REVIEW ARTICLE

Vaccine Adduct Microneedle Fabrication through 3D Printing Technology: A State-of-Art Review

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Abstract

The use of attractive, minimally invasive puncture devices called microneedles (MNs) penetrates the skin without discomfort and enables the transdermal administration of active substances, including drugs and vaccines. MNs are also significant in disease diagnosis, monitoring, and cosmetics. MN geometry and shape are essential factors in affecting performance and therapeutic efficacy, whereas traditional manufacturing techniques including molding might not be able to enable fast design changes. In this regard, the manufacturing of MNs through the use of 3D printing technology allows for the quick and precise development of complicated MN prototypes as well as the availability of MN devices that may be configured to have the appropriate shape and dimension. Additionally, by combining MNs with 3D printing exhibits significant promise for the production of efficient transdermal drugs and vaccine delivery systems as well as medical devices. Unlike traditional intramuscular or subcutaneous delivery using hypodermic needles, MN-based vaccine created by 3D printing technology distributes vaccine directly into the skin, which is thought to be an immunologically far more relevant vaccination location than underlying tissue. The purpose of this review is to convey the benefits of using 3D printing technology as a novel tool for MN fabrication. Different 3D printing techniques are shown, and typical MNs produced using such techniques are highlighted in detail.

Key words: 3D printing, additive manufacturing, lithography, microneedles, vaccines

INTRODUCTION

Novel drug delivery technologies are increasingly important in pharmaceutical research. The distribution of novel compounds is becoming a bigger problem, despite the fact that drug development projects continue to produce a tonne of excellent work. However, the majority of them have permeability and solubility issues, which make it difficult to disperse them using conventional method. There are a variety of drug delivery methods that are approachable, including the most common ones such as oral, parenteral, ocular, and topical as well as less common ones such as nasal, pulmonary, and buccal. Each of these routes has distinct benefits and drawbacks. Transdermal drug delivery offers a number of advantages over drug administration, including the ability to retain plasma concentrations, prevent first pass metabolism, increase patient compliance, enhance drug absorption, and prevent against gastrointestinal degradation.[1] Transdermal drug delivery will be beneficial by making changes in chemical and physical methods which minimize the effect of stratum corneum's barrier. In recent decades, there has been a significant development in the field of novel transdermal drug delivery system that employs microneedles (MNs), and it is a combination of hypodermic needle and transdermal patch. MN technology is being used to improve transdermal drug delivery, and it received a lot of attention and is moving rapidly toward commercialization.[2]

Vaccination, one of the most efficient immunological preparations of the adaptive immune system, has historically reduced mortality and morbidity for various infectious diseases. Depending on the formulation, vaccines can be divided into a number of categories: living viruses are present in live-attenuated vaccinations, which are unable to infect

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healthy people. The microbial pathogens used in inactivated or killed vaccinations are dead or dead-like. A weakened form of the toxoids found in pathogenic bacterial products makes up toxoid vaccinations. The polysaccharide used as an antigen in the conjugated vaccine is made of bacterial outer membrane.[3] Numerous factors, such as stability, cost-effectiveness, the convenience of administration, and the capacity to successfully invoke an immune response, should be taken into consideration when designing the vaccine. The method of vaccination has been recognized as a vital factor in ensuring the safe and effective administration of the vaccine. There are several common ways to administer vaccines, including intramuscularly, intradermally, subcutaneously, and orally.[4] Most vaccinations are given intramuscularly or subcutaneously by injection, which may be uncomfortable or painful for the persons who have a needle phobia. Moreover, the use of hypodermic needles to deliver the vaccine via these routes generates hazardous waste, increases the possibility of injuries caused by needles, and encourages the usage of reused needles.[5] To overcome these obstacles, novel transdermal delivery of vaccine methodologies must be developed.

