Journal of Pharmaceutical Research International

33(62B): 104-113, 2021; Article no.JPRI.80082
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Stereolithography (SLA) 3D Printing Technology in Microneedles

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i62B35176

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/80082

Review Article

Received 24 October 2021
Accepted 28 December 2021
Published 29 December 2021

ABSTRACT

Many of the drugs show enzymatic degradation in gastrointestinal tract (GIT) or they show difficulty in permeation. In these cases, microneedles (MN) based transdermal drug delivery system offers attractive alternative to conventional needle-based and oral drug delivery systems. Microneedle drug delivery system consists of an arrangement of micrometric arrays which can be formulated with the use of different polymers and technologies. This present review is related to manufacturing of biocompatible microneedles" formulated with an aid of stereolithography (SLA) - a 3D printing technique in which microneedle patches of different shapes are constructed in the form of layers. The MN patches could be coated using inkjet printing. An SLA printer could be employed to print pyramid needle-based arrays. X-ray computer micro tomography (CT) and scanning electronic microscopy (SEM) could be used to assess the standard of the formed microneedles and subsequent coatings. In vitro studies using Franz diffusion cells could be done further to analyze drug permeation rate and calculation of flux. Microneedles could be constructed by using a 3D printing stereolithographic technology, and combining it with a highly appropriate coating method like inkjet printing, which can lead to a high-paced drug delivery microneedle systems via skin.

Keywords: Microneedles; inkjet printing; stereolithography; Franz diffusion cell; 3D printing.

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1. INTRODUCTION

The capacity to efficiently transmit medicines via the human skin, known as transdermal drug delivery (TDD), is an intriguing idea that aims to overcome the drawbacks of conventional administration routes [1-2]. However, the transdermal technique is not widely used due to limits imposed by the framework of skin barrier, particularly the stratum corneum [3]. Microneedles (MNs) are generally microdevices that can puncture the outermost, most impermeable layer of human skin and transmit active substances which including medicines, ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and nanovaccines [4] directly into the derma. And with their small size, they do not pass through any metabolic systems, leaving epidermal nerves intact after insertion [5]. They also enhance bioavailability because the medication does not pass through any metabolic processes [6]. Multiple methods for MN-mediated drug administration are used, including solid, coated, hollow, hydrogel-forming, and soluble MNs [7]. MNs have been investigated in the following areas: (a) antimicrobial wound therapy (b) endothelial cell [8-9] proliferation, c) scar repair [10-11] and (d) the treatment of chronic wounds [12-14] and burns over various physiological time scales related to wound type and wound healing [15-16]. Examples include biointerfacing, wound detection, and smart bandages that integrate detection and distribution [17-18]. The most commonly utilized production process is micromolding [19-25]. Other approaches include direct photolithography [26], solvent casting [27] mold-based etching [28], drawing lithography [29] all of which are based on the polydimethylsiloxane (PMDS) polymer casting micromolding process. Although Ovsianikov et al. [30] investigated 3D printing for MNs in 2007 utilising a lithography-based multiphoton polymerization technique of printing, the tendency to print biocompatible and biodegradable materials from customary 3D printing methods, such as stereolithography [SLA], Selective Laser Sintering (SLS), CLIP, and Digital Light Processing (DLP) [31-33], has received the most attention. The AM procedures described in ISO/ASTM 52900:2015 have been used to classify biofabrication techniques [34]. SLS and, more precisely, SLA 3D printing has gathered immense popularity due to the higher resolution and potential to generate firm attributes lower than 100 m, which are optimal for microneedle specs. However, untreated photopolymers used within commercial 3D printers exhibit low biocompatibility, which turns them into a potential danger to live-cell components [35-38].

