address challenges such as bioavailability, stability, and sustained release, making them particularly beneficial for self-administration and mass immunization programs. Recent studies have highlighted the successful use of microneedle patches for delivering vaccines against infectious diseases, such as influenza and COVID-19, with enhanced immunogenic responses. Additionally, microneedle patches have been explored for pain management, hormone therapy, and cancer treatment, demonstrating improved therapeutic outcomes.

Despite their numerous advantages, challenges such as large-scale manufacturing, regulatory approval, and cost-effectiveness remain significant hurdles to widespread adoption. Innovations in biomaterials, nanotechnology, and 3D printing are expected to further refine microneedle technology, increasing its efficacy and accessibility. The future of microneedle patches lies in the development of smart, responsive systems integrated with biosensors for real-time monitoring of drug release and patient response. This review provides a comprehensive analysis of microneedle patches, their mechanisms, applications, advantages, challenges, and future prospects in drug delivery and vaccine administration.

INTRODUCTION

Conventional drug delivery methods, including oral administration and hypodermic injections, often face challenges related to bioavailability, patient compliance, and safety. Microneedle patches (MN), a revolutionary transdermal drug delivery system, provide an efficient and painless alternative for delivering vaccines, biologics, and small-molecule drugs [1]. MN patches consist of arrays of micron-scale

needles that create microchannels in the skin, facilitating drug absorption while bypassing the first-pass metabolism associated with oral drugs [2]. Additionally, microneedle patches offer advantages such as reducing pain, eliminating needle phobia, and minimizing the risk of needle-stick injuries and cross-contamination [3]. Their ease of use makes them particularly attractive for mass immunization programs and self-administration by patients.

The microneedle drug delivery method was created in response to the issues with the transdermal patch and the hypodermic needle, and it is believed to be a combination of the two. The main issue with transdermal technology is that many medications cannot penetrate the skin quickly enough to have the desired therapeutic effect. Using microneedles, researchers have created a sophisticated technique that permits hydrophilic high molecular weight substances to penetrate the stratum corneum. When medications are administered with a microneedle, the stratum corneum layer is penetrated, allowing more drug molecules to penetrate the skin. This technique is characterized by its enhanced permeability, effectiveness, self-administration, quicker beginning of action, and higher patient compliance. (4)

Accurate microneedle metering and dosage loading are crucial when delivering delicate medications like insulin and chemotherapeutics. Since digestion and first-pass metabolism are avoided, microneedle patches usually require a lower dosage than oral consumption to provide equal therapeutic efficacies (5). When compared to the oral route, the pharmacokinetics of microneedles demonstrate a rapid absorption in the bloodstream, which can be beneficial for treating localized disorders with far lesser drug loading. The medication kind, intended course of therapy, and patient profile all have a significant impact on the amount of drug loading for microneedles. Because manufacturing techniques and medication loading procedures are controlled, MNs provide a highly precise delivery mechanism.

However, the physiology of the skin, the surrounding environment, and the method of application to the skin's surface can all affect how well the drug dissolves at skin interfaces. (6)

Method of Preparation of Microneedles:

Microneedles are prepared using various fabrication techniques depending on their composition and intended application. Some of the commonly employed methods include:

1. Mold-based Fabrication/Micromolding:

This involves using micro-molding techniques where a polymer or hydrogel solution is poured into a preformed mold and solidified. This method is widely used for dissolving and hydrogel-forming microneedles (7). A negative mold with hollow slots for loading material is used in the process. The mold is then removed once the substance has undergone a cooling and curing procedure. Materials like ceramics, hydrogels, and polymers can be processed using this method.