MNs, as their name indicates, are miniature needles that are smaller than 1 mm in diameter and are used to administer vaccines or other active ingredients through the skin. The stratum corneum, the skin's outermost layers, is physically punctured by the MNs, and perforations in the skin permit the drug to penetrate through it. In comparison to conventional transdermal delivery systems, it can deliver drugs faster and more effectively.[6,7] 3D printing technology found to be a new accessible, cost-effective promising solution for the manufacturing of MNs. It is a novel manufacturing process called three-dimensional printing (or 3D printing) that developed solid items by assembling them in several thin layers. The International Standard Organization defined the term "3D printing" as "*the fabrication of objects through the deposition of a material using a print head, nozzle, or other printer technology*."[8] Fast prototyping, solid free-form fabrication, and additive are the terms used to describe 3D printing. 3D printing has many benefits over conventional manufacturing techniques such as its capacity to construct complex geometrical items, the simplicity of producing customized doses, patient-specific device designing, as well as highly complicated and customizable fabrication. Medical equipment (implants and prostheses), individualized medications (3D printed tablets), and tissue and organ regeneration may all be manufactured with excessive accuracy and precision due to 3D printing's adaptability and customization.[9,10] The first 3D-printed drug (levetiracetam) received approval for oral administration by the US Food and Drug Administration (FDA) to treat epilepsy in 2015.[11] During the 2020 worldwide pandemic, in large-scale production, 3D printing has observed its huge benefit of these products in a time when face masks and face shields were extremely desirable for protecting health-care professionals in the fight against COVID-19.[12] Several research have proven that MNs may be produced via 3D printing in a repeatable manner with great resolution and quality, including the needle's height, tip radius, base diameter, needle shape, thickness, and density. Moreover, the majority of 3D printing techniques use polymers with tunable, biocompatible, and biodegradable qualities to fabricate MNs. Due to its immense potential, 3D printing technology has become known as a novel and promising technique to assist in the development of innovative designs, increased efficacy, and greater usefulness of MNs.

MNs

The active transdermal drug delivery method known as MNs is intended for use in the place of standard syringe injections. The stratum corneum is penetrated and the medicine is delivered using a minimally invasive technique using the MN array. These arrays are made up of tiny needles that range in height from 25 μm to 2000 μm.[13,14] MNs have been utilized for various types of activities, such as delivering drugs and vaccines, applying cosmetics, and diagnosing diseases. When drugs are delivered through a MN technique, the ability of drug molecules to permeate through the stratum corneum layer allows for greater skin penetration. The technology's distinguishing characteristics include improved patient compliance, self-administration, improved permeability, and increased efficacy by disturbing the stratum corneum and allow the passage of large molecule through enhanced penetration.[15,16] The hypodermic needles penetrate up the dermis which contain pain receptors, where it can deliver 90–100% of the loaded drug, but it is very painful for patients, whereas a MN patch delivers the drug 100% effectively and painlessly as it bypasses the stratum corneum layer and going straight to the epidermis part of the skin.

Different types of material used for the formation of MNs are categorized, as given in Figure 1.

HISTORY OF MNs

Robert Chambers first used the word "microneedle" in scientific literature in 1921, when he injected the needle into the egg's nucleus. German dermatologist Dr. Ernst Kromayer used various-sized motorized dental burs to treat hyperpigmentation, scarring, and other skin conditions in 1905.[17] Henry *et al.* proposed the first MN for transdermal distribution in 1998, and it was made from silicon wafers using ion etching and photolithography; this study explained how to improve drug distribution across the skin by using microfabricated MNs.[18] In 2002, a report on the use of MN technology for cutaneous immunization was released. In a mouse model, Mikszta *et al.* reported the success of silicon microprojections for plasmid DNA immunization. Based on scores for erythema and edema, the study also evaluated the safety of the microprojections in human test subjects. In 2003, McAllister *et al.* presented the first study

