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A COMPREHENSIVE VIEW ON MICRONEEDLE DRUG DELIVERY AND ITS UTILIZATION IN THE FIELD OF PHARMACY

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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.

KEYWORDS: Micro needle drug delivery, Nanotechnology, cancer applications.

INTRODUCTION

Microneedles are a drug delivery system that uses micrometer-sized needles to create microscopic pores in the skin, allowing drugs to be delivered directly to the epidermis or dermis. Microneedles can be made from a variety of materials, including silicon, glass, metals, ceramics, polymers, and sugars. The type of microneedle and the material it's made from determines the fabrication method. Microneedles are micron-scale needles that generally range from 25 to 2500 µm in length, 20 to 250 µm in width, and 1 to 25 µm in tip diameter . which can be arranged as individual needles, a row of needles, or needle array patches depending on the applications.

Arthritis is one of the important diseases affecting contemporary human health, and generally refers to inflammatory diseases that occur in human joints and surrounding tissues.[1] In particular, transdermal drug delivery to the joints involves not only the skin barrier but also the joint capsule barrier, making it challenging to transfer drugs into the joint cavity efficiently by typical transdermal routes.[2] It has been estimated that 10 million Britons and 52.5 million Americans were diagnosed with arthritis, according to statistics published in 2020. The prevalence of arthritis over the age of 20 years was 24.7%, with OA accounting for 9.7%, RA for 4.2%, other arthritis for 2.8%, and unknown type for 8.0%.[3]

Specifically, they are a needle-like drug delivery system with a needle length of 25–1000 µm and a pointer size in the micron range. MNs penetrate the stratum corneum (SC) to form microchannels that cross the barrier layer and carry drugs to the upper dermis and distribute them to the body circulation to produce systemic pharmacological effects. The length of the MNs can be increased to promote vertical diffusion of the drug, thus allowing the drug to accumulate locally, resulting in enhanced local pharmacological effects.[4] A US patent filed by Russell Frederick Ross in 2010 described a MN transdermal device for the delivery of RA therapeutic drugs.[5]

Syringes and hypodermic needles have been used to deliver drugs to patients for more than 160 years and are still the most routine and effective means.[6] The skin is the largest organ, and is a strong biological barrier, preventing infectious diseases and harmful substances from entering the body. However, the skin is also a major barrier to the effective delivery of drugs to lesions via percutaneous administration, while meanwhile also being susceptible to pain.[7] The latter is composed primarily of cholesterol, triglycerides, and ceramides, forming a dense structure with lipophilic properties (1.4 g/cm3). Due to the dense structure, it is almost impossible for drugs with molecular weight >500 Da and Log P in the 1–3 range to penetrate the cuticle.[8]

The MN delivery system, which consists of an array of submillimetre-sized needles (up to 1500 μm in length) attached to a base support, has been shown to be able to penetrate into the viable epidermis of the skin, bypassing the stratum corneum (SC), the outermost layer of the skin. In this way, the delivery of pharmaceutical ingredients becomes possible in a pain-free manner, as the MN delivery system avoids interfering with the dermal layer, which is where all nerve fibres and blood vessels are mainly located. The system has been proven as a valuable technique in delivering drug molecules with higher masses (over 500 Da) and various polarities. The therapeutic ingredients include small molecules; biomacromolecules (proteins, hormones, peptides); vaccines for SARS, MERS, and COVID-19; and genes.[9] it took some time for the benefits of microneedles to be widely recognised. It was not until 1998 that a report was released that looked at the potential use of microneedles for vaccines.[10] The shortcomings associated with the MN system, however, should be addressed in the early stages of productdevelopmen.[11]

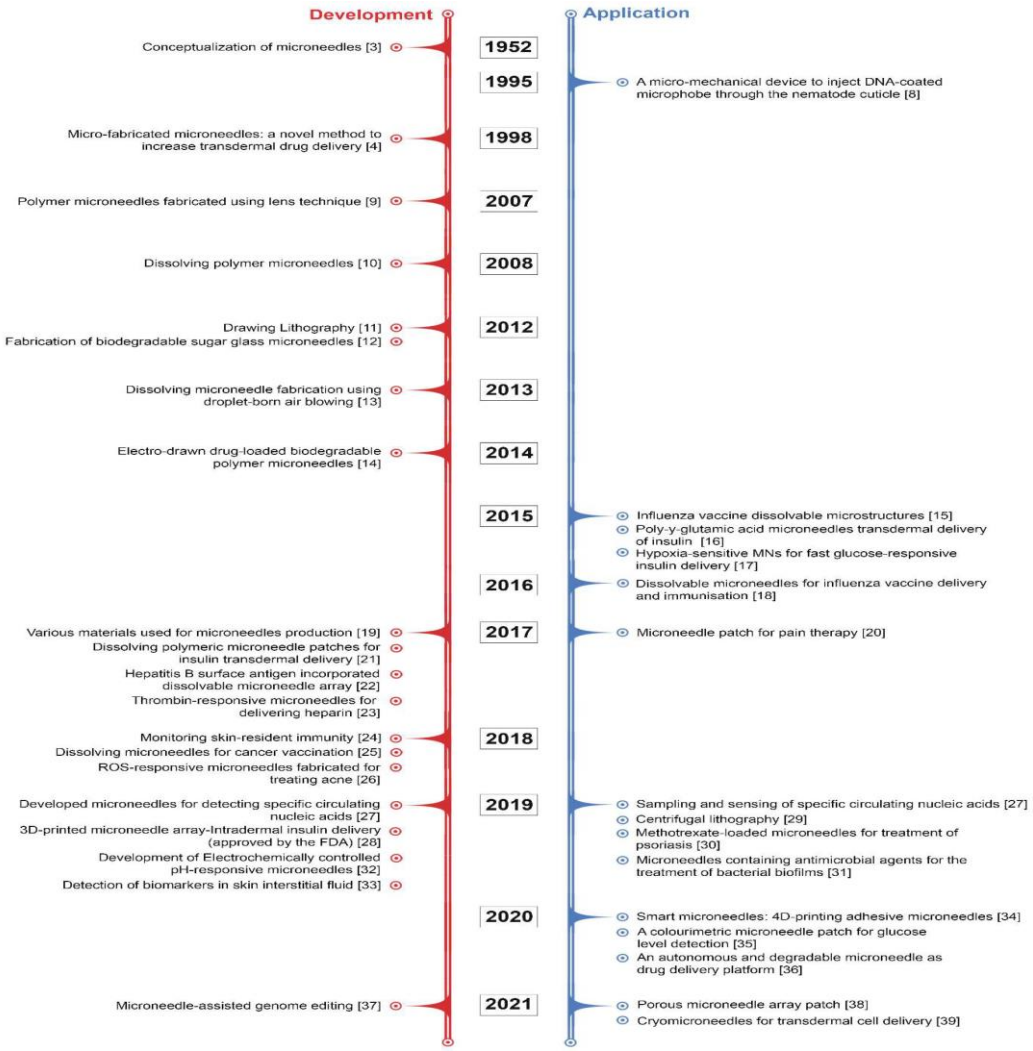

Figure 1. Some of the pioneering and key developments in MN research.

Microneedles drug delivery system

Microneedles (MNs) are a promising treatment for arthritis because they can deliver drugs transdermally without causing pain and with reduced risk of infection.

Painless MNs are usually less than 800 micrometers in size and don't cause pain.

Reduced risk of infection The risk of microorganisms entering the body through the needle tip is low.

Improved bioavailability MNs bypass the first-pass effect, which can lead to improved bioavailability and reduced systemic toxicity.

