IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Microneedles Technology For Pain Less Drug Delivery

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➢ Abstract

Microneedle (MNs) technology is a recent advancement in biomedical science across the globe. The current limitations of drug delivery, like poor absorption, low bioavailability, inadequate skin permeation, and poor biodistribution, can be overcome by MN-based drug delivery. Nanotechnology made significant changes in fabrication techniques for microneedles (MNs) and design shifted from conventional to novel, using various types of natural and synthetic materials and their combinations. Nowadays, MNs technology has gained popularity worldwide in biomedical research and drug delivery technology due to its multifaceted and broad-spectrum applications. This review broadly discusses MN's types, fabrication methods, composition, characterization, applications, recent advancements, and global intellectual scenarios.

➢ Introduction

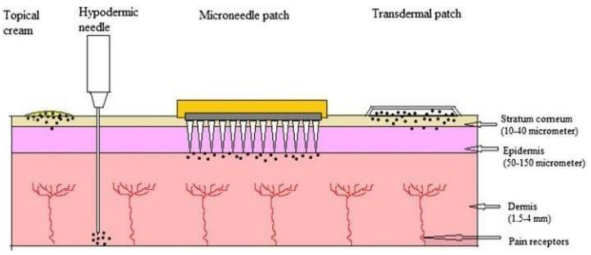
Drug Delivery System

Drugs have been delivered in a variety of pathways to improve the quality of health and extend human life. Drug delivery systems have seen drastic improvements from chewing of therapeutic leaves to capsules, pills, injectables, and implantable devices. Over the years, the therapeutic efficacy of a drug has been enhanced by targeting the localized ailment region while reducing its toxic effect to healthy cells.

Higher absorption and transport of the drug can be achieved to relieve distressing symptoms for patients. There are different routes for drug delivery into the human body, which include oral, parenteral, inhalation, transdermal, etc. [1]. The oral route is the oldest route that is convenient for patients with acceptable ease of administration. For long-term medications, the oral route has side effects because it impacts vital organs such as the liver and kidneys. The parenteral route introduces hydrophobic drugs to the human body using intramuscular, subcutaneous, and intravenous pathways. As parenteral drug delivery is a rapid delivery method, it is considered the optimal choice of drug delivery in an emergency. However, the parenteral route can often be quite painful and is thus not a preferred route for many patients. The inhalation route is designed to transport the drug directly to the lungs. This route is painless, comfortable, and designed to target diseases

linked with the respiratory systems or certain drugs that are shown to be efficacious via the air–blood barrier. There are however certain disadvantages and risks associated with overdosing through self-administration by the patients that require multiple doses (3 to 4 times) each day. Attempts have been made to further improve dose efficacy and potency of such types of drugs to reduce their risk to patients by identifying optimal material matrices and tunable release kinetics. Finally, the transdermal drug delivery (TDD) route focuses on administering drugs through the layers of skin discussed in detail through the next few sections. For example, TDD can be used as an alternative to oral drug delivery in neonates and geriatric patient populations who may often struggle to swallow oral drugs.

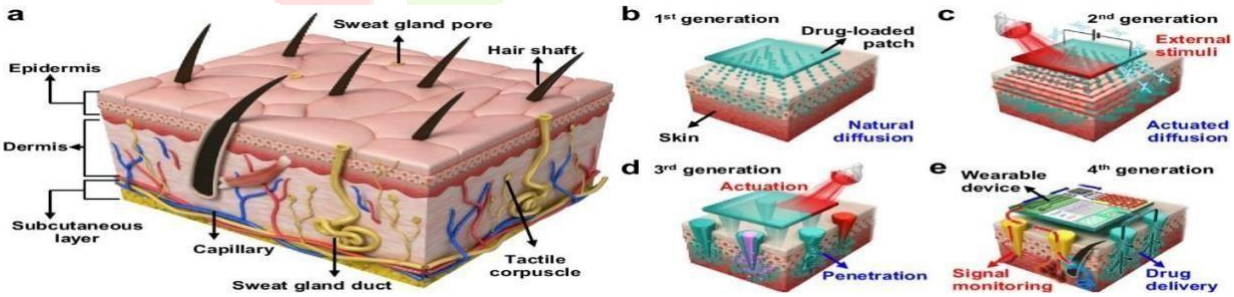
Transdermal Drug Delivery (TDD)



Transdermal drug delivery starts with applying the drug directly to the skin. The drug penetrates through the stratum corneum passing through the epidermis and dermis The drug is available for absorption when it reaches the dermal layer. This method aims to deliver the drug molecules to the bloodstream by controlling diffusion through the skin. Different transdermal drug delivery systems are presented in Figure.