Benefits of this method include cost effectiveness, simplicity, and ease of replication. With the use of this technology, materials may be gradually added to the microneedles and composites. To overcome the difficulties in filling the mold cavities, many mold-filling techniques are used, including centrifugation, suction, infiltration, spin coating, imprinting, atomized spray, etc. (8)

2. Laser Cutting and Etching:

In order to manufacture accurate microstructures, laser cutting or etching processes are frequently used to fabricate microneedles made of silicon and metal. Solid microneedle arrays are made by laser cutting, which uses an infrared laser and computer-aided design software. The desired shape, size, and structure of microneedles can be effectively achieved with this method. This method is beneficial because it enables the creation of both a single array of microneedles with various geometries and two-dimensional arrays of metallic microneedles (9)

3. Photolithography:

A technique commonly used in microelectronics, photolithography enables the precise structuring of microneedles by exposing a light-sensitive material to UV light through a patterned mask. The microneedles formed by phtolithiography are strongly influenced by the presence of micro lens resulting in shaper microneedles as compare to cylinderical microneedles formed by planar photomask. The lens equation is

used as a prediction model for approving microneedles length (10)

4. **Electrospinning :**
An innovative technique for creating MNs is electrospinning, which spins polymer solutions into nanofibers using electricity. Thin, consistent, and continuous nanofibers are produced with this technique, and they may find value in a number of medicinal applications. Because electrospinning may produce nanofibers made of one or more polymers, a variety of microneedles can be designed. The ability to create MNs in a variety of sizes and forms is one of the main benefits of electrospinning. To suit the intended use, such as tissue engineering or medication administration, the nanofibers' size and form can be altered. Additionally, a variety of applications can be developed because to the process's ease of control and relative affordability. (11)

5. **3D Printing:**
Emerging advancements in 3D bio-printing allow for the fabrication of highly customized microneedles with precise drug-loading capabilities, enhancing personalized medicine applications . Microneedles can also be created with complex three-dimensional structures. It includes a wide range of methods, including projection-based printing (PBP), continuous liquid interface production (CLIP), stereolithography (SLA), two-photon polymerization (TPP), liquid crystal display (LCD), selected laser sintering (SLS), selected laser melting (SLM), and others. (12).

6. **Injection Molding :**
A popular and cost effective method for producing microneedles on a wide scale is injection molding. A mixture of metal and polymer is injected into the mold's cavities by the injection machine. Improved injection flow rates, accurate metering, and outstanding uniformity are all provided by injection molding. The method's drawbacks include its labor-intensive nature, difficult control over small shot size, and costly equipment. (13) A comparison method for the manufacturing of microneedles is shown in table 1.

Table 1: Manufacturing methods of Microneedles

Method	Suitable Materials	Advantages	Limitations	Ideal Applications	References
Micro-molding	Biodegradable polymers, sugars	- Scalable, cost-effective - Simple for dissolving MNs	- Risk of incomplete mold filling - Not ideal for metals	Dissolving and coated MNs	(14)
Photolithography	Silicon, SU-8, some polymers	- High precision and reproducibility - Good for prototyping	- Expensive - Brittle and non-biodegradable materials	Solid MNs for research and diagnostics	(15)
Laser Cutting/Ablation	Metals, polymers	- Fast and contactless - Good for high-strength MNs	- Tip sharpness may be poor - Produces rough edges	Solid metal MNs for skin penetration	(16)
3D Printing	Photopolymers, biodegradable polymers	- Customizable shapes - Rapid prototyping - Multi-material possible	- High cost - Limited resolution for sharp tips	Personalized or hollow MN designs	(17)

Injection Molding	Thermoplastics, biodegradable polymers	- Suitable for mass production - Repeatable	- High tooling cost - Limited to thermoplastics	Commercial microneedle manufacturing	(18)
Electrospinning	Biodegradable polymers (e.g., PCL, PLGA)	- Forms nanofiber-based MNs - Excellent drug-loading potential	- Requires post-processing to form MN shape - Fragile, low mechanical strength	Nano-fiber reinforced MNs for sustained delivery	(19)

Types of Microneedles:

Microneedles can be classified into several types based on their composition, fabrication method, and drug delivery mechanism. The main categories include **solid, coated, dissolving, hollow, and hydrogel-forming microneedles (Figure 1)**. Each type has unique characteristics that make it suitable for specific applications in transdermal drug delivery, vaccination, and cosmetic procedures.:

1.Solid Microneedles:

Solid microneedles are usually utilized for pre-treatment of skin before drug **application.** By forming microchannels in the stratum corneum, these microneedles improve the permeability of medications that are subsequently applied. Materials like silicon, titanium, stainless steel, and biodegradable polymers are frequently used in their fabrication.