Sustained release MNs can provide a sustained and localized release of drugs, which can reduce the frequency of administration.

Improved compliance MNs can improve patient compliance, especially for those who are afraid of long metal needles.

Advantages and Disadvantages Of microneedles as a drug delivery system

Advantages

Painless: Microneedles can deliver drugs without causing pain.

Better bioavailability: Microneedles can improve bioavailability.
Avoids gastric irritation: Microneedles can avoid gastric irritation.
Drug stability: Microneedles can improve drug stability, eliminating the need for cold-chain storage and transportation.
Potential for large molecules: Microneedles can deliver large molecules like insulin and nucleic acids.
Potential for vaccines: Microneedles have potential for vaccine delivery.

Disadvantages
Limited dose: Coated microneedles can only deliver a small dose of medicine.
Cost: Microneedles can be expensive to make and store.
Skin irritation: Microneedles can cause skin irritation or allergic reactions in sensitive skin.
Skin infections: Holes left by microneedles can cause skin infections.
Skin penetration: Skin variables like thickness and hydration can affect how deep microneedles penetrate the skin.
Eregulatory guidance and standardized quality control systems.

Types of MNs
The development of a safe, fast, effective, and convenient drug delivery method is the main purpose of MNs research. According to different drug delivery methods, MNs can be divided into solid MNS.
1.Solid MNs
Solid MNs are made of silicon or metal without carrying drugs, which can be used for skin pretreatment. The MNs are removed after the punctured epidermis forms microchannels, and the drug preparation is applied to the puncture site and then diffuses into the body through the channels.[12]

In addition, silicon or metal materials have good mechanical force, but not enough bending force, so there will be a high risk of “breaking” during insertion, resulting in residual needle bodies being left behind.

2. Coated MNs
However, the amount of drug-coated on the MNs is usually small, and the application scope is limited to just those cases where the drug effect is strong and the amount of drug required is small, such as vaccines.[13] Methods for enhancing the stability of the drug coating and reducing the loss rate of the drug under the premise of ensuring the efficient release of the drug require more research in the future. In addition, it causes waste, as the used needles need to be discarded.

3. Hollow MNs
However, the manufacturing process of hollow MNs is precise and the manufacturing cost is high. The disadvantage is that the pinhole is easily blocked by the skin tissue, and the angle of the needle wall is not designed properly, which can lead to the drug spilling out of the skin during injection; furthermore, the physical strength of the needle is low, and it can easily break and remain in the substance. Figure: Among the various MN types, hollow MNs have the largest amount of one-time infusion and the most accurate dosage, and the speed can be freely adjusted (similar to injection). However, the manufacturing process of hollow MNs is precise and the manufacturing cost is high.

4. Soluble or Degradable MNs
Soluble or degradable MNs are a kind of MN that is being studied a lot at present. The MN body can be made of biodegradable or water-soluble polymers (polylactic acid, polycarbonate, polyglycolic acid, polylactide ethyl lactide, etc.). After entering the skin, the needle body is degraded or dissolved within minutes or hours, whereby the needle body separates from the substrate and releases the internal drug after degradation or dissolution.[14]

5. Swellable MNs
Swellable MNs are a relatively new kind of MN, and are prepared from a cross-linked hydrogel and can expand but not dissolve after absorbing interstitial fluid (IF). This kind of hydrogel MNs can be loaded in two ways: one is to pre-position the drug at the base of the MNs, and after piercing into the skin, the hydrogel absorbs the intercellular fluid to expand, forming a gel channel.[15] After penetrating the skin, the fluid penetrates, the needle swells, and the drug is released 1addition the application of swellable MNs is not limited to drug delivery, but can also be used to extract IF for subsequent analysis.[16]

6. Porous MNs
Porous MNs have recently been researched owing to their distinctive and unique characteristics, where porous structures inside MNs with continuous nano- or micro-sized pores can transport drugs or biofluids by capillary action.[17] As a result, porous MNs have received relatively little attention in the past due to their complex manufacturing process and the ease with which they fracture. In recent years, porous MNs have shown promise for drug/vaccine delivery and ISF extraction/biosensing. In addition, as low-invasive partial breaking of the stratum corneum and the wholly interconnected micropores, porous MNs have been successfully applied for efficient drug delivery (penetration) and analysis of ISF (extraction).[18]

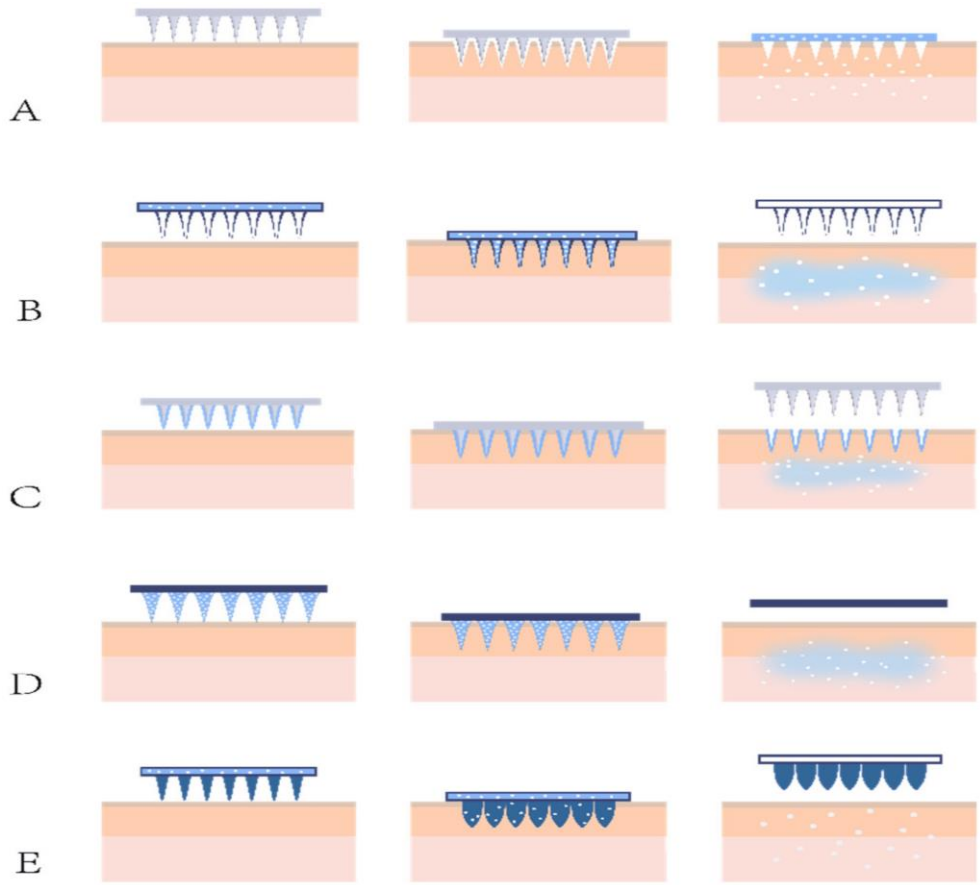

Figure 2: Drug delivery mechanisms for various types of MNs. (A) Solid MNs: Used for skin pretreatment, forms microchannels and is then removed, followed by the use of a topical formulation containing the drug for delivery of the drug through the microchannels, (B) Hollow MNs: After insertion into the skin, the drug loaded in the internal cavity of the MNs flows out, (C) Coated MNs: After insertion into the skin, the drug film wrapped in the outer layer of the MNs is released into the body, (D) Dissolving MNs: After insertion into the skin, the MN matrix dissolves into the body along with the drug encapsulated in it, (E) Hydrogel-forming MNs: After insertion into the skin, the MNs expand to form microchannels inside but does not dissolve, and the drug enters the body through the microchannels.