Prausnitz and Langer have divided the transdermal drug delivery history into four generations as shown in Figure. The first generation focused on providing a low drug load by introducing patchbased technologies using natural diffusion. The second generation focused on using the chemical

precursors to actuate drug delivery. The third generation include technologies such as thermal ablation, electroporation, and microneedles, which can precisely target the drug upon entry into the stratum corneum. Finally, the fourth generation involves the combination of sensing modalities along with drug delivery microneedles to control the release of pharmaceutical agents with high precision. Transdermal drug delivery (TDD) has several advantages over other drug delivery methods. TDD has the ability to deliver the drug to the blood with the desired dosage in a sustained and well-controlled manner. Another advantage of the transdermal route is the reduction of the side effects of drugs by preventing drugs from reaching critical organs such as the liver and kidneys .



Microneedle (MN) for Transdermal Drug Delivery

MN technology is a mode of active transdermal drug delivery and is intended to be used a as a replacement to the traditional syringe injections. The MN array is used to penetrate the stratum corneum and deliver the drug with a minimally invasive action. These arrays are micro-sized needles with a height ranging from 25 to 2000 μm. MNs have been used for different

applications such as drug and vaccine delivery, cosmetic, and disease diagnostics. MN have various structural arrangements, shapes, forms, and materials along with different manufacturing methods which are further illustrated in this review paper.[3]. Figure show some current commercial MN devices. Donnelly et al. argued that 30% of the most recent scientific literature in “transdermal delivery technology” accounted

for microneedle studies. The MN drug delivery route can be impacted by external environments such as skin physiology, physiochemical properties, and ambient conditions. These include the relative humidity and temperature in the vicinity of the application area. Too sparse (low humidity) will retard the release of drugs to the skin layers, however too high humidity (such as sweat) can interfere in the drug release kinetics due to excess water and presence of other salts thereby changing the osmotic gradient for transdermal drug delivery. Furthermore, an excess of perspiration can prevent the adhesion of the microneedle patch to the skin further retarding elution of drugs through the skin. Similarly, very low or very high pH ranges around the skin region can result in lower permeability of the drug into the stratus corneum and beyond.

Excessive lipid films on the skin form a barrier layer to the stratus corneum and defatting this layer can assist in transdermal absorption. Raising the skin temperature can enhance permeation of drugs due to increase diffusivity and vasodilation of skin vessels. Dosage loading and metering accuracy of microneedles is an important aspect while administering sensitive drugs such as insulin and chemotherapeutics. Typically, microneedle patches require lower dosage as compared to oral ingestion for providing equivalent therapeutic efficacies as digestion and first-pass metabolism are circumvented. The pharmacokinetics of microneedles shows rapid uptake in the bloodstream that can be advantageous for treating localized ailments with much lower drug loading when compared to the oral route. Hollow microneedles serve as drug reservoirs and have the potential to carry higher dosages as compared to solid microneedles. Solid microneedles made from ceramic or metal materials can be coated using inkjet and spray atomization techniques with highly precise drug formulations. The quantity of drug loading for microneedle is highly dependent on the drug type, desired treatment plan, and patient profile. MNs offer a highly precise delivery mechanism due to control of manufacturing processes and drug loading procedures. However, the dissolution of the drug within the skin interfaces can depend on the skin physiology, ambient environmental conditions, and application mode to the skin surface.

Economic Value and Statistics

The economic value of microneedle patches into the current influenza vaccine market in United States was assessed by utilizing a susceptible-exposed-infectious-recovered (SEIR) transmission model. The results show that the incremental cost-effectiveness ratios (ICERs) with healthcare provider administration are less than or equal to $23k per quality-adjusted life years and a market share of 10 to 60%.[4] On the other hand, the ICERs are less than $1.4k for self-administration. The MN market rose from $5 billion in 2000 to $24 billion in 2013. By 2025, the market size of global TDD is estimated to expand to about $95 billion. According to a Future Market Insight recent report, by 2030, the MN drug delivery system market will approach $1.2 billion with a Compound Annual Growth Rate (CAGR) of 6.6%.

Advantages

A MN is considered to be one of the best ways for transdermal drug delivery due to the fact that drugs administered though this procedure bypass vital human organs such as the liver. Furthermore, it eliminates the pain associated with IV injection by providing a pain-free experience. As a result, it is considered the best choice for people who have needle phobia (trypanophobia). Microneedle transdermal drug delivery application does not require trained personnel thus facilitating ease of use. Furthermore, this reduces the