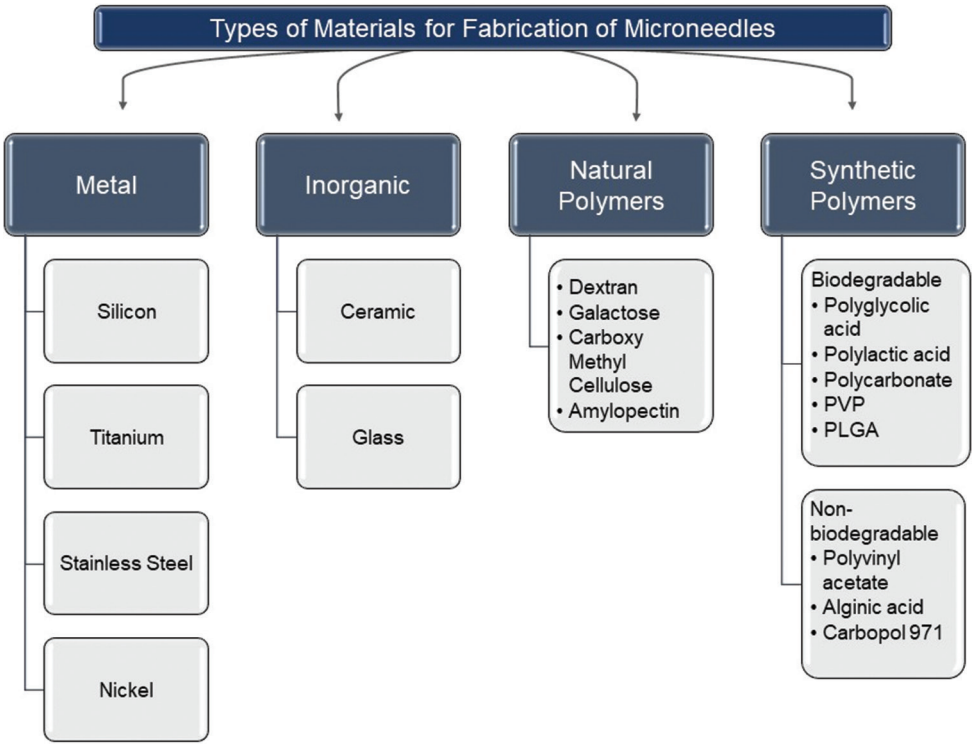

Figure 1: Different types of materials used for the formation of microneedles (Original figure)

outlining the viability of transdermal macromolecule and nanoparticle distribution facilitated by MN. Insulin, albumin, and latex beads with a diameter of 100 nm were delivered through the skin of a human corpse using solid and hollow MNs. According to Miyano *et al.*, the first soluble MNs were described in 2005.[19] Ascorbate-2-glycoside was used as a model therapeutic molecule in the preparation of a variety of maltose MNs, which were then tested on healthy human subjects. The MNs were well tolerated, and when placed on the skin, they spontaneously disintegrated, releasing ascorbate into the dermis and epidermis. After using an MN-roller on a patient's target skin, Fernandes saw tighter skin and fewer wrinkles. Across the past 10 years, MNs have been investigated and designed for a number of functions, including biological fluid collection, allergy testing, immunization, and photodynamic therapy, in addition to esthetic and medication delivery.[16]

MN PLATFORMS FOR VACCINE DELIVERY

There are different types of MNs [Figure 2].

Solid MNs

These are the most basic type of MN device; they are typically 70–800 mm long and stacked in arrays that are one or two dimensions to produce a MN patch. Solid MN patches can be applied to the skin without covering anything, and when they are removed, the pores on the skin's surface are made visible.[20] Drugs or vaccines are given to treat skin surfaces permeate into the skin through pores developed by the MN pre-treatment. Mice were immunized using this method with positive results for the diphtheria toxoid vaccine and negative results for the influenza subunit vaccine. The alternative method for administering vaccines through solid MNs is to coat water-soluble vaccine formulation in MN patches prior to implantation. When coated MN patches are applied, the vaccine dissolves, and then the patch releases the vaccine into the skin and then it is removed. Inactivated influenza immunizations against the Chikungunya virus, hepatitis C, West Nile virus, and herpes simplex virus 2 DNA, as well as vaccines against influenza and the human papillomavirus, as well as live MVA and adenoviruses, are among the solid MN patches with vaccine coating.[21,22]

Dissolving MNs

Dissolvable MN arrays were the keystone of a recently developed and extremely effective method for MN-mediated vaccine administration.[20] The incorporation of vaccination into MNs is the basic principle underlying designs for dissolvable MNs made of hard polymeric or sugar. Dissolvable MNs are inserted into the skin, which causes the MN matrix to dissolve when water evaporates from the opening skin pores. The vaccine is then released and frequently disperses into the skin. The component is water-soluble, safe, suitable hard when dried, and compatible materials with vaccines must be employed in the construction of the dissolvable MN matrix. It has been successfully used to deliver influenza vaccine produced in cell culture using dissolving MNs,