➢ **Advantages:**

- Strong mechanical properties ensure deep penetration into the skin.
- Useful for increasing transdermal absorption of large-molecule drugs.
- Can be designed with sharp or blunt tips based on application needs.

➢ **Limitations:**

- Requires a separate step for drug administration, reducing ease of use.
- May cause skin irritation due to prolonged mechanical impact. (20)

2. Coated Microneedles:

Coated microneedles are solid microneedles covered with a thin layer of drug formulation, which dissolves upon penetration into the skin. These microneedles allow for precise dosage control and rapid drug release. They are typically used for vaccine administration and localized drug delivery.

➢ **Advantages:**

- Immediate drug release upon skin penetration.
- Useful for vaccine delivery with minimal patient discomfort.
- Reduces the need for reconstitution or additional application steps.

➢ **Limitations:**

- Limited drug-loading capacity due to the thin coating layer.
- Requires specialized coating techniques to ensure uniform drug distribution. (21)

3. Dissolving Microneedles:

Dissolving microneedles are composed of biocompatible and biodegradable materials such as sugars, polysaccharides, and polymers (e.g., polyvinyl alcohol, hyaluronic acid). The drug is encapsulated within the microneedles and is released as the microneedles dissolve in the skin.

➢ **Advantages:**

- Eliminates the risk of needle-stick injuries and biohazardous waste.
- Controlled release of encapsulated drugs.
- Highly suitable for vaccines and peptide-based therapeutics.

➢ **Limitations:**

- Limited mechanical strength compared to metal microneedles.
- Requires precise formulation to maintain stability during storage. (22)

4. Hollow Microneedles

Hollow microneedles resemble conventional hypodermic needles but on a microscale. These microneedles contain a central lumen through which liquid drugs can be injected into the skin .They are particularly effective for delivering biologics, insulin, and vaccines in controlled doses.

➢ **Advantages:**

- Suitable for continuous or bolus drug delivery.
- Can be used to administer larger volumes of liquid formulations.
- Precise dose control enhances therapeutic outcomes.

➢ **Limitations:**

- More complex fabrication process compared to solid and dissolving microneedles.
- Potential clogging of the needle lumen may reduce efficiency.
- Higher risk of leakage or incomplete drug delivery. (23)

5. **Hydrogel-forming Microneedles**

Hydrogel-forming microneedles consist of cross-linked polymer networks that swell upon contact with interstitial fluid, allowing for controlled drug release over time. These microneedles do not dissolve but act as a reservoir to release drugs gradually.

➢ **Advantages:**

- Prolonged and sustained drug release.
- Can be loaded with high molecular weight drugs and proteins.
- Provides enhanced biocompatibility and minimal skin irritation.

➢ **Limitations:**

- Requires optimization of swelling properties for effective drug diffusion.
- Some hydrogel materials may degrade over time, affecting performance.(24)