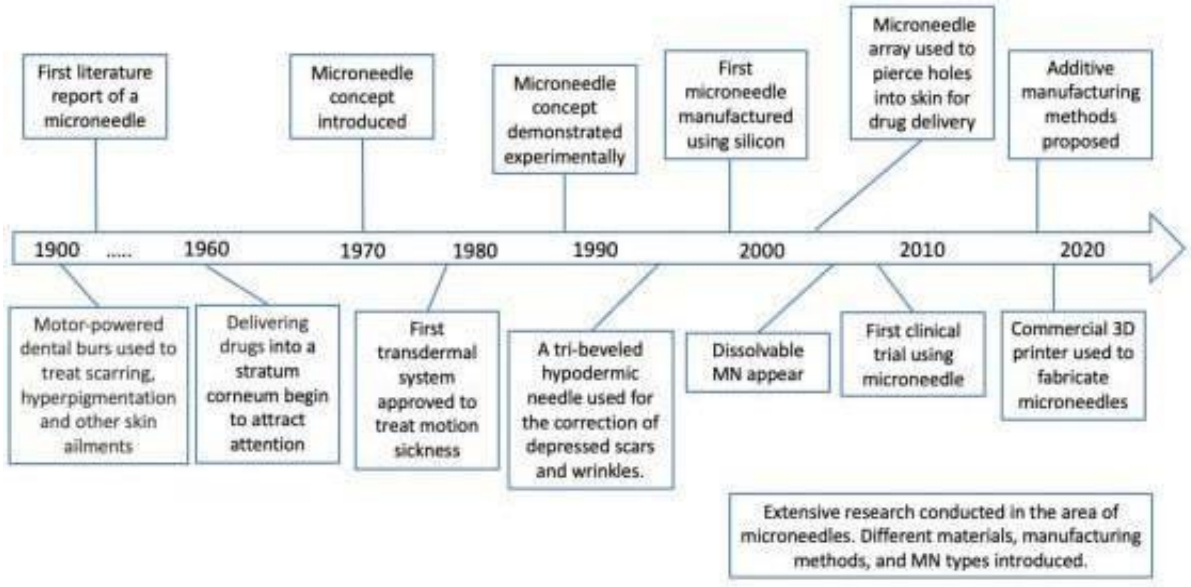
risk of transmitting infection into the body. The stratum corneum acts as a barrier to prevent molecules of any therapeutic agent to pass through the skin and reach the epidermis or dermis layer.[5] A microneedle has the ability to bypass the stratum corneum barrier and deliver the drug into the epidermis or the upper dermis layer without causing any pain [45]. Furthermore, the MN array is long enough to penetrate the stratum corneum and short enough to prevent damage to the dermis or reach nerve endings thus painless.

Disadvantages

The use of a microneedle for transdermal drug delivery introduces disadvantages such as extended application time, multiple patches within a given area, requirement of specific mechanical strength, and a good biocompatible material. Rzhevskiy et al. stated that Polymers 2021, 13, 2815 6 of 34 the difficulty in acquiring significant pharmacokinetic data via the MN patch route can impact the dosing parameters and could potentially result in adverse side effects.[6] Baraiya et al. argued that MN depth design should also be strongly considered while contemplating the differences in the thickness of the stratum corneum and other layers of the skin from a varied patient population. The effectiveness of drug delivery and permeation kinetics also depends on the MN device being inserted orthogonal to the skin surface. There is a possibility that the drug dose may escape, or the needles may struggle to penetrate the skin at non-conformal angles. Moreover, repetitive applications of microneedles may result in scarring of the skin surface. There may also be certain drawbacks with respect to the shapes and conformation of needle structures, thus affecting their efficacy. For hollow MNs, for example, their micropores can sometimes get blocked due to compressed tissue for certain skin types, thus affecting their delivery kinetics and penetrability. There
are however certain innate drawbacks of using TDD technologies in general that are not specific to just MNs. These include skin irritation, redness, pain, swelling, infection at the application site, etc...