Parameters Affecting MN Insertion

The capability of MN patches to adequately puncture the skin is a vital requirement. When addressing this matter, the skin's characteristics, which might vary across the body and vary from person to person, should also be taken into account. an approach of "one-size-fits-all" cannot be envisaged in any design and development stages for any MN application. Infiltration and active delivery performance of MNs are strongly related to the geometry of individual MNs and the array, MN materials, the MN management method, and the characteristics of skin tissue[19] Depending on the target medicines and applications, the microneedle mechanical strength, insertion depth, and drug release profile could be finely tuned by modifying the microneedle shape and composition.

The geometry: The geometry of MNs is a parameter that should be taken into consideration early on when developing MNs for clinical applications. Superior capacity to insert into the skin was observed for the sharper edges of the triangular and square MNs compared to the hexagonal MNs. In a recent study, cone-shaped MNs were discovered to possess the ideal geometry for the delivery of ovalbumin and transcutaneous immunisation, with both greater needle insertion and a fast dismantling time for a more potent immune response obtained.[20]

Tip diameter and Sharpness: Tip diameter is another parameter for MN insertion. Relatively blunt MNs (tip diameters of 60–160 µm) require a relatively high insertion force (0.08–3.04 N) for controlled applications of MNs and are linearly reliant on the tip frontal area.[21] A 25-microneedle array with a tip radius of <100 nm requires an insertion force of 10 mN per microneedle for effective penetration into the skin.[22]

Length: Because the thickness of the SC and other skin layers differs across individuals, the particle insertion depth may also vary. The transport capability of the skin, once a MN patch has been applied, will depend on the perforation depth of the tissue. However, if rapid delivery to the bloodstream is the goal, it may be

preferable to create pores that reach the dermis, where capillaries are located. This may be one reason for assorted microneedle lengths that have been reported to date. In addition to the shorter microneedles, there have been many studies that used long microneedles (up to 1000 μm long) to increase insulin permeability into the skin.

Interspace (centre-to-centre spacing): The skin is a topographically diverse surface capable of withstanding significant deformations prior to penetration. A significant number of distinct punctures must be generated when there is a high-density array of microneedles (e.g., more than 500/cm2). This can result in increased feeling for the patient and may require the use of a larger/stronger device for certain applications. Needles with increasing width, length, and density can result in larger, longer, and more crowded holes, through which a higher amount of medication may diffuse. However, more tightly placed needles may cause the "bed-of-nails" effect too.[23]

Biocompatibility, Biodegradability, and Stability

One of the safety aspects of MN systems in clinical use is biocompatibility. To ensure that MN products are acceptable for human exposure, several tests are required to evaluate their biocompatibility based on contact periods of less than 24 h, between 24 h and 30 h, and more than 30 h.[24] Dissolvable MNs are very susceptible to the surrounding humidity; therefore, the storage environment should be dry and cool for prolonged stability and extended shelf-life.

Loading Capacity and Dosage Accuracy

Loading capacity: A coated microneedle device can only deliver a bolus dose of around 1 mg of medicine. Although hollow microneedles allow for continuous infusion or "as-needed/on-demand" dosing, central exits may be obstructed by compressed skin tissue after microneedle insertion. This can make it difficult to administer large dosages, and much of the dose can be lost on the skin's surface. As a result, the time of application and the inability to monitor dose delivery have caused reluctance to use this technology for certain clinical applications.

These advantages, however, might be lost if just a tiny fraction of the administered dosage reaches the skin. While this is not an insurmountable obstacle to this technology, vaccines, in particular, require a threshold dosage to induce immunity, which might be more difficult to achieve when depending on passive diffusion.

Dosage accuracy: The dosage accuracy of MN delivery systems in continuous drug delivery is an issue that requires close attention. Several methods using separable microneedles have been proposed for minimising the patch-wearing time and quickly removing the formulation from the MNs.[25] Encapsulating drugs in the matrices of MNs is possible if dissolvable microneedles are fabricated primarily from hydrophilic, biocompatible, and biodegradable materials, and if the cargo can be discharged entirely within the skin's interstitial fluid without leading to unwanted debris. Relatively large doses and the controlled release (slow or fast delivery) of various drugs can be transferred without issues of leakage.

Skin Irritation and Recovery

ogenic nature of the skin makes it a highly responsive organ towards the MN delivery of any therapeutic agent. Mild and temporary erythema may develop as a side effect depending on the size, substance, and type of the given medication. Skin irritation, sensitisation, and immune response must also be evaluated as part of the safety assessments of MN products during clinical trials. On the other hand, great immune responsiveness of the skin may present an opportunity for MN-based vaccine delivery if other obstacles have been addressed properly, as discussed.

Cost of Microneedle Fabrication

Current microneedle manufacturing processes need to be improved to reach large-scale production in order to completely transfer microchip-based microneedles into therapeutic applications. Until now, extensive economic evaluations of the technology have not yet been quantified thoroughly, but it is not difficult to predict that, as with every new technology, the clinical use of MNs can be comparatively expensive due to the complex fabrication and storage procedures and the slow and long approval process. (range USD 1.24–USD 2.06), respectively, assuming that the MN vaccine method is more heat-stable and requires cost-effective cool chains. The total costs of the vaccination program were estimated to be USD 1.5 million for MN-based administration compared with USD 2.5 million for SC administration. The authors commented that the cost-effectiveness of MN patches depends on numerous factors, including approval rates and the effectiveness of the MN patches in relation to the traditional subcutaneous vaccine delivery method.[26] The choice of materials is also of utmost importance and should be compatible with the laden cargo for optimal insertion and delivery performance without any deleterious effects on the bioactivity and stability/viability of the therapeutic agents. For optimisation, an ideal production method should aid easy, rapid, and cost-effective modifications in the material and geometry parameters.

Sterilisation of the Microneedle Patches

MN patch sterilisation is another challenge that should be taken into account early on when MN-based products are aimed for commercial application. If sterilisation is necessary, then the method of choice will be critical, because the most widely used methods, such as moist heat, gamma or microwave radiation, and ethylene oxide may deleteriously affect any cargoes with sensitive ingredients, including biomolecules, vaccines, peptides, and/or even the microneedles themselves.[27] The effects

of various sterilisation methods, such as moist and dry heat sterilisation and gamma radiation, on dissolving and hydrogel-forming MNs have been studied, with ibuprofen and ovalbumin as model drugs.[28] It was found that no measurable bioburden was detected, and levels of endotoxin were under the FDA limits if aseptic preparation was followed. However, moist and dry heat sterilisation damaged all formulations, whereas the gamma irradiation at a sterility assurance level (SAL) of 10−6 (according to the British Pharmacopeia) can be used for sterilisation without causing structural damages or affecting delivery capabilities of hydrogel-forming MNs. The radiation, however, destroyed ovalbumin and changed the appearance of ibuprofen. Alternative methods for delicate MNs have been proposed.[29] It is clear that the information available in the literature is rather limited, and therefore, the sterilisation of MN-based products requires extensive research before going into commercial production and approval; this presents one of the most important challenges in MN-based delivery systems. In particular, endpoint sterilization for MN products requires a great deal of attention, as MN manufacturing under an aseptic condition could be both complicated and costly.