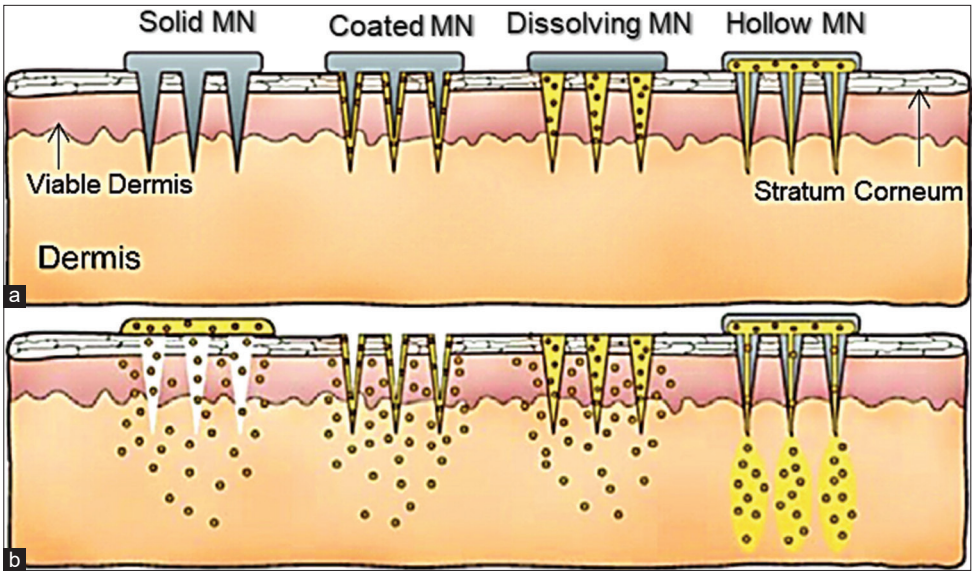

Figure 2: (a) Most common types of microneedles (MNs); (b) MNs pass through the outermost layer of skin to deliver vaccines with different mechanisms (Reused with permission)[17]

mainly composed of trehalose and carboxymethylcellulose. In order to examine the effectiveness of vaccines for tetanus, diphtheria, influenza, and malaria, Matsuo *et al.* used hyaluronic acid-based Microhyala, a distinctive dissolving MN array.[22-24] In each case, the immunization outcomes were comparable to those obtained through the parenteral route.

Coated MNs

Inconveniences caused by the two-step administration technique of solid MNs led to the development of coated MNs. The appropriate dose of vaccination can be administered once the needle is in the skin; however, the size of the needles limits how much vaccine can be delivered to them. According to studies, a patch with several hundred MNs and a surface area of 10–20 cm^2 can deliver up to 1 mg of drug.[25] Coated MN vaccine administration is thus restricted to vaccine formulations that may induce significant immune responses even at low doses.It has become fascinating to coat solid MNs with antigenic material since this strategy requires minor modifications to conventional procedures such as loading stainless steel, titanium, and silicon projections, spray coating, and repeated dip coating. A unique immunization method with live virus vaccines was introduced by Vrdoljak *et al.* in Ankara. It included the introduction of live recombinant adenovirus and modified vaccinia virus.[26] ImmuPatch, a type of silicon pyramidal MN with wet-etched surfaces, was used to spray-coat vaccination particles.