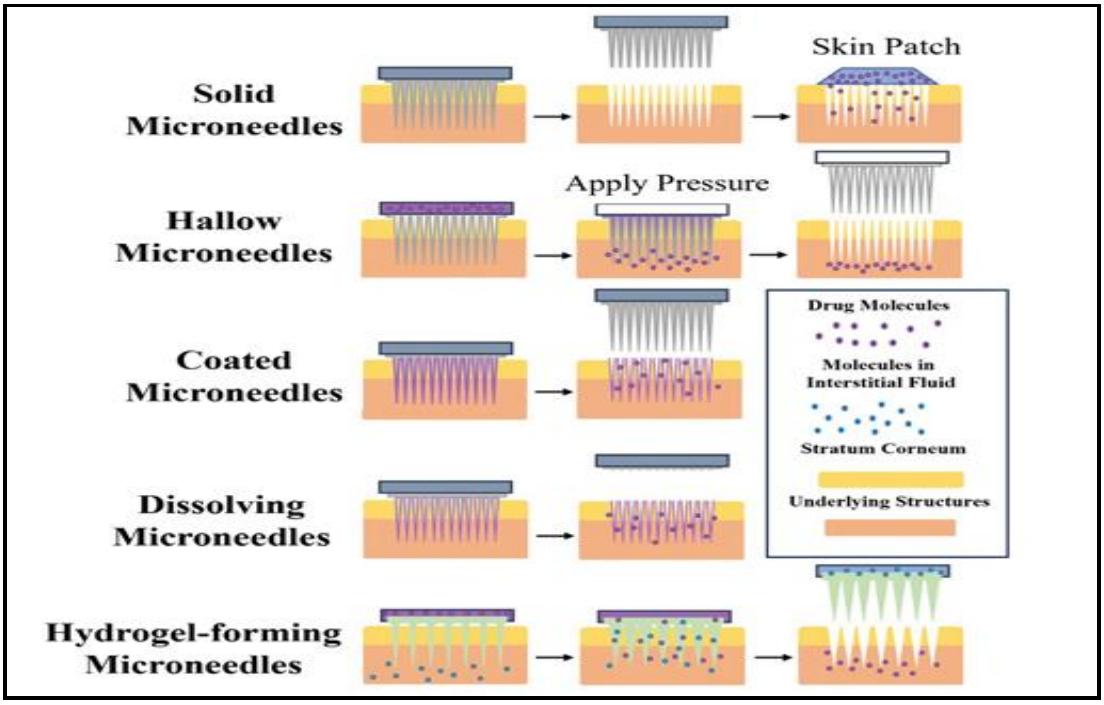

Figure 1 : Different types of microneedles and their mode of action during drug delivery (25)

Material Selection for Microneedles Depending on the intended purpose, the materials utilized to create the microneedles should be both biocompatible and biodegradable. It ought to possess enough mechanical strength to pierce the skin without creating any negative consequences.

Microneedles are made from a variety of materials, including metals and polymers (Table 2). The three

main categories of materials are metals, polymers, and inorganic materials.

Table 2: Materials Used for Microneedles in Analgesic Drug Delivery

Material Type	Example Materials	Mechanical Strength	Biocompatibility	Advantages	Limitations	Common Applications	Suitability for Analgesics	Reference
Metals	Stainless steel, Titanium, Nickel	High (penetrates thick skin)	Generally good (nickel may cause allergy)	Strong, reusable, high penetration efficiency	Non-biodegradable, may cause discomfort or infection	Solid and hollow MNs	Ideal for fentanyl, morphine delivery	(26)
Silicon	Doped silicon, Amorphous silicon	Moderate-high, brittle	Moderate; may cause micro fractures	High-precision manufacturing, reproducibility	Brittle, expensive, biohazardous fragments	Research-based MNs, solid MNs	Suitable for experimental analgesic delivery	(27)
Polymers	PLA, PLGA, PVP, PVA, CMC	Moderate, customizable	Excellent; widely used in biomedical devices	Biodegradable, tunable drug release	May require insertion force enhancers	Dissolving/ coated MNs	NSAIDs (e.g., ketorolac), lidocaine	(28)
Sugars	Trehalose, Maltose, Sucrose	Low to moderate	Excellent; stabilizes biomolecules	Fast-dissolving, suitable for peptides	Fragile, humidity-sensitive	Dissolving MNs, peptide-based drugs	Peptides (e.g., CGRP antagonists), local anesthetics	(29)
Ceramics	Alumina, Silica, Calcium phosphate	High	Excellent; some resorbable	Strong, chemically inert	Brittle, fabrication issues	Implantable MNs	Suitable for sustained-release pain relief	(30)
Hydrogel	Gelatin, Hyaluronic acid, PEG	Low-moderate; swells in skin	Excellent; bio-derived	Soft insertion, sustained release	Weak penetration force	Swelling MNs, transdermal gels	Topical NSAIDs, mild analgesics	(31)