Regulation of the Microneedle Patches

The quality of submissions received from combination products employing microneedles has been a source of concern for the US FDA, particularly in the areas of stability testing, content consistency, risk analysis, sterility validation, and manufacturing. The number of MN-based medicinal products for therapeutic applications is rising exponentially. The FDA has stated "Regulation of combination products must take into account the safety and effectiveness questions associated with each constituent and the product as a whole".[30] The current strategy of product-specific approval (rather than specific MN-systems) for the licensing of microneedle products adopted by the regulatory bodies causes great delays in approval, thereby restricting the commercialisation of MNs. To promote the commercialisation of MN products, the cGMP and quality control should be merged, and licencing regulations must be defined clearly, covering the shape, formulation, sterilisation, and packaging.

In addition, robust guidance is required to fully classify MN-based products; nevertheless, it has been proposed that this would most likely come within the medical device category for monitoring/diagnostic applications, and as a "combination product" (drug and device) or "drug product" for the delivery of drugs or vaccines.[31] Once this distinction is made, it may be possible to adapt existing quality control procedures for MNs. The current standard quality control methods may not be completely suitable to MN products due to the inherent differences between transdermal patches and hypodermic needles. If all remaining concerns can be suitably addressed to meet the needs of both regulators and patients, the goal of bringing MN-based products to the transdermal market will soon become a reality. In 2020, the first new drug application for a pharmaceutical microneedle patch, Qtrypta, was submitted to the Food and Drug Administration (FDA) by Zosano Pharma. The patch is a titanium microneedle with a coated zolmitriptan for At the beginning of the 20th century, lipophilic acute migraine treatment.

Microneedle Production

The first solid MNs were made of silicon[32], as industrial high-precision microelectronics tools and silicone flexibility enabled the production of MNs. However, their main disadvantage is the breakage of the silicon MN due to their brittle nature. Nowadays, MNs come in a variety of shapes and sizes, as well as materials (Table 1), including stainless steel[33.34], Metal MNs have sufficient mechanical strength to penetrate the skin, but their disadvantage is that they generate potential biological waste.[35,36] The manufacturing methods for solid or hollow MNs, described in the following sections, include MEMS, lithography methods, laser cutting, laser ablation, metal electroplating, isotropic and anisotropic etching.[37]

Microneedle Production Methods

Microelectromechanical Systems (MEMS)

Solid and hollow MNs, as well as molds for dissolving MNs, have been manufactured directly from a suitable material substrate using MEMS methods.[38] The production involves a precisely controlled three-step process: deposition, patterning, and etching of materials.[39,40]

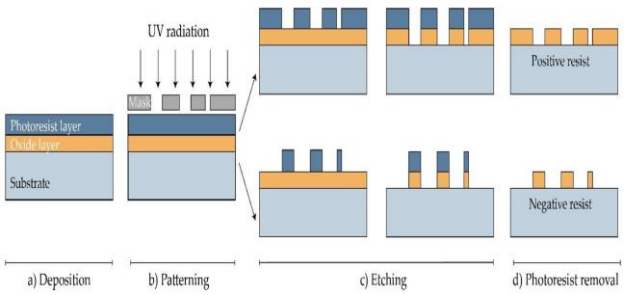

Figure 3:

Manufacturing of MNs using photolithography.[117] (a) Deposition: As a substrate, Si wafer is exposed to steam or humidified to produce the wafer with an oxide coating. Then, the photoresistive material is spin-coated onto a substrate. (b) Patterning: Mask guided UV radiation is exposed to the photoresistive material. (c) Etching: soluble resist material is removed and SiO2 film etched. (d) Photoresist removal: in this step, the photoresist layer is removed.

In the first step, a film with a thickness between a few nanometers and 100 μm is formed on a substrate by a chemical (CVD) or physical vapor deposition (PVD)[41] Figure 1. Drug delivery mechanisms for various types of MNs. (A) Solid MNs: Used for skin pretreatment, forms microchannels and is then removed, followed by the use

of a topical formulation containing the drug for delivery of the drug through the microchannels, (B) Hollow MNs: After insertion into the skin, the drug loaded in the internal cavity of the MNs flows out, (C) Coated MNs: After insertion into the skin, the drug film wrapped in the outer layer of the MNs is released into the body, (D) Dissolving MNs: After insertion into the skin, the MN matrix dissolves into the body along with the drug encapsulated in it, (E) Hydrogel-forming MNs: After insertion into the skin, the MNs expand to form microchannels inside but does not dissolve, and the drug enters the body through the microchannels.

Then, a two-dimensional master pattern of the desired material is transferred from the original photomask to the photosensitive-coated substrate during the second phase of the process, called patterning. In most cases, a silicon wafer is used as a substrate, and the transferring process is made using a radiation source with one of the lithography process (photolithography[51], ion beam lithography, or X-ray lithography.[42]

Laser Cutting

Metal MNs can be manufactured by 3D laser cutting.[43,44,45,46,47,48], laser ablation.[49,50,1], and electroplating or electroless plating of metal onto positive or negative MN molds.[52]

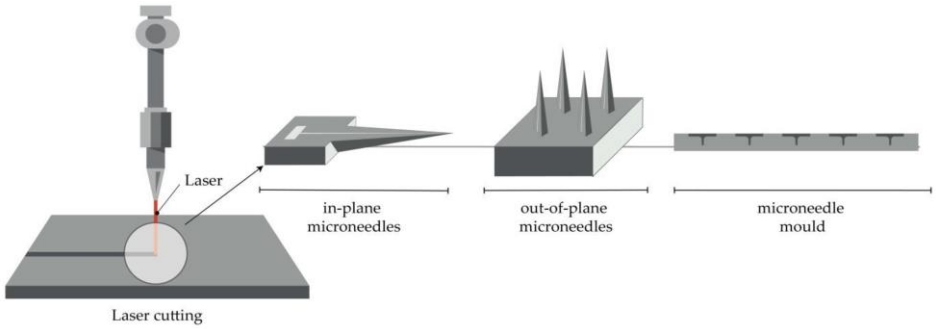

Figure 4: Principle of manufacturing of MNs (in-plane and out-of-plane) and MN molds by the laser cutting.

Arrays of solid MNs are produced by cutting stainless steel or titanium sheets in the shape of MNs with an infrared laser (Figure 4). The desired shape, geometry, and dimensions of MNs are created using some of the computer-aided design (CAD) software. The laser beam follows the predetermined shape of the needle, then MNs are cleaned in hot water and bent at 90 degrees, vertically from the plane of the base. In order to deburr, reduce the thickness of MNs and sharpen the tips, MNs are subsequently electropolished, washed, and dried with compressed air. This manufacturing method can be used to produce a single row of MNs of different geometries, as well as two-dimensional rows of metallic MNs.[53,54,55,56,57,58]

Laser Ablation

This method is a top-down method for processing materials, including metals. Light pulses give the bulge of the desired shape on a metal plate, thus forming solid metal arrays[59] In 2020, Evens et al. introduced a novel method for the production of solid polymer MNs using laser-ablated steel molds. This mold was also employed in the injection molding process for the production of the polymer MNs. In this way, a height of MNs can be varied, and a sharp tip radii can be obtained using this low-cost production method.