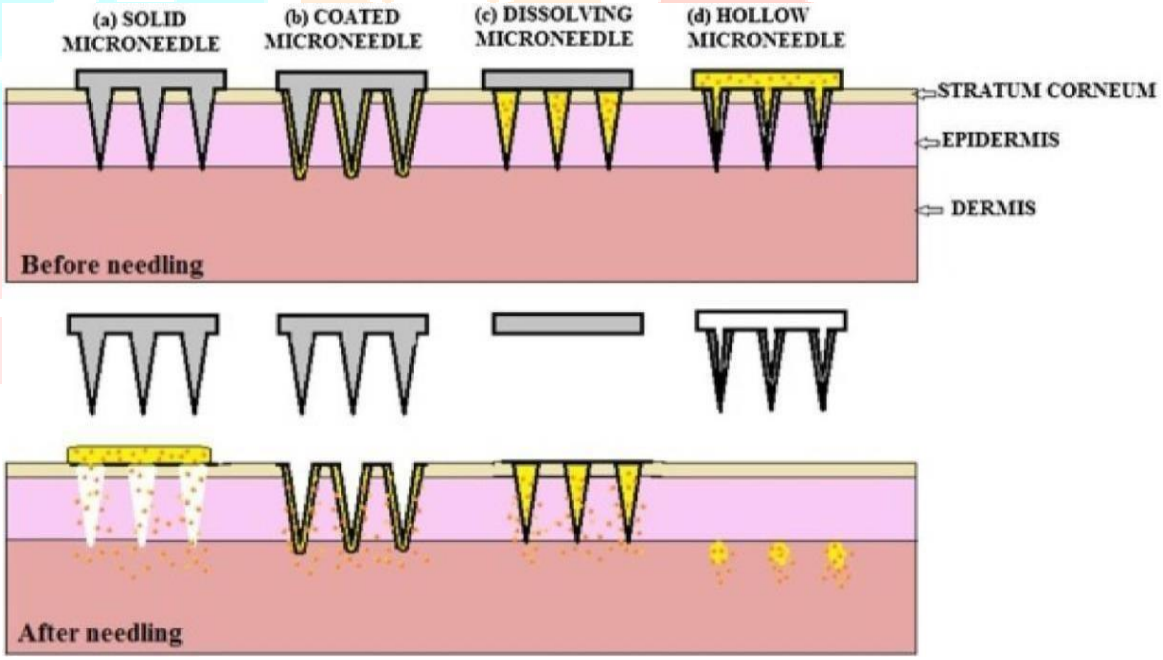
- Microneedle History

Over the years, microneedle concepts have evolved from the use of large needles to the current modern design of microneedles (Figure). In 1905, Dr. Ernst Kromayer, a German dermatologist, treated scarring, hyperpigmentation, and other skin ailments by using different sizes of motorpowered dental burs. The first piece of literature that mentions microneedle use was in 1921 by Chambers where he injected the needle into the egg's nucleus. In the 1960s, delivering drugs by injection into the stratum corneum began to attract attention. Subsequently, the microneedle concept was introduced in the 1970s; however, this concept was not demonstrated experimentally until the 1990s. [7] In 1979, the first transdermal system was approved for use to deliver scopolamine by applying a three-day patch to treat motion sickness. In 1994, a sub Cision surgery was performed by
Orentreich where he inserted a tri-beveled hypodermic needle into the skin to release fibrous strands. This surgery targeted the cutaneous defects located under the skin which were responsible for depressed scars and wrinkles. The first microneedle for transdermal delivery was proposed in 1998 and was fabricated from silicon wafers through ion etching and photolithography. The study described the use of microfabricated microneedles for the purpose of enhance drug delivery across the skin. This paper led to extensive research conducted in the microneedle domain. Different materials such as glass, ceramic, metal, and polymers were introduced to fabricate microneedles. In 2004, a microneedle array was used to pierce holes into the skin for transdermal drug delivery, which led to several fabrication methods and materials being explored for the purpose of TDD. Solid, coated, hollow, dissolvable, and hydrogel-forming MNs are all different types of MNs. Furthermore, various manufacturing methods such as laser ablation, photolithography, micro-injection molding, etc. These discoveries led to the first reports of a dissolvable microneedle being used for TDD in 2005. According to clinicalTrials.gov website, to date, 43 clinical trials have been completed using microneedles, with the first microneedle clinical trial completed in 2007 (accessed on 30 June 2021, 5 p.m.). Recently, additive manufacturing methods to fabricate MN molds were developed to provide low-cost solutions for micro-mold manufacturing. Reports showing the use of commercially available 3D printers to fabricate the MN master mold presented a new age for device fabrication and possibilities for custom built large-volume manufacturing of MNs.