Mechanism of Drug Delivery

Similar to a typical transdermal patch, the microneedle medication delivery method temporarily disrupts the skin by placing one to hundreds of microneedles in arrays on a small patch. When applied, this patch penetrates the stratum corneum, avoiding the outermost layer of the skin. The medicine can be directly injected into the upper dermal or epidermal layers thanks to the microneedle device. The medication then enters the bloodstream and, once it reaches the site of action, produces a therapeutic effect.(32)

Evaluation of Microneedles

The medication can be encapsulated (liposomes, nanoparticles, or nanoliposomes) or put onto or into the microneedles in suspension or dispersion form. Depending on the kind of formulation utilized in the microneedles, a number of physicochemical characteristics, such as particle size, polydispersity index, viscosity, and zeta potential, can be assessed for the loaded drug. (33)

Tests for drug release, adhesion, and penetration are conducted on a patch that is applied following pre-treatment. Transmission electron microscopy, X-ray scattering, and dynamic light scattering can all be used

to determine the liposomes' or nanocarriers' size, internal structure, and crystallinity. Drug dispersion and microneedle stability investigations can be conducted under various temperature, pH, and in-vivo physiological settings (cell line or tissues). Additional testing are conducted on the developed microneedle, including solubility studies, drug content, in-vitro release tests, and biocompatibility investigations. (34)

1.Dimensional evaluation:
The needle geometry is assessed and the microneedle's tip radius, length, and height are measured using a variety of techniques. Electrical or optical microscopy are the most widely used techniques. A 3D image analysis improves the needle geometry and aids in quality control. For this, confocal laser microscopy and scanning electron microscopy (SEM) have been employed. (35)

2.Mechanical properties or insertion forces:
A microneedle must be sharp and slender enough so that it can easily penetrate into the skin and also be strong enough so that it does not break when inside the skin. Two important factors for a safe and efficient design of microneedles are the force at which the microneedle loses its structural integrity and the insertion force. The ratio of these two forces is called as the 'safety factor'. The ratio is preferred to be as high as possible (36)

3.In-vitro skin permeation studies:
To determine whether a medication has penetrated the skin, diffusion cell apparatus is utilized. The experiment, which is positioned between the donor and receptor compartments, mostly uses pig ear skin. The permeation profile of treated and untreated skin were compared for analysis.

4.In-vivo animal studies:
Research using animal models in vivo Rats without hair can be employed in the research. The animal must be anesthetized using an appropriate procedure. Trans-epidermal water loss (TEWL), which is assessed both before and after microneedle treatment, is one of the criteria taken into account. This parameter is measured with a Delfin Vapometer. (37)

Therapeutic Applications of Microneedle Patches:

1. Drug Delivery:
In 1998, a solid silicon MN was used as the first MN for medication delivery. Human growth hormone was transdermally administered to hairless rat skin using a dissolvable MN patch. A caffeine-loaded MN patch that dissolves was effective in controlling the weight of obese mice and serving as a therapy strategy for obesity.
Additionally, MNs have been utilized for transdermal delivery of a number of medications, including paracetamol, ibuprofen, and ketoprofen. Some other drugs administered through micorneedles includes L-ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine, hydrochloride, ketoprofen, and glycerol. (38)

2. Vaccine Delivery:
Compared to conventional injections, microneedle patches have shown improved immune responses, which makes them a viable method of administering the COVID-19, measles, and influenza vaccinations. In order to overcome the difficulties involved in the process, microneedle-based vaccine delivery through the skin barrier—including live attenuated, inactive, pathogen component, RNA, protein, and toxoid vaccines—has become a viable substitute for conventional vaccine delivery techniques. The ability of electroporation to improve the intracellular transport of genetic material, including DNA and RNA, is a viable method for enhancing the immunogenicity of medications and vaccines. (39)

3.Pain Management:
Microneedle patches loaded with analgesics such as lidocaine provide localized pain relief in a controlled manner. Local anesthesia in the oral cavity using injections is a painful and unpleasant experience. In order to overcome the problem and improve compliance by the patient, lidocane hydrochloride loaded in dissolving hyaluronic acid microneedle patch was fabricated by Zhu et al. (40)