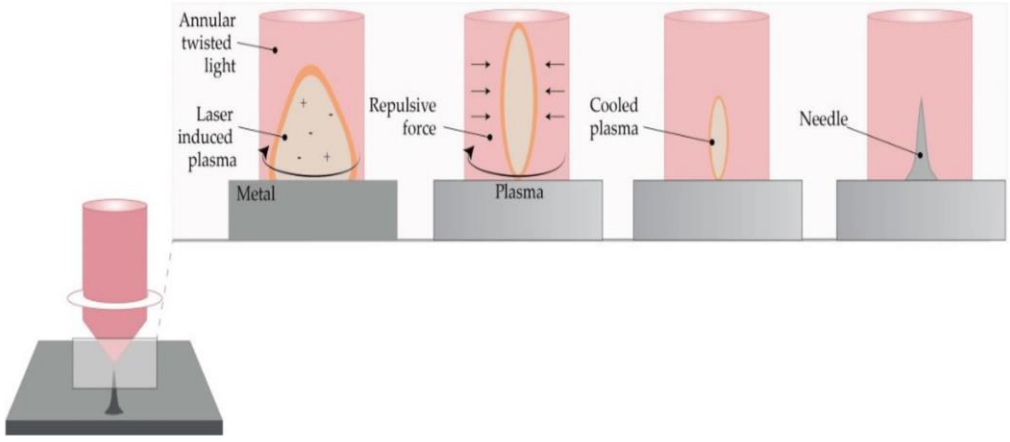

Figure 5: The principle of metal MN fabrication using twisted light with a spin by Omatsu et al.

Micromolding Method (Solvent Casting)

Dissolving MNs are usually produced by filling a previously prepared MN mold with the liquid formulation. Generally, the mold is made from a silicon wafer as a starting material. .Afterwards, the wafer is oxidated at 1000 °C. A needle geometry is patterned using lithography methods, followed by RIE while CVD is used for coating a wafer. A liquid polymeric solution ispoured into prepared molds, and then, air voids are removed with vacuum or centrifuge .Interestingly, micromolding has even been used for the production of ceramic MNs.

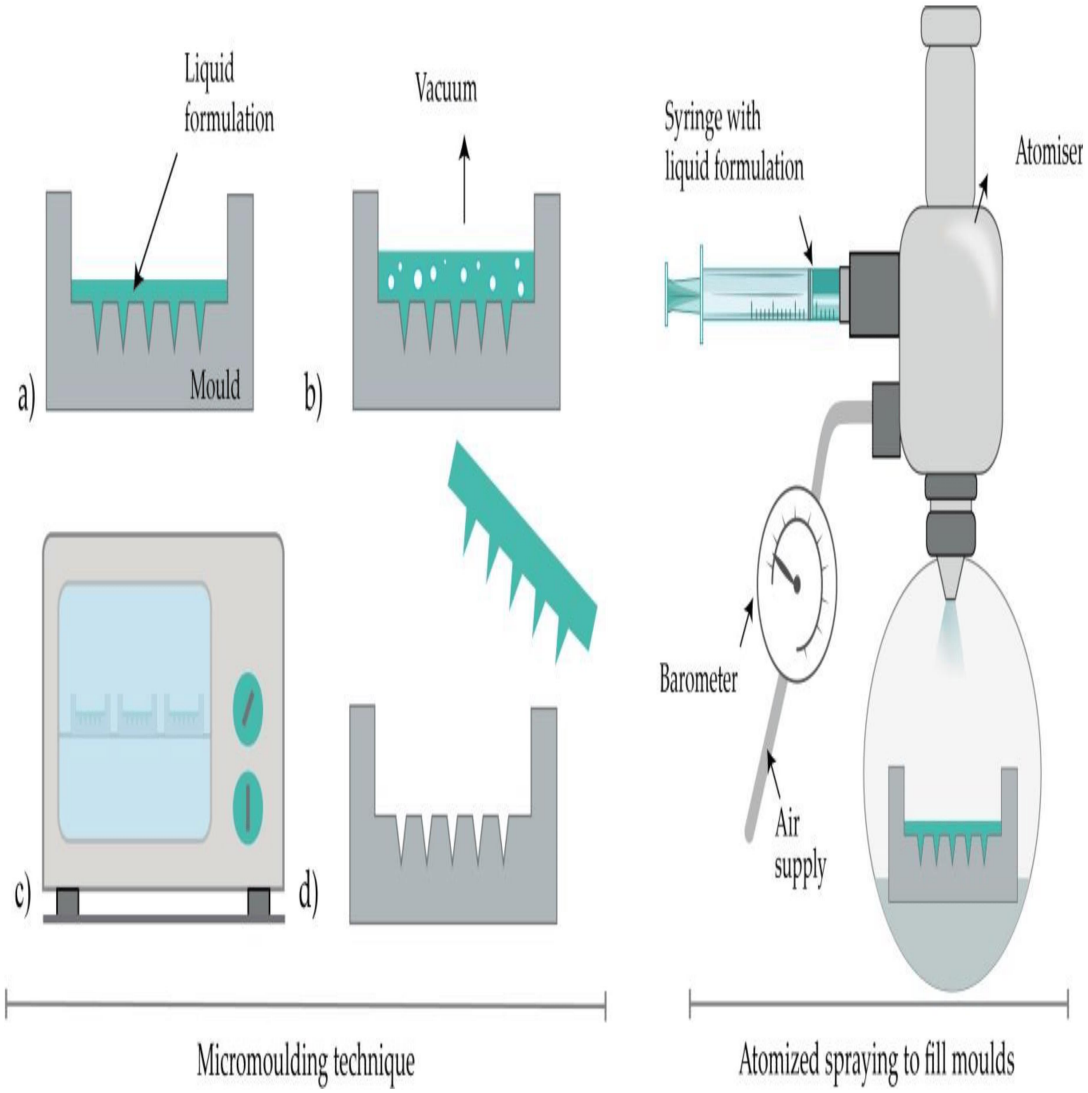

Figure 6: Left: MN production with micromolding (left) consisted of (a) pouring the liquid formulation, (b) vacuum degasification, (c) drying and (d) removal of MNs from the mold. Right: Atomized spraying to fill molds.

Atomized Spraying Method

This method overcomes the problems associated with the limited capacity for mass production of dissolving MNs with the desired geometry and physical characteristics. Also, the problems linked to the effects of liquid surface tension and viscosity when filling the MN molds can be minimized. Dissolving MN can be produced from the sugars (trehalose, fructose, and raffinose) or polymers (PVA, PVP, CMC, HPMC, and sodium alginate). Briefly, a nozzle connected to an air source and liquid formulation produces an atomized spray. The formulation is filled in PDMS molds and dried for 2h at ambient temperature. Laminte-layered and horizontally-layered dissolving MN can also be produced by this method.

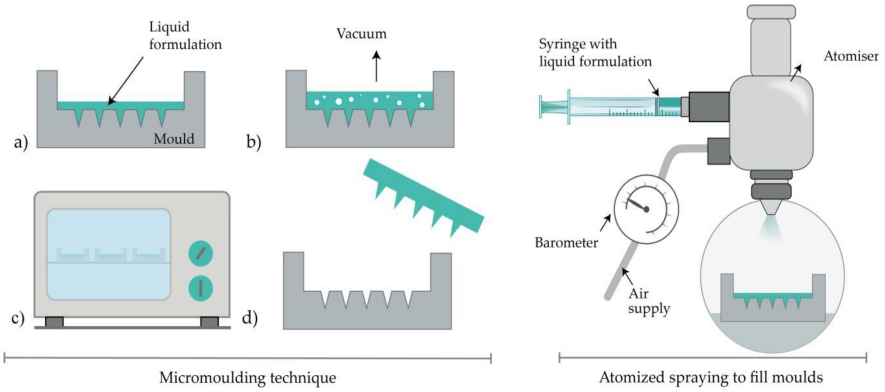

Figure 6: Left: MN production with micromolding (left) consisted of (a) pouring the liquid formulation, (b) vacuum degasification, (c) drying and (d) removal of MNs from the mold. Right: Atomized spraying to fill molds.