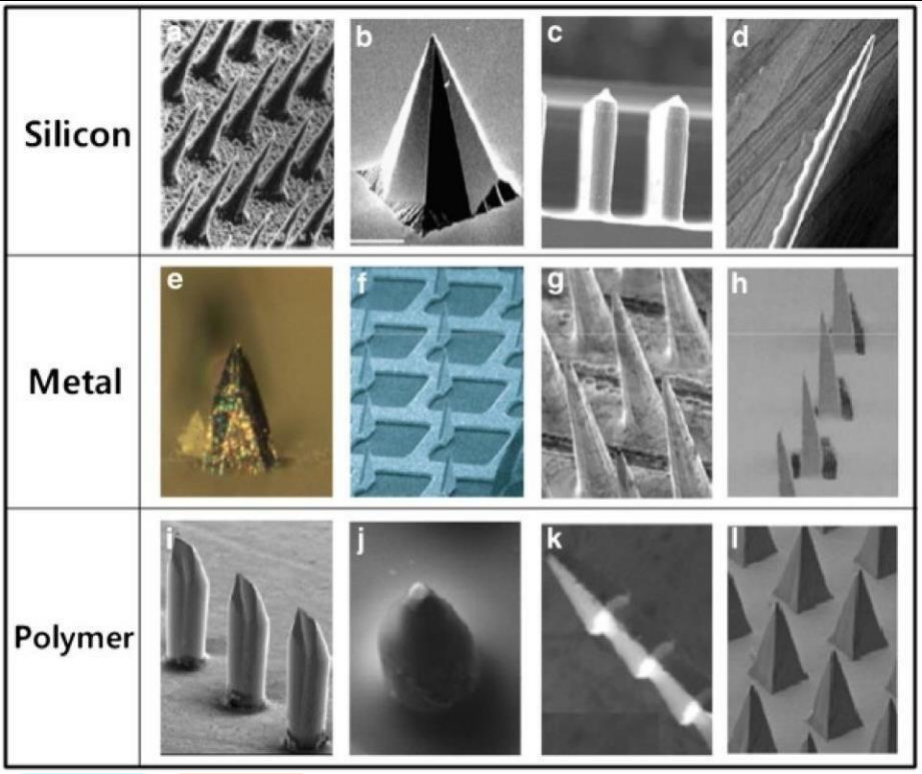
➢ Microneedle Types

A variety of materials such as silicon, stainless steel, sugar, and polymers have been used to fabricate solid, coated, hollow, or dissolvable microneedles (Figure).[8] Each type of the microneedle has their unique characteristics, advantages, disadvantages, applications, and material type.



Solid Microneedle

This type of microneedle structure is designed to penetrate the stratum corneum in order to enhance drug delivery to the dermis to improve the bioavailability and kinetic transport across the skin [9]. In comparison to intramuscular delivery, the solid mi- Polymers 2021, 13, 2815 8 of 34 croneedle is suitable for delivery of vaccines as it lasts longer and possesses a more robust antibodyresponse. Solid microneedles are easy to manufacture, have superior mechanical properties and sharper tips when compared to hollow microneedles. Moreover, the solid microneedle can be fabricated from different materials such as silicon, metals, and polymer

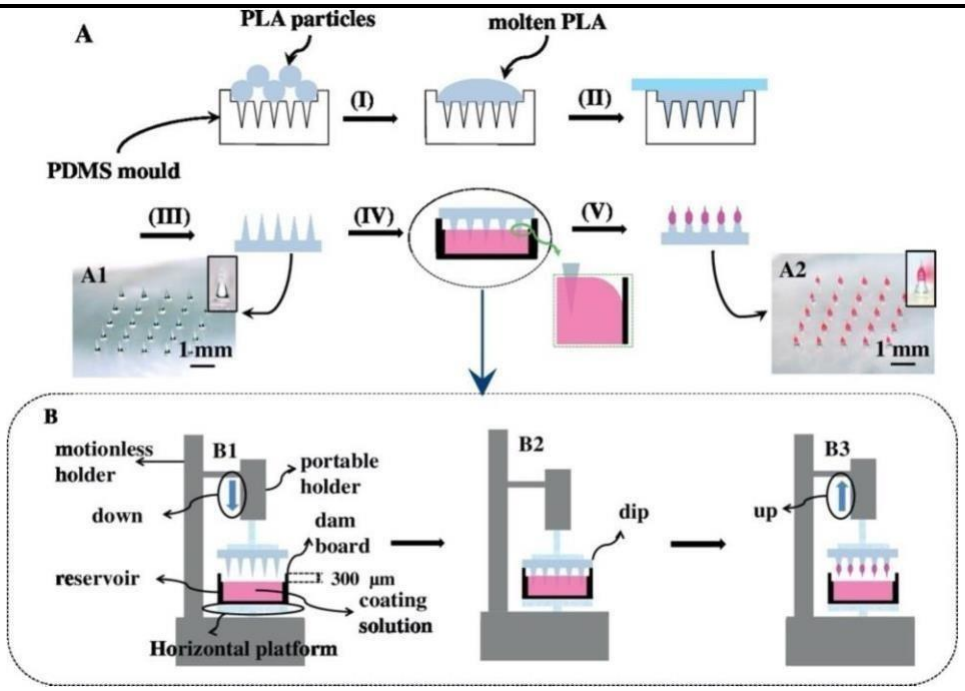


Hollow Microneedle

The hollow microneedle consists of a design with a hollow/empty core/chamber in which drug fluid is injected/stored (Figure) . Compared to the solid microneedle, the hollow microneedle can handle a large dose/amount of drug solution.[10] A hollow microneedle also has the ability to
deliver the drug into the viable epidermis or dermis which is suitable for high molecular weight compounds. Additionally, it controls the drug release over time which makes it suitable for use with liquid vaccine formulations. Unlike solid microneedles, which primarily elute drugs based on the osmotic gradient, hollow microneedles are an active drug delivery system forming a conduit for drug diffusion into the dermis based on a non-pressurized drug reservoir. Both material
formulation and fabrication parameters of hollow microneedles can be leveraged to enable tunable release kinetics.[15] Higher concentration drugs can result in burst release drug profiles, whereas matrix loaded drugs can enable a steady-state drug release lasting days to weeks depending on the application intent