Hollow MNs

Hollow MNs are microneedles that are used to administer liquid formulation directly to skin. Hollow MN designs come in two different varieties. A single MN is used, giving the impression of a tiny conventional hypodermic needle. These MNs are organized into arrays to facilitate the simultaneous distribution of a vaccine formulation over a larger region of skin. As a result, the vaccine might be administered more rapidly and have higher bioavailability and antigen use. When compared to other MN platforms, which need the use of dried vaccines, the use of hollow MNs has the significant advantage of permitting the use of liquid vaccine formulations.[27] For application, hollow MN devices, on the other hand, usually need into a needle or another liquid vessel and may even need the assistance of trained personnel. Needles typically have a length of 1–1.5 mm and deliver <200 µL of fluid. Vaccine delivery is intended to be an improvement over the Mantoux approach (shallow angle needle insertion used in cutaneous needle method) that can be challenging to use and has varied results in terms of dermal call response.[28,29] The most effective commercial use of the vaccine MN-delivery systems was a single hollow MN device-based influenza vaccination. Early and subsequent research using rabbit models for anthrax immunization revealed a 50-fold dose reduction comparable to intramuscular injection when using hollow MN. According to studies, hollow MNs are used to administer a combination vaccine that protects rhesus macaque monkeys from anthrax, botulism, plague, and *Streptococcus pneumoniae* fluid overload.

FABRICATION OF MNs USING 3D PRINTING TECHNOLOGY

The 3D printing of MNs typically involves three essential steps. Initially, computer-aided design software is used to sign a 3D object, a common and printer-friendly file format, such as standard triangulation language, is used to export the 3D object, and finally, layer by layer, the object is printed. Other fabrication techniques are enlisted in Figure 3.

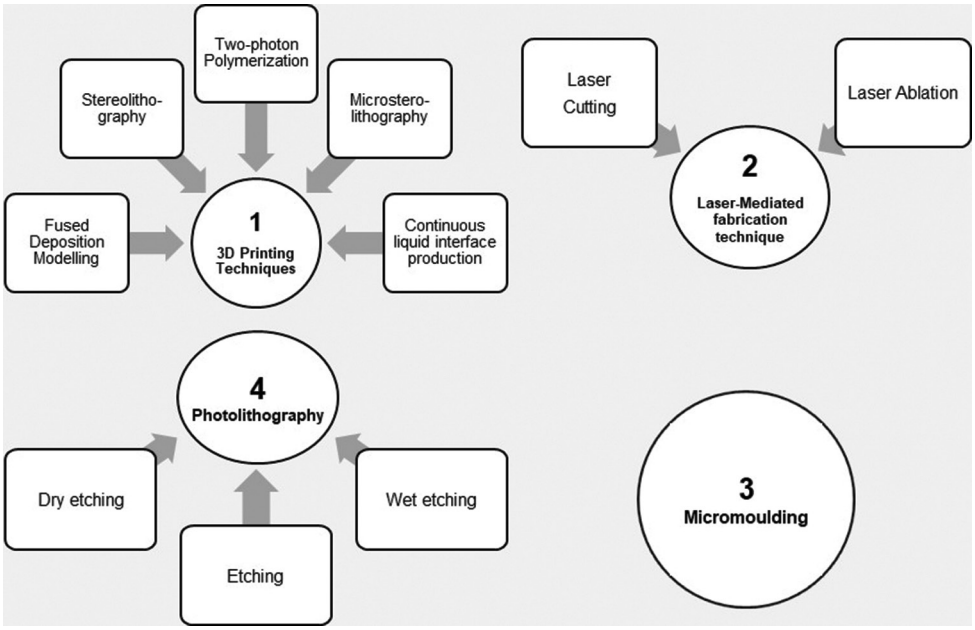

Figure 3: Different types of methods used for fabrication of microneedles (Original figure)

Fused deposition modeling (FDM)

FDM is the 3D printing technology that is most economical. The core of the FDM method is the hot-melt expulsion of thermoplastic polymer fibers at the 3D printer. At the same time as the print head travels in line with the template in the 2D slice, the polymer filament gets polymerized and deposited on the print station. Repetition of this procedure leads to the construction of a 3D structure in which the initial and second polymer layers are fused together and raised vertically. The 3D structure hardens after the temperature falls beneath polymer's melting point, after which point it is prepared to be removed from the print station.