Droplet-Born Air Blowing Method (DAB)

This method, in which polymer droplets are shaped into MNs with the use of air blowing, enables production under mild conditions, without the use of UV radiation or heat In short, the process begins by dispensing the prepared solution on two plates (upper and lower), then placing the upper plate downwards to allow contact of droplets. The upward movement of the upper plate elongates the viscous solution. In the next step, air blowing removes the residual water and solidifies the droplets in the desired shape by pulling the droplet from a substrate, as illustrated in Figure 7. A novel method that uses a shadow mask enabled a uniform MN production, and it overcame low throughput-associated problems in the droplet formation. Using this method, the authors reported controlled drug dosage with optimization of hole width and thickness of the shadow mask.

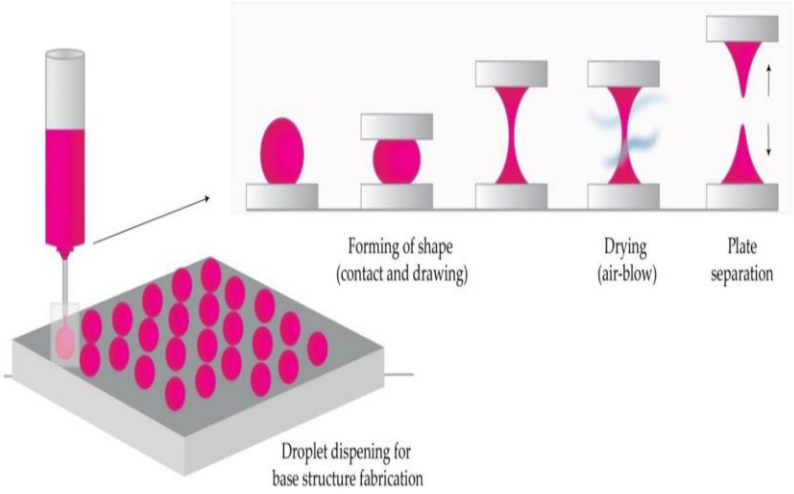

Figure 7: The principle of droplet-born air blowing (DAB) methods.

Fused Deposition Modelling (FDM)

The preparation for printing MNs with typical FDM printers starts with designing MNs using CAD software and optimizing its geometry according to the printer specification. Then, the suitable thermoplastic material, in the form of a filament, is fed into the printer by rollers, where it is heated to just above its softening point (glass transition temperature Tg) by heating elements into a molten state. The melted or softened material, guided by gears, is moved towards the head end where it is extruded from the printer's head, through a nozzle and subsequently deposited layer-by-layer on a build plate, cooling and solidifying in under a second (Figure 8) The printer's head moves within the x- and y-axes, whereas the platform can move within the z-axis, thus creating 3D structures.

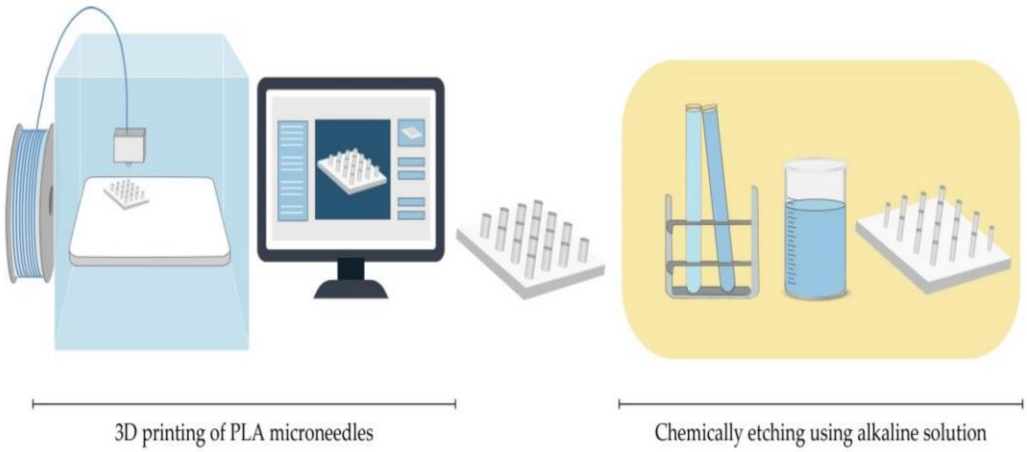

Figure 8: Fabrication of MNs by Fused deposition modelling (FDM) methods, followed by etching in alkaline solution.

Fabrication of MNs by Fused deposition modelling (FDM) methods, followed by etching in alkaline solution. Processing parameters that should be optimized during an FDM process include nozzle diameter, feed rate, the temperature of both the nozzle and the building plate, printing speed, the height of the layers, and part built orientation.

Although FDM is a versatile and cost-effective MNs manufacturing method, its main limitation is low printing resolution. Luzuriaga et al. reported for the first time combination of FDM with a post-fabrication etching step to obtain ideally sized and shaped needles .Camović et al. also successfully used FDM to print MNs, which were subsequently coated.

Microneedle Coating Techniques

Solid MNs can be coated with the drug-containing dispersion, which provides a rapid drug release from the coating into the tissue .However, it is hard to achieve a suitable drug release profile because of the limited surface where the drug can be inserted, which is caused by specific MN's structure. Problems with stability, uniformity, consistency, and reproducibility may also occur. During the coating process, the drug can be lost from the MN surface. The non-uniform coating thickness of the drug on the MN surface may lead to inaccurate dosing. All those drawbacks should be considered when choosing the right method for coating MNs with drug-containing dispersion.[60]

Dip-Coating

Dip-coating is a method that selectively coats the MN shaft without contaminating the base substrate of the MN array by immersing MNs in drug formulation. Different aqueous, organic solvent-based, or molten liquid can be used. Dipping results in forming a liquid film on the MN surface followed by drying where the adherent liquid film is converted into a solid coating. The viscosity and surface tension of the coating solution should be adjusted carefully to prevent the rising of coating solution upon the MN shaft to the base substrate. The selective coating of the MN shaft can be achieved by masked dip-coating or thin-film dip-coating. Masked dip-coating implies the use of a masking plate, which disables the passing of the coating solution to the base substrate .In thin-film dip-coating, the thickness of the coating solution is lower than the height of the MN, which assures the insignificant capillary rise of the coating solution and, therefore, prevents possible contact between coating solution and base substrate .Titanium MNs, dip-coated with recombinant human growth hormone, provided similar absolute bioavailability as commercial subcutaneous injections. The authors concluded that the lack of pain and ease of administration might lead to the replacement of these injections with MN patches .Layer-by-layer coating represents a modified dip-coating method. Electrostatic interactions are used to create a layered coating on the MN surface, unlike the classic coating method where the coating is based on the viscosity of the solution. In the case of DNA or protein molecules, the solution contains negatively charged DNA and positively charged polymer, which leads to the formation of a polyelectrolyte multilayer on the MNs. Chemically modifying the MN surface or precoating multiple alternate layers of negatively and positively charged polymers is necessary to acquire the desired charge polarity.

Gas-Jet Drying

Gas-jet drying is a method where the drug suspended in a coating solution gets transitioned into the gas phase using a gas-jet applicator (Figure 9). It is suitable especially for curved MNs, because the slow drying process, specific for dip-coating, is not convenient in this case. Wet coating liquid on the surface of the MNs has the potential to move and change its thickness and, consequently, the dose accuracy. This method is also appropriate for small (<90-micron length) and very closely spaced (~20,000 cm−2) MNs.