Coated Microneedle

The coated microneedle is a solid-type MN coated with a drug solution (Figure). Typically, it carries a smaller amount of the drug depending on the thickness of the coating layer. The success of delivering drug using a coated MN depends on the ability to reliably coat a controlled drug layer onto MNs. A coated MN has the ability to deliver proteins and DNA in a minimally invasive manner. An advantage of a coated MN is rapid delivery of the drug to the skin; however, the remnant drug at the tip of the needle might infect other patients.[11] Finally, the results of the delivery of the vaccine using coated MN were similar to vaccines using intradermal and intramuscular routes

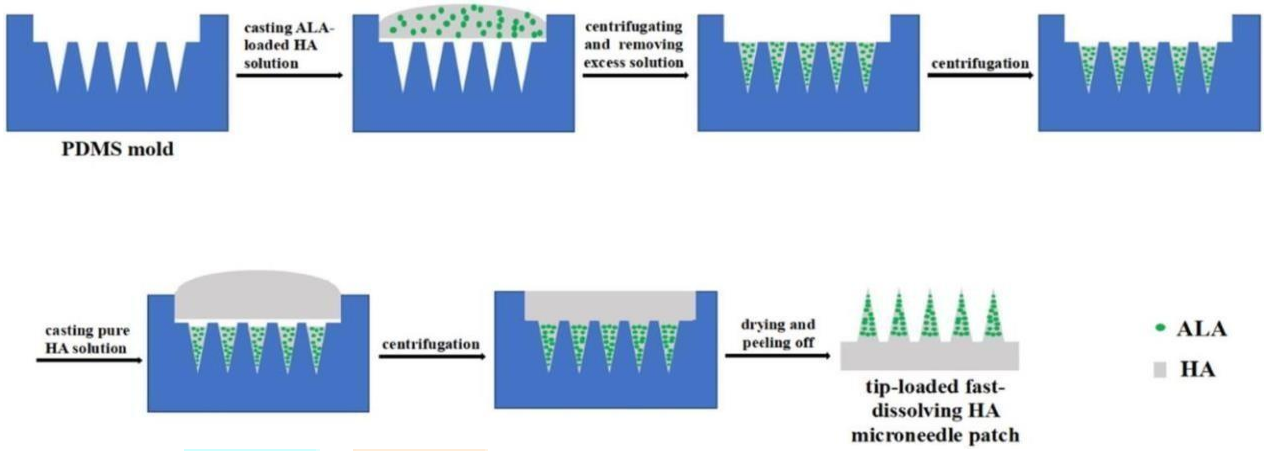


Overview: Microneedle Types

MN Type	Characteristics	Advantages	Disadvantages	Application	Material
Solid	Creates channels in the skin to allow drugs reach the lower skin layer. Adequate mechanical strength. Sharper tip.	Allows more drugs to pass into the skin. Easy to manufacture.	Damage to the skin and microincisions need to be closed to avoid infections.	Drug delivery Cosmetic	Silicon Metal Polymer
Hollow	Empty shape to be filled with the drug. Ability to control drug release over time.	Handles a large dose/amount of drug solution.	Weak needles. Requires intensive care in terms of needle design and insertion method. Might cause leakage and clogging.	Disease diagnosis	Silicon
Coated	Carries less amount of the drug due to the design. Ability to deliver the proteins and DNA in a minimally invasive manner.	Deliver the drug quickly to the skin.	Prone to infection	Drug delivery Vaccine delivery	Silicon
Dissolving	Facilitates rapid release of macromolecules.	Ease of administration for patients with one step application.	Requires technical expertise to manufacture. Takes time to dissolve.	Drug delivery Cosmetic Vaccine delivery	Polymer

Dissolving MN

The dissolvable MN first appeared in 2005 and is a promising technique based on its characteristics. These characteristics include facilitating the rapid release of macromolecules, and a one-step drug application which promulgates the ease of drug administration.[12] Due to improvement observed in applying dissolvable MNs following "poke-and-release", this approach is consider better than other approaches. The dissolvable MN tip can be loaded in a timely manner via a two-step casting method (Figure). Upon insertion of the dissolvable MN into the skin, the drug-load releases and diffuses easily by dissolution of the needle tip.