Solid MNs have been fabricated using this printing technique. The utilization of a wide variety of thermoplastic polymers, including polylactic acid (PLA), acrylonitrile butadiene styrene, nylon, polyetherimide, thermoplastic polyurethane, and polyethylene terephthalate modified with glycol, is the significant advantage of FDM.[30] In comparison to other additive manufacturing techniques, FDM has lower resolution, and printing has intrinsic limitations with respect to intrinsic dimensions and surface roughness limitations. Until now, this method is quick, cheap, and employs very simple materials. It is also quite reliable. The renewable, biodegradable thermoplastic polymer PLA has FDA approved and used to print several MN array types, and it was then etched chemically using an alkaline solution. Luzuriaga *et al.* described the first attempts to apply FDM techniques in the construction of MNs. Solid PLA MNs of required size and shape were created by Camovic *et al*. by using FDM and a chemical etching method.[30,31] Hollow MNs were developed using an FDM printer and incorporated into specialized, configurable bandages by Derakhshandeh *et al.* for the therapy of severe wounds. These bandages have the ability to actively control the release profile of various medications, including vascular endothelial growth factor (VEGF).[32] It has been successfully demonstrated *in vitro* that the MNs are effective delivering the active ingredients through necrotic tissues and the covering of a wound. Administering VEGF transdermally to the chronic wounds of diabetic mice successfully improved wound closure, re-epithelialization, angiogenesis, and hair formation.

Stereolithography (SLA)

In 1988, 3D systems developed the SLA method, which depends on the UV laser photopolymerization of liquid resin in a vat.[33,34] Typically, SLA printers have a resin tank and a printing platform. The cross-section is solidified after being drawn by a UV laser onto a photopolymer resin solution. In order to fabricate solid MNs, SLA 3D printing is widely employed. Ochoa *et al.* described the first MN fabrication using SLA. The MN master was constructed using SLA 3D printing and then utilized as a mold for molding agarose gel, which maintained the MN's structure due to the gel's isotropic shrinkage. The agarose gel was dried and then utilized as a mold to construct MNs from polydimethylsiloxane polymer. Krieger *et al.* were the ones who created the "print and fill" technology to create customized MN molds. Coated MNs have also been fabricated using SLA 3D printing.[35] For instance, in the production of MNs, Pere *et al.* used both inkjet printing and SLA 3D printing with an insulin coating.[36] There are various reports that highlight the potential of SLA-printed MNs as protein or drug carriers, such as anticancer drugs (e.g., insulin) as it is reported that MNs produced with SLA have a regular, smooth texture that makes it possible to manipulate the surface modification by pouring a drug or protein solution over MN surfaces that have been specifically targeted. Due to this, patients can receive their prescribed dose and regimen with accuracy.

Two-photon polymerization (TPP)

The three processes that make up TPP are initiation, propagation, and termination. A femtosecond laser beam is utilized to disrupt the chemical interactions that photoinitiator molecules have with one another. This causes the photoinitiator molecules to become excited and disintegrate into radical species. In this radical species, monomers are involved, during the propagation process to produce monomer radicals. When two radicals from different monomers combine, the polymerization process is terminated.[33] Hollow MNs were traditionally constructed by TPP. TPP has traditionally been utilized to fabricate hollow MNs. Doraiswamy *et al.* reported the development of the first MNs made using TPP, which were made from organic-inorganic hybrid materials.[37,38] The HT1080 epithelial-like cells could proliferate in these MNs similarly to polystyrene and extracellular matrix, and they demonstrated the ability to puncture pig skin without shattering. In more recent times, Moussi *et al.* created hollow MNs attached to a drug carrier utilizing TPP in a single treatment. A drug carrier was attached toward the MN's back, which enhanced the dose of drug that was given to the skin through the MNs' channels.[39] Szeto *et al*. demonstrated the ability of TPP 3D manufactured hollow MNs to permit intracochlear perilymph collection.

Continuous liquid interface production (CLIP)

In order to develop an innovative substitute for the normal layer-by-layer SLA technique, Carbon3D Corp. designed CLIP technology. The key to this technology is the oxygen diffusion layer development, which facilitates the subsequent oxygen diffusion printing to prevent radical polymerization. According to Johnson *et al.*, CLIP can be used to design better MNs from a variety of polymers in a range of geometries and morphologies, such as turret, needle, layered, and prismatic MNs.[40,41] According to the study investigations, rhodamine B was encapsulated in MNs, which could be swiftly delivered into *ex vivo* mouse skin by the MNs manufactured by CLIP. Johnson *et al.* further showed that the only modification required was to the resin inside the vat at the specified printing time to create MNs with a PCL basement loaded with rhodamine B and an acrylic acid tip loaded with fluorescein. This might promote the proliferation of MNs which are polydrug loaded.