4.Hormone Therapy:
In diabetic individuals, microneedles greatly improve glucose management by facilitating the transdermal administration of hormones such as insulin. The contraceptive, levonorgestrel, was administered via a

microneedle patch made of PLA and PLGA. The microneedle patch's special design allows the needles and backing layer to separate within five seconds of application by creating a bubble between the MNs and the backing layer. The contraceptive medication is released continuously via the needles, which stay in the skin and have a long-lasting effect (41)

5.Cancer Treatment:

Microneedle patches have been effectively used to deliver chemotherapy drugs, improving medication penetration and reducing systemic side effects. Because of its minimally invasive nature and capacity to provide medication directly to the afflicted area, microneedle patches have gained significant interest in the treatment of superficial cancer. According to a study, PROTAC can be administered using a microneedle patch to treat breast cancer. Microneedle technology in conjunction with immunotherapy is a novel method of drug delivery for the treatment of cancer. Using therapeutic medicines like adoptive cellular therapy, or vaccinations, immunotherapy uses the body's immune system to combat tumor cells. (42)

6.Cosmetic and Dermatological Uses:

In dermatology, microneedles are frequently utilized to administer targeted medication delivery for pigmentation and acne conditions, as well as anti-aging chemicals and skin rejuvenation treatments. The use of microneedles in cosmetics is becoming more and more popular, particularly for treating scars and imperfections and for improving the appearance of skin. The microneedle approach was used in an effort to deliver certain active chemicals used in cosmetics, such as retinyl retinoate, eflornithine, and ascorbic acid (43)

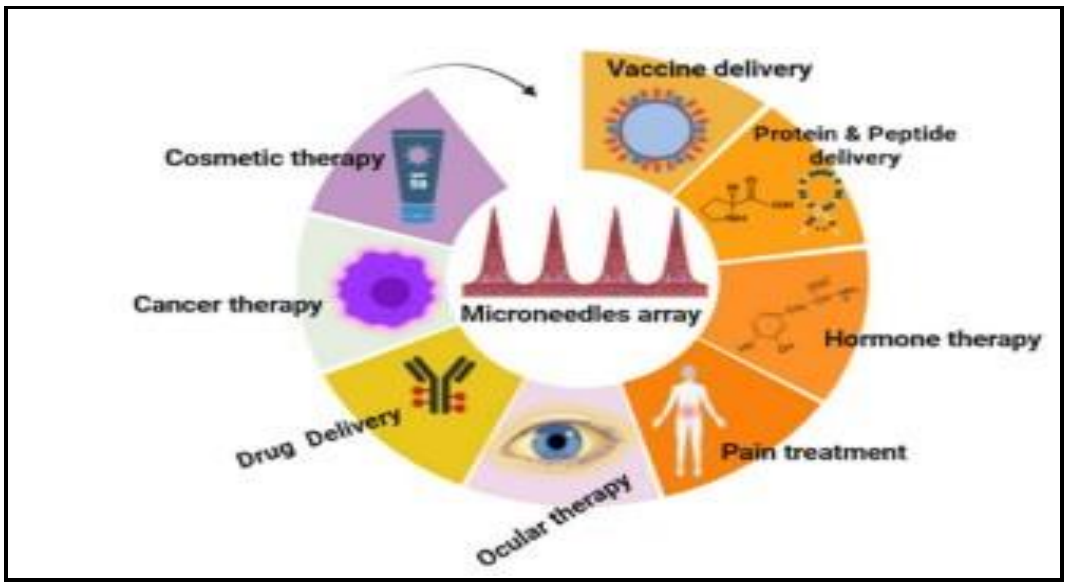

Figure 2 : Schematic illustration of the various applications of microneedles (44)

Limitations of Microneedle Drug Delivery:

Due to their low drug-carrying capacity, microneedles make it challenging to include medications in high dosages. Polymeric MNs break readily and have a low mechanical strength. Polylactic acid has occasionally been utilized to give MNs mechanical strength. The skin's elasticity stops microneedles from penetrating and delivering the trapped medication to the intended location. The skin's thickness, suppleness, and level of moisture must all stay constant for MN dosage to be accurate. The distribution of thermolabile medications would be hampered by high-temperature microneedle manufacturing, which would also lead to a shortage of materials suitable for microneedle construction and blockage of the microneedle bore, which would reduce penetration and efficacy. The development of microneedles is further hampered by inadequate quality control standards for large-scale manufacture and a lack of regulatory requirements in manufacturing methods. (45)

Challenges and Future Prospects

Despite the promising advantages of microneedle (MN) systems for drug delivery, including minimally invasive administration, enhanced patient compliance, and bypassing first-pass metabolism, several challenges must be overcome for broader clinical translation and commercialization.