MN MATERIALS

MN Type	Advantages	Disadvantages	Manufacturing Method	MN Type Fit
Silicon	Flexible enough to manufacture desirable shapes and sizes.	Time-consuming fabrication. High cost. Possibility of skin fracture	Etching	Solid Hollow Coated
Metal	Good biocompatibility and mechanical properties. High fracture toughness Strong and hard to break.	High startup cost. Required post-fabrication process. May cause an allergic Reaction.	Laser ablation Etching Injection mold	Solid Hollow
Ceramic	Possesses chemical and compression resistance.	Low tension strength	Micromolding Lithography	Solid Hollow
Polymer	Excellent biocompatibility. Low toxicity. Low cost.	Low strength	Lithography injection molding Casting Laser ablation	Solid Hollow Coated Dissolving

MN Manufacturing Methods

Manufacturing Method	Description	Advantages	Disadvantages
Laser Ablation	Uses a focused optical light beam to fabricate a MN array on a substrate.	Less time consuming.	Might cause a crack or fatigue resistance on the substrate (MN array). High cost. Not suitable for large production.
Lithography	Transfers the master pattern of the geometric shapes onto the surface of a substrate.	Produces MN from a variety of material. Very precise geometries Smooth vertical sidewall.	Time consuming.
Micro-molding	Replicates a master mold and casts the mold with a solution.	Used for mass production. Cost effective.	Controls the depth of penetration. Drug load capacity. Mechanical behavior.
Injection molding	Injecting molten plastic materials into a mold.	Mass production.	High initial cost (machine equipment cost). Complex processes.
Additive manufacturing	Printing the MNs layer by layer.	Customizable Design.	Requires a high-quality 3D printer. Offer limited accuracy.

- MN Applications

MNs have attracted extensive interest by researchers, scientists, and industry participants. Several studies have demonstrated the potential and ability to administrate MN in different fields.[16] These include drug delivery, vaccine delivery, disease diagnostic, and cosmetics application.

Drug Delivery

The first application of MN for drug delivery was by using a solid silicon MN in 1998 . A dissolvable MN patch was used to deliver human growth hormone for transdermal delivery to hairless rat skin. A dissolvable caffeine loaded MN patch was able to control the weight of obese mice and work as an anti-obesity treatment plan. A coated MN patch was used to deliver salmon calcitonin. A solid microneedle was used to deliver a protein antigen (ovalbumin) into hairless guinea pig skin. Solid silicon and metal MNs were used for the delivery of calcian, BSA, and insulin. Furthermore, MNs have been used for transdermal permeation for several drugs such as ibuprofen, ketoprofen, and paracetamol.[14] Other drugs administrated via microneedles include L-Ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine, hydrochloride, ketoprofen, and glycerol. Despite the fact that most studies used microneedle array for drug delivery into mice, pig, human skin, there were other studies which successfully demonstrated microneedle injection into chicken thigh, and brain tissue.

Vaccine Delivery

A dissolvable MN is a common type of MN used for vaccine delivery purposes. The dissolvable MNs were used to replace hypodermic injection needles that were typically used to administer vaccines. Unlike other types of MN, the dissolvable MNs are biocompatible, robust, scalable, and do not generate biohazardous waste. Dissolvable MNs were used to deliver vaccines for malaria, diphtheria, influenza, Hepatitis B, HIV, and polio. Even though dissolvable MNs are most frequently used for vaccine delivery, coated MNs arrays have also been successfully used for vaccination purposes.[17] A study used a simple, safe, and compliant vaccination method to improve the immune system for pigs by administering bacillus Calmette– Guérin (BCG) vaccine with a coated MN.

Disease Diagnosis

Disease diagnosis and therapeutic efficacy can be monitored via several established bioassays that sample body fluids to assess and monitor health conditions.[13] The current methods induce pain, require specialized techniques, tailored equipment, and professional medical personnel. However, microneedle technology offers bioassays solution with painless experience and simple implementation. A hollow MN has the ability to diagnose several diseases such as cancer, diabetes, and Alzheimer's disease. Patient health

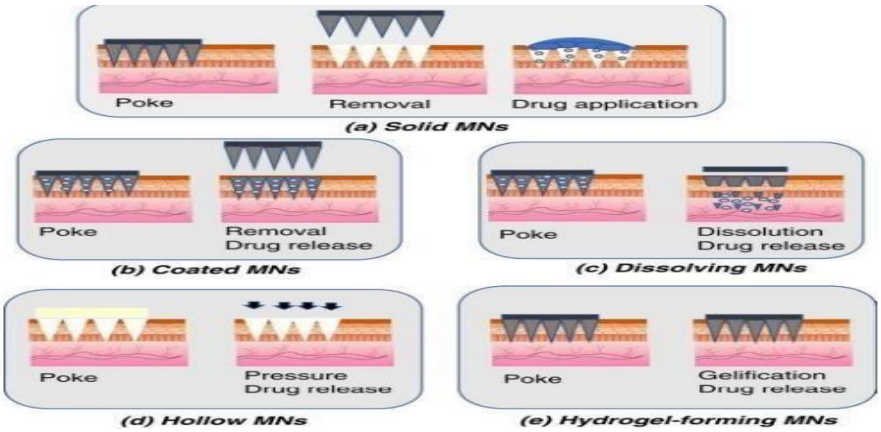
monitoring is another application of the MNs. For example, a hollow glass MN may be used to investigate the glucose level.