2. FABRICATION OF MNS

2.1 Design Structure and Material

Krieger et al., 2019 [39] "classify MNs into coated, solid, hollow, hydrogel-based, porous, and swellable forms, with complicated geometries including honeybee inspired, angled, and arrow-head MNs (Fig. 1). MNs must have a high level of structural homogeneity to enable high-throughput manufacturing. Several geometrical variables should be addressed in the design and production of MNs, including their height, breadth, aspect ratio, and tip thickness procedure to provide a final product with optimum mechanical integrity, desired target capacity of the injected medication, robust signal extraction, and minimal patient suffering. A greater aspect ratio of needles, for example, might result in easier insertion and less discomfort, but worse mechanical strength and integrity [39-40].The manufacturing of MNs has been reported to use a wide range of materials. Polymers, metals, and inorganic materials are among them [41] While inorganics like glass, silicon, and ceramics, as well as metals like titanium and aluminum, were first utilized to make MNs, polymers and hydrogels have lately gotten a lot of attention due to the requirement for biodegradable and dissolvable MNs."

Advances in polymer chemistry and the development of novel manufacturing methods such as 3D printing have made polymeric MNs possible [42]. The materials commonly utilised in 3D printing methods are listed in Table 1.

2.2 Introduction to 3D Printing Technologies

The 3D model is divided into layers(0.01mm thick or less in most cases) by the software that is used for 3D printing ."The printer then traces each layer onto the build plate, and after the pattern is finished, the build plate is lowered and the next layer is placed on top of the previous one." Because the procedure involves extracting material from a prepared block, typical production processes are referred to as 'Subtractive Manufacturing.' Milling and cutting are examples of subtractive manufacturing procedures. This sort of procedure generates a lot of waste since the material that is chopped off can't be used for anything else and is simply discarded [46].

2.3 3D Printing Technologies in Fabrication of MNs

Reasoned by the higher resolution and boarder spectrum to select the materials of these techniques, SLA, DLP, MPP, and “photopolymer jetting” are bringing in greater attentions for the production of MNs. In a dynamic mask projection microstereolithography (SLA) system, for example, SLA was utilised to fabricate poly(propylene fumarate) (PPF) MNs. The manufactured MNs were 1000 metres tall, 200 metres wide at the base, and 20 metres wide at the peak [47]. Furthermore, the SLA 3D printer was utilised to manufacture biocompatible polymeric MNs with a precision of 25 m along Z - Axis and a resolution of 140 m along X - Axis, and afterward insulin solutions were subsequently coated on the needles using the technique of inkjet printing [48]. DLP was utilised to manufacture MNAs on custom built parabolic surfaces employing castable resin, which then had to be cured for two hours to treat any uncured resin remaining on the surface. MNAs were manufactured with "XY resolution", a "printing layer height of 50 m", a "base diameter of 300 m", and a "height of 900 m" utilising this 3D printing technology [49]. Using drop cast IP-DIP resist on a single-side polished silicon wafer, TPP lithography was used to create cylindrical, pyramidal, and conical biocompatible magnetic MNs.MNs with a 630 nm base diameter, a 1:10 aspect ratio, a 12 m pitch, and a 120 nm thickness iron coating were produced by TPP. Using IP-S photoresist, researchers created hollow MNs with an outside tip diameter of 50 m, an inner diameter of 30 m, a tapered angle of 5°, and a height of 200 m using the TPP 3D printing technique. Another study made MN patches for medicine distribution using an extrusion-based 3D printer with two nozzles [50].

MNs can be made through additive manufacturing by 3D printing them or by creating female master moulds. Mold-based methods may be used to mass-produce MNs from a variety of materials, including biocompatible hydrogels. For producing customised replica moulds, a two-step SLA-based “print and fill” approach was developed (Fig. 2). First, an SLA 3D printer was used to create the MNA master. A UV-curable resin was then utilised to achieve the necessary MN length. Finally, utilising the 3D printed MNA master, a silicon female master mould was created [51-52].