Challenges:

- The production of microneedles with precise geometry, consistent drug loading, and mechanical robustness is technically demanding. Ensuring reproducibility and tip sharpness in high-volume manufacturing is a persistent barrier. Complex fabrication methods such as two-photon polymerization or multilayer molding may yield high-resolution structures but are time-consuming and costly, limiting scalability (46)
- Maintaining the stability of sensitive bioactive molecules such as peptides, proteins, or analgesics (e.g., opioids, NSAIDs) during MN fabrication and storage is challenging. Many microneedles require incorporation of cryoprotectants or stabilizers, which complicates formulation.
- Variability in skin characteristics such as hydration, thickness, and elasticity across patient populations (e.g., pediatric vs. geriatric skin) can affect microneedle penetration and drug delivery efficiency. This raises concerns over dosing accuracy and therapeutic outcomes.(47)
- Regulatory bodies such as the FDA and EMA lack dedicated guidelines for microneedle-based products. Developers must navigate complex pathways involving device-drug combination approvals, biocompatibility testing, and clinical validation, which can delay market entry
- Sophisticated fabrication processes and specialized materials (e.g., biodegradable polymers, medical-grade metals) can drive up production costs. This limits the feasibility of large-scale deployment, especially in resource-limited settings where access to pain relief is already inequitable. (48)

Future Prospects

- The integration of biosensors and microelectronics into microneedles is an emerging field. Smart MNs can enable **real-time monitoring of biomarkers** such as interstitial glucose or inflammatory cytokines and dynamically adjust drug release based on patient feedback (49). For analgesia, this could translate into adaptive delivery of opioids or NSAIDs in response to pain signals.
- Research is progressing toward **stimuli-responsive MNs**, which release drugs in response to pH, temperature, or enzymatic changes. This can enhance localized delivery of analgesics to inflamed or injured tissues, improving efficacy while minimizing systemic exposure.
- The development of **next-generation biomaterials**—such as composite hydrogels, silk fibroin, and nanoengineered biopolymers—offers improved mechanical strength and programmable degradation rates. These materials can enhance MN performance and patient safety while eliminating the need for patch removal. (50)
- With advances in high-resolution 3D printing and digital microfabrication, **patient-specific MN patches** may become feasible. These could be tailored based on individual pharmacokinetics, pain thresholds, or therapeutic regimens, aligning with the goals of personalized medicine (51)

Conclusion:

A promising new biomedical science method for TD medication delivery is through microneedles. It works well for delivering a wide range of medications, such as hormones, vaccinations, and theranostic agents. The range of polymers allows for the creation of MNs with a wide range of biomedical uses. The main benefit of drug delivery using MNs is painless penetration into the stratum corneum. The broad-spectrum applications of MN technology in the transport of both large and small molecules are being demonstrated. The mechanical strength, medication loading capacity, and biodegradability of MNs are all being improved by researchers. Millions of people worldwide could have their lives improved by this technology.

For the delivery of small or macromolecules, numerous MN systems with unique delivery mechanisms have been created and employed during the last few decades. According to recent studies, the transdermal administration of tiny molecular medicines, salt forms, excipients, and other

formulation elements is more effective when the skin microchannel life time is temporarily disrupted.

This review also highlights the research gap for MN fabrication and illustrates various MN design types, materials, and manufacturing techniques. MNs could be investigated, nevertheless, in the areas of diagnosing and treating orphan diseases, delivering more advanced biologicals and theranostic agents, enhancing the efficacy and safety of treatment, and making it affordable for the general public.

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