Microstereolithography

In comparison to SLA, microstereolithography is a high-resolution, simple fabrication process that can construct 3D composites with more accuracy and it is also known by the term direct light projection 3D printing technology. Scanning, projection, and submicrometer resolution are the three major parts of the microstereolithography principle. Researchers started designing of thin-walled hearing aid shells by employing eShell which is a biodegradable, economically accessible acrylate-based polymer. Furthermore, MNs or MN master templates are prepared by using microstereolithography. Generally, resin was used to construct the MN base, and biodegradable poly was used to build the MN bodies (propylene fumarate). First, using visible light dynamic mask microstereolithography, Gittard *et al.* developed eShell 200 MNs by coating their surface with a thin layer of zinc oxide or silver using pulsed laser deposition.[33] In the agar diffusion experiment, silver and zinc oxide-coated MNs showed antibacterial activity against the two common Gram-positive bacteria that cause skin infections, *Streptococcus pyogenes* and *Staphylococcus aureus*. For the prospective therapy of skin cancer, Lu *et al.* manufactured dacarbazine-loaded poly (propylene fumarate) MNs using digital micromirror devices. Targeting joint inflammation in trigger finger disease, Lim *et al.* developed customized MN splints.[42,43] Initially, a liquid form of diclofenac diethylamine was used to "patch" the finger. In order to penetrate the SC in addition to provide transdermal distribution of drug, an MN splint made of solid MNs was then placed on the finger.

Selective laser melting (SLM)

With the aid of high-energy laser beams, powders can also be utilized as 3D printing materials in technologies including direct metal laser sintering, selective laser melting, and selective laser sintering (SLS, SLM) (DLMS). In this fabrication method, 3D objects are manufactured layer by layer by melting and merging densely packed, microscopic powder particles of materials such as metal, plastic, polymers, or ceramics using a computer-controlled, high-power laser. The desired shape and qualities are then achieved by a 3D structure made of these solidified particles. The powder bed is filled by DLMS without the use of a binder or fluxing agent utilizing metallic alloy powders including bronze, steel, stainless steel 316 L, titanium, or Al-30% silicon. Alternatively, metallic alloys such as titanium, nickel, aluminum, and stainless steel are examples of materials utilized in powder-based printing technology.[44,45] MNs created by SLM have undesirable rough surfaces since powders are used as the raw material, requiring also another polishing step.[28] Several post-processing techniques can generally be used to reduce the surface roughness of SLM-produced components. This comprises vibratory finishing, drag finishing, electropolishing, chemical polishing, sandblasting, shoot peening, and grinding.

CONCLUSION

The potential benefits of MNs have recently increased the availability of research papers concerning various forms of MNs, comprising hollow, solid, coated, and dissolving ones with multiple feature sizes for a range of biomedical applications, such as for drug administration, vaccine distribution, biosignal monitoring, and sample collection.

Several MN fabrication techniques, including additive and subtractive procedures as well as cutting-edge 3D printing technology, were suggested. The current review provides an overview of the advantages of MNs fabrication, as well as the techniques that may be designed to make MNs through 3D printing, and recent developments in vaccinations and drug delivery. To regulate and reduce the incidence of life-threatening diseases on global health-care systems, regular and continuous health monitoring and immunization are necessary. Conventional methods can substantially satisfy the requirement for diagnostic procedures, but they have limitations, such as poor patient compliance, high costs, and limited accessibility, which create a stress of life-threatening diseases on health-care systems all over the globe. There are still some difficulties in this area, unfortunately. For instance, there are requirements for further studies on the materials used to make MNs to improve their capacity to absorb liquids, allowing for an increased drug load in applications such as vaccine delivery or drug delivery. Furthermore, the majority of the reported cases have been researched using simulating tissues and animals.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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