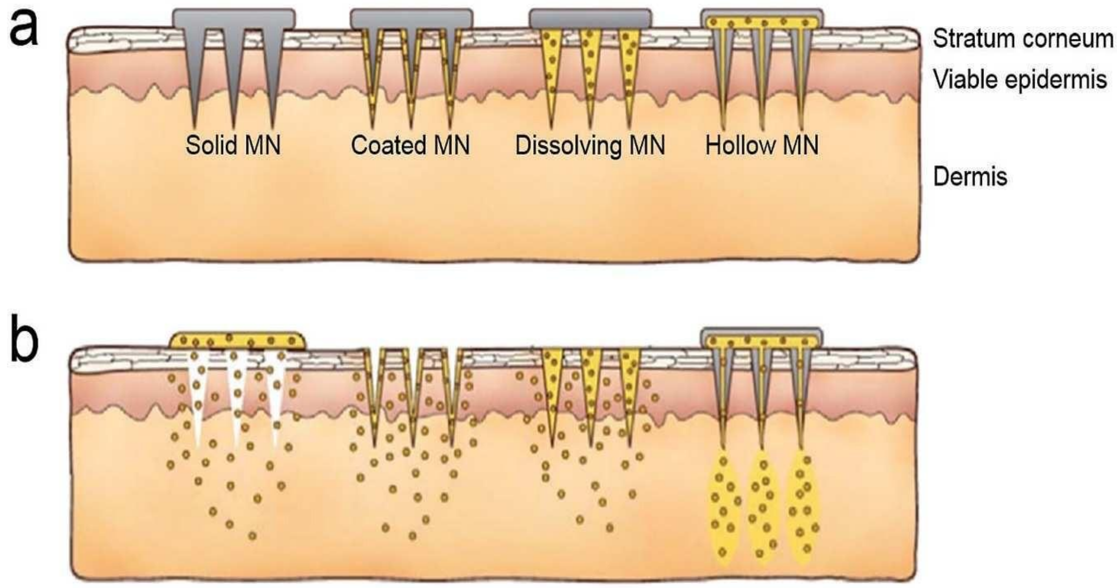

Fig. 1. The many varieties of microneedles (MNs) and their distribution methods are depicted in this diagram. (a) The most prominent MNs are solid, coated, dissolving, and hollow. (b) MNs use a variety of strategies to deliver desired cargo to the dermis layer, including transporting drugs through the skin's outer layers (Kim et al., 2012). With the author's permission, this work has been adapted (Kim et al., 2012). 2013 (Elsevier)

Table 1. The most prevalent additive manufacturing methods, the materials used, the spatial resolution, as well as the benefits and negatives of each [43-45]

Methods	Typical Materials	Resolution	Advantages	Drawbacks
Stereolithography (SLA)	Resins with "photo-active monomers acrylates – epoxides" "(Ligon et al., 2017)" - DC 100 (Extremely Precise) - DC 500 - DL 350/360 (High Changeability) - AB 001 - GM 08 (High Changeability) - DM 210 - DM 220 -	10 µm "(Ngo et al., 2018)"	Fine spatial resolution - high grade "(Ngo et al., 2018)" - remarkable uniformity - exemplary surface condition "(Ligon et al., 2017)"	Quite a few materials are supported. - printing is time consuming - printing is costly "(Ngo et al., 2018)" - insufficient biocompatibility - mechanical properties are constricted "(Ligon et al., 2017)"
"Digital Light Processing (DLP)"	"Acrylates - epoxides - plas range (High resolution and chemically resistant) - superCAST – superWAX"	25-100 µm	Maximum printing precision at a minimal price, Low manufacturing time than SLA, and less prone to " oxygen inhibition " than SLA - higher quality standard of surface are needed - accompanied by a small starting vat volume.	Confined characteristics of the mechanical section.
Two/Multi Photon Polymerization (TPP / MPP)	Acrylates	100nm-5 µm	Vast spatial resolution	"Low build pace - limited material"
3D printing (Binder jetting	Strech – "PLA – ceramics"	100 µm	Higher pace due to allowance of multi-material.	Irregular surface finish limits the strengths of parts.