Cosmetic Application

MNs have widely been used in cosmetic applications such as skin treatment and hair growth. Kim et al. developed a hyaluronic acid-based dissolvable MN patch for the intradermal delivery of ascorbic acid and retinyl retinoate. Kumar et al. showed an enhancement of local delivery of eflornithine (used to reduce facial hirsutism) in vitro and in vivo using a solid MN. Further, MN technology was able to treat two patients suffering from alopecia areata disease.[18] These patients experienced hair growth after treatment. Effective clinical trials have been conducted in atrophic facial scarring, atrophic acne scars, and hypertrophic burn scars using a MN.[20] Microneedles are considered as an effective treatment for cosmetic applications related to aging, skin lesions, vulgaris, and wrinkles. With an increasing demand of cosmetic products, microneedles (patches and rollers) have a high potential in the future.

- Microneedles as a revolutionary approach in the management of pain

The conventional treatment options available for the management of pain results in side effects and poor patient compliance on long term usage. Recent advances in drug delivery technology radically changed the way of detection, treatment, and prevention of disease. Therefore, to overcome demerits of the conventional treatments and to provide patient compliance for their long-term usage in the management of pain and inflammation, MNs proved as a revolutionary approach. It is an
amalgamation of hypodermic injections and transdermal patches. These are simple, painless, and safest drug delivery system that involves the rapid onset of action, accurate drug dosing, avoiding first-pass metabolism, and high drug bioavailability. These advantages of MNs over other drug delivery methods lead to it as a rapidly growing technology. They permeate the superficial layers of the skin and transfer medications directly to the skin's epidermis and deeper ermal layer, which is not achievable with traditional topical patches or semi-solid gel or cream preparations due to the stratum corneum. The chronic pain- associated diseases require site specific delivery of therapeutics and MNs provide sustained and site-specific drug delivery by maintaining a consistent plasma medication concentration for prolonged duration. [19]It lowers the frequency of dose regimens in chronic conditions. This led to the improvement in the physiological and pharmacological responses. In a study, Amodwala et al. fabricated meloxicam loaded MNs for the site-specific delivery of meloxicam. The fabricated MNs could penetrate the stratum corneum and effectively distribute the meloxicam at the targeted site. Approximately 63.37 % of the meloxicam was delivered to the targeted site of action through MNs. MNs possess higher bioavailability because of the quick onset of action that will help in providing relief from pain to the patients. Its self-administration feasibility makes it a better choice of treatment. As a result, when treating chronic conditions that require treatment for a longer time, the risk of toxicity is quite low with MNs. The conventional cream formulation of lidocaine requires a minim application duration of 60 min-2 h in order to give an adequate analgesic effect for an average duration of action of 30–60 min. This was overcome by fabricating its coated MNs which was applied for 1–5 min only to provide the same analgesic effect. The various kinds of MNs have evolved for the management of pain are solid MNs, coated MNs, dissolving MNs, hollow MNs, and hydrogel forming MNs. Each type has its own set of characteristics, some are employed just to generate pores in the stratum corneum, some are precoated with the medication solution, some are dissolvable, and some are prefilled with the drug solution.



(a) Solid MNs (Poke and patch); (b) Coated MNs (Coat and Poke); (c) Dissolving MNs (Poke and dissolve); (d) Hollow MNs (Poke and flow); (e) Hydrogel-forming MNs.

- Conclusion

This review article extensively describes the type of microneedle, fabrication material, detailed casting methods and techniques, and its applications. Microneedles have been fabricated using different materials, like silicon, metals, polymers, and ceramics, by several fabrication methods, i.e., lithography, wet and dry etching, laser cutting and micro molding. The practical use of microneedles has been acknowledged and gained widespread attention. Optimization of sharpness, length, insertion force and velocity, and other parameters have allowed reliable microneedle insertion into the skin. Nowadays, MNs are the leading novel technology for several fields of drug delivery, such as intradermal, ocular and intracellular drug delivery. However, the transdermal route is still the leading application area for MNs, especially vaccine-based delivery. MNs technology creates a new horizon in cancer therapy through efficient drug delivery of anticancer vaccines and drugs. Various chemotherapeutic agents, genes and proteins can be efficiently delivered through MN-based devices. Patients and clinical workers are highly inclined to prefer microneedle-based delivery over hypodermic injections according to surveys. Human subjects report little or no pain associated with most microneedle designs. After microneedle treatment, the skin often shows mild, transient erythema, but there is currently no evidence of increased infection risk at the treatment site. Big pharmaceutical giants are currently working on the developments and commercialization of microneedle-based drug delivery systems; this technology is rated in the top 10 recent technologies.
Patients, healthcare providers and companies have established interest in the technology.
Microneedles are poised to make an expanded impact on clinical medicine over the coming years.

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