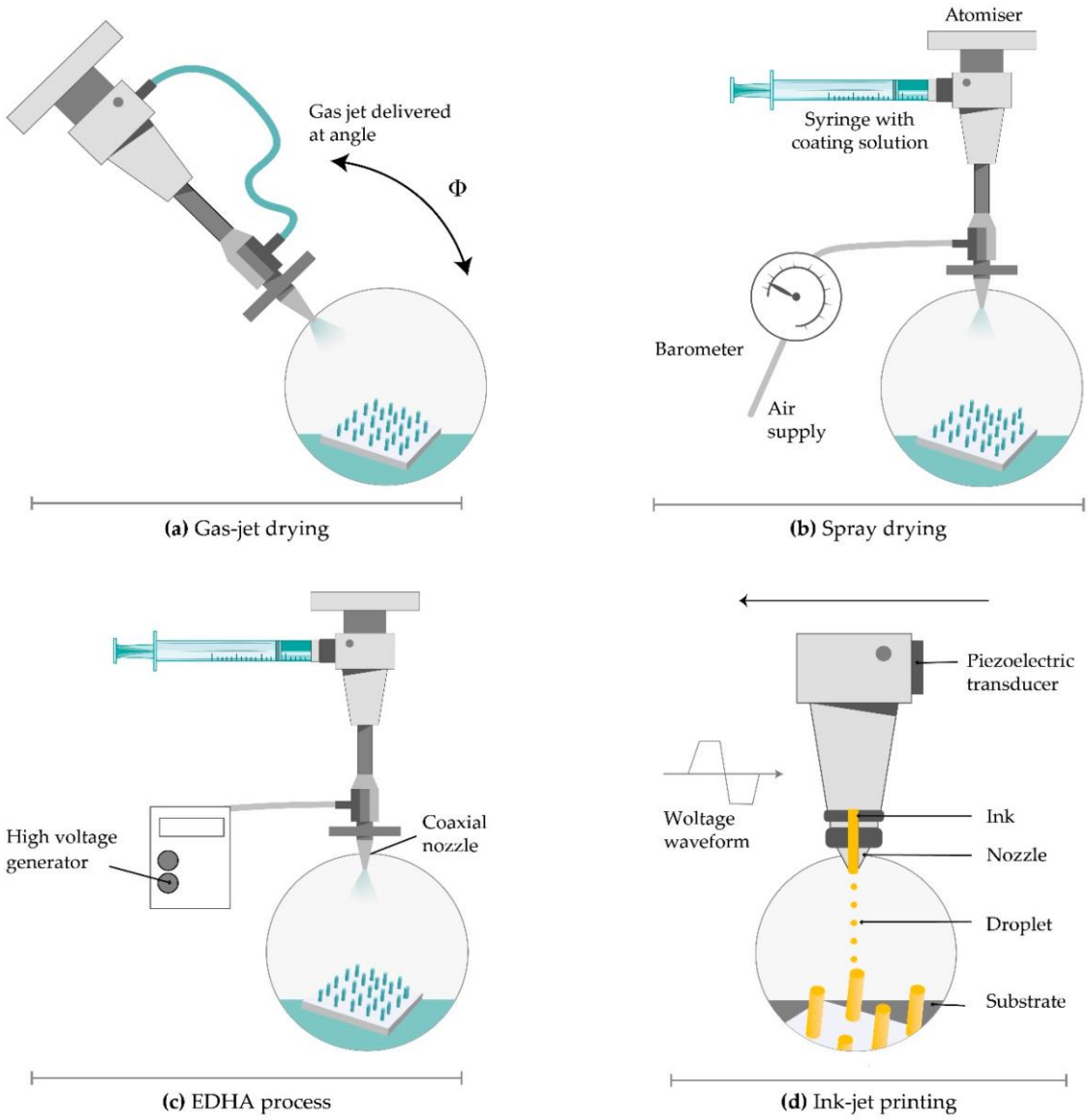

Figure 9: Coating techniques for MNs. (a) gas-jet drying; (b) spray drying; (c) electrohydrodynamic atomization (EHDA) processes; (d) ink-jet printing.

The improved delivery of large vaccine molecules, through the SC, can be achieved by modifying the gas jet method for coating MNs. Raising the incident angle from 20° to 70°, removing the patch edge, and rotating the patches during the coating process ensured the uniformity and relocation of the drug from the whole MNs only to the tips. Much lower doses provided an equivalent protective immune response as the intramuscular injection. These MN patches also contributed to extended and improved vaccine stability.[61]

Spray Coating

Spray coating implies using fluid pressure to create droplets. An intact film-coat is formed from fine droplets (<280 µm), which are deposited on MN array and then, outspread and coalesced. The first step is atomization, which generates fine droplets. Then comes the deposition and adherence of droplets, which collide on the surface. The last step is a coalescence of droplets on the substrate to form an intact film coating .The nozzle design, concentration, input ray, physicochemical characteristics of the coating solution (viscosity, surface tension, and density), and processing parameters like air-to-liquid mass ratio, the duration of spraying, atomization air pressure, gun-to-surface distance, and air cap setting determine the droplet size. The deposition of droplets on the surface is determined by spray velocity and spray density.

Piezoelectric Inkjet Printing

Piezoelectric inkjet printing provides a controlled and precise MN coating with liquid droplets (1–100 pl), which is followed by solidification. The method is compatible with different aqueous and organic solvents. The low viscosity of the formulation is preferable to prevent clogging the small jetting nozzle. The voltage supplied material connected to a piezoelectric transducer

produce vibrations to eject drops from the nozzle .A modified method called thermal inkjet printing implies drop production by increasing the formulation temperature a bit higher than its boiling point. This method provides coating MNs with poorly soluble drugs. Biodegradable PGA MNs were coated with voriconazole and showed antifungal activity.

From Clinical Trials to Commercial Development

Up to now, MNs with a broad range of geometries, with or without a MN application device, have been fabricated using different manufacturing methods from a variety of materials. Although MNs have been extensively studied for transdermal drug delivery and vaccine delivery, these systems can also be designed for delivery targeted to other tissues such as oral mucosa, vaginal mucosa, anal sphincter muscles, and hair follicles.

During the last 5 years, there have been a variety of completed clinical trials involving the use of MNs. The majority of these clinical trials involve the use of MN injection systems and MN array-based patches, in order to prove the efficacy and safety of MN delivery systems versus traditional delivery systems. Most of the MN devices are still in clinical trials, and only a few of them are currently available in the market. The first commercialized MN device was developed by Becton-Dickinson Technologies named Soluvia® (Figure 10A) although some authors suggest that this device does not contain truly MN arrays, but rather very short hollow needles that allow successful ID injection from a conventional syringe barrel.

In February 2010, the FDA approved MicronJet® by Nanopass Technologies. This single-use MN device composed of four hollow silicon needles shorter than 500 mm in length attached to a plastic device, was used to deliver insulin, lidocaine, and influanza vaccine intradermally.

In 2009, the company completed Phase 1 clinical trial with the aim of comparing glucose pharmacokinetics and insulin pharmacodynamics injected via the Micronjet® with a conventional needle for the delivery of insulin.

Figure 10: Current MN devices. (A) Soluvia®, (B) MicronJet®600, (C) Microstructured Transdermal System®, (D) QtryptaTM, (E) SCS Microinjector®, (F) Microinfusor®, (G) MicroCor®, (H) Bullfrog® Micro-Infusion Device.

Mercator MedSystems, Inc. developed a very interesting MN-based device named Bullfrog® Micro-Infusion Device (Figure 10H) in order to safely inject therapeutic molecules through blood vessel walls into adventitial tissues. The device is tipped with a balloon-sheathed MN. This device has received 510(k) marketing clearance from the FDA is CE Marked.

Above mentioned MNs devices, especially marketed ones, should encourage researchers and companies to move toward large-scale manufacture and design of MN devices using different novel materials and production methods.

Challenges of the Microneedle Delivery System

Endorsing the translation of MNs from research laboratories to the relevant industries is an exciting but demanding task for the near future. To translate this innovative technology from the lab bench to feasible products in the relevant markets, some crucial questions and challenges should be considered promptly. We hereafter discuss these challenges and active strategies to address these difficulties, which could determine the future of the field and its commercial applications.

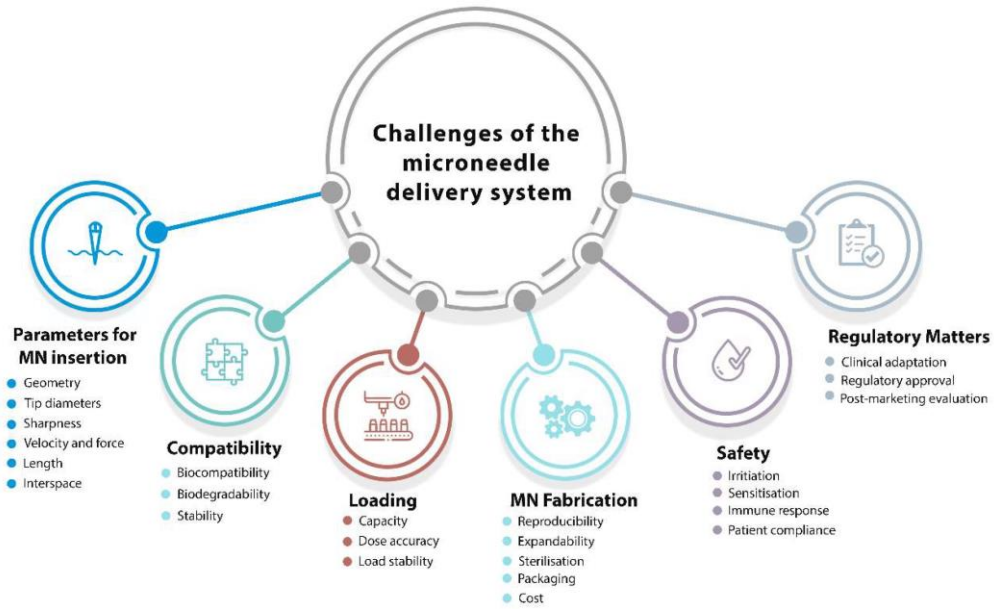

Figure 11: Factors effecting development of microneedle-based delivery system.

Applications of MNs

The MNs were first introduced for drug delivery applications, and the major objective was the enhanced permeation in the skin using solid and hollow MNs compared to conventional hypodermic needles. The MNs were filled with drug solutions or formulations, or they were coated for improved intradermal drug delivery. 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.

Intradermal Drug Delivery through MNs Formulations

Drug delivery to the skin is challenging as it may be a local application or systemic delivery as a result of the stratum corneum's highly tough and barrier properties. However, the human stratum corneum thickness is (10–15 µm), and it still prohibits the drugs at therapeutic levels.

Small Molecules (Low Molecular Weight Drugs)

The small molecule or low molecular weight drugs have higher skin diffusion coefficients than the larger molecule or biomolecule, which could easily penetrate the skin. This is so that the small molecule is quickly delivered into the skin using MNs.

Rojekar et al. have formulated dissolving MNs containing the etravirine and etravirine nanosuspension for long-acting drug delivery and improved HIV infection therapy. They have demonstrated the robust nature of MNs, with significant drug deposition of 12.84 ± 1.33% ex vivo, in neonatal porcine skin for 6 h. The in vivo pharmacokinetic studies demonstrated improved parameters; Cmax exhibited by DMNs containing ETR powder and ETR NS was 158 ± 10 ng/mL and 177 ± 30 ng/mL, respectively. It was also revealed that the improved t1/2, Tmax, and mean residence time (MRT) compared to intravenous ETR solutions indicated the long-acting nature of etravirine delivery using DMNs.

Large Molecules (Biotherapeutics)

Protein and peptides are very unstable and degraded after oral administration. Transdermal drug delivery could avoid this issue; however, delivering all kinds of molecules is difficult due to challenging skin barriers.

Ocular Drug Delivery

Bypassing the ocular barrier with minimum invasion is the advantage of MNs over intravitreal injection. Several studies demonstrated the application of MNs in ocular drug delivery. Patel et al. demonstrated the successful delivery of micro and nanoparticle suspension in the suprachoroidal space of pig, rabbit and human eye (ex vivo) using hollow MNs. Optimizing dimension and process parameters concluded that efficient drug delivery could be achieved with a needle length of 800–1000 µm and pressure of 250–300 kPa Through their research, Jiang et al. also endorsed the application of MNs technology in ocular drug delivery. Using the coated solid MNs, the intrascleral and intracorneal delivery of drugs, protein, and DNA was assessed. The successful delivery of drugs in the ocular system with minimum invasion was observed.

Vaccine: A vaccine is a complex biological preparation or formulation. It successfully offers active acquired immunity to a specific disease. Vaccines consist of the killed or weakened form of disease triggering microorganisms, toxins or one of its surface proteins.[62] Vaccines could stimulate the body's immune system and protect the host system against future infections or diseases.

Dissolving MNs loaded with vaccines and hydrophobic adjuvants for improved cancer therapy %# (Adapted with permission from Ref. Copyright 2018 American Chemical Society).

Diagnosis:The painless withdrawal of the biological fluids from the body is the major advantage of MNs over conventional blood collection techniques. Various biomarkers present in interstitial fluid beneath the skin can be useful for diagnosing various diseases like diabetes, cancer, arthritis, etc., and helpful, timely medical intervention. Multiple research studies demonstrated the usefulness of MNs for disease diagnosis .Along with vaccination, the MNs can be used to diagnose various skin diseases in pediatrics like psoriasis and other inflammatory conditions.

Cancer Therapy: 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. The researchers fabricated the near-infrared responsive 5-indocyanine green and fluorouracil containing monomethoxy-poly (ethylene glycol)-polycaprolactone nanoparticles delivered through dissolvable MNs efficient therapy of human epidermoid cancer and melanoma.[63] Moreira et al. demonstrated the efficient delivery of doxorubicin and AuMSS nanorods through polyvinyl alcohol/chitosan layer-by-layer MNs, resulting in efficient cancer chemo-photothermal therapy. The drug delivery through MNs improved permeation and bioavailability at the tumor site.[64] Hao et al. demonstrated the application of MNs in skin cancer therapy. The researchers fabricated the near-infrared responsive 5-indocyanine green and fluorouracil containing monomethoxy-poly (ethylene glycol)-polycaprolactone nanoparticles delivered through dissolvable MNs efficient therapy of human epidermoid cancer and melanoma.[65]

Conclusion and future prospects

Micro needle drug delivery as a distinctive component within the field of nanobiomaterials, have garnered significant attention from researchers and are increasingly being acknowledged for their diverse applications. The emergence of microneedle development presents novel opportunities in the medical realm, particularly in addressing complex human diseases such as tumors and neurodegenerative disorders. The consumer preference for various magnetic nanomaterial products in the market is attributed to their convenience and eco-friendly nature, rendering them well-suited for contemporary in vitro biomedical applications. Consequently, MNPs are anticipated to play a pivotal role as the "material of the future" and will have a significant impact on all areas of pharmaceutical development.

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