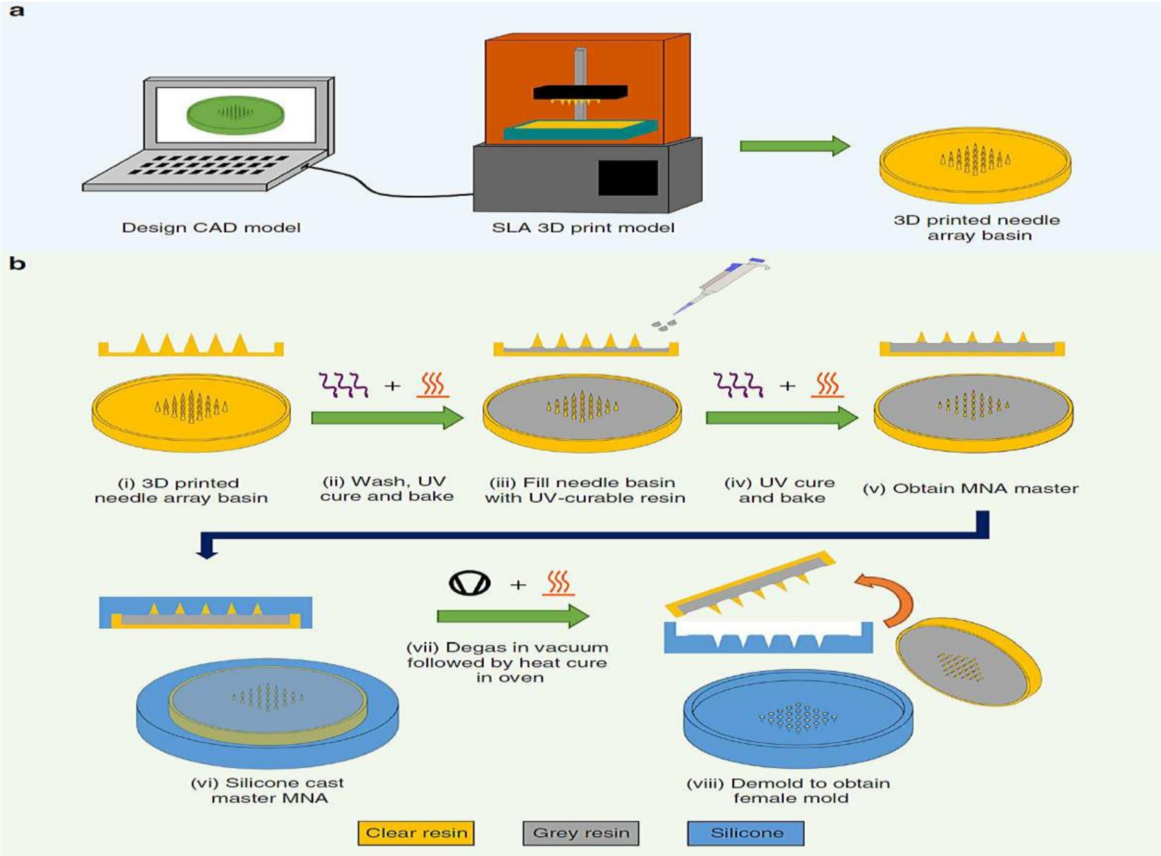

Fig. 2. Fabrication of a microneedle (MN) using stereolithography (SLA) 3D printing and a replica mould approach. (a) Following the design technique, the projected structure was 3D printed using a SLA printer. (b) The microneedle arrays (MNA) master was made by UV-curing the 3D printed MNs and then filling the basin with UV-curable resin to reach the desired MN height. After that, the final female master mould can be created using silicone, degassed in a vacuum chamber, and heated in the oven (Krieger et al., 2019). With the author's permission, this work has been adapted (Krieger et al., 2019). Nature, Springer, 2019

3D printing with controlled shape deformation, also known as 4D printing, is one way for creating bioinspired MNs with curved barbs, increasing MN adhesion to the tissue by 18 times. SLA was used to construct MNs with a 400 m base diameter, a 4 mm length, and a 10° cone tip angle. The barbs have a base diameter 200 μm and a length of 450 μm. One of the variables that have a detrimental impact on the surface quality of 3D printed MNs is the layer-by-layer nature of the 3D printing process [53-55]. Continuous Liquid Interface Production (CLIP), a single-step continuous AM process based on vat polymerization, was designed to swiftly prototype MNs to address this limitation. CLIP used polyacrylic acid, trimethylolpropane triacrylate, photopolymerizable derivatives of polyethylene glycol, and polycaprolactone to build MNs of 1000 m height, 333 m base width, and 2.3 m tip radius.

3. EMERGING APPLICATIONS IN BIOMEDICAL ENGINEERING

3.1 Drug Delivery

Immunology, cosmetics, diagnostics, and the ongoing and steady release of medicinal therapy substances via the skin after topical therapy are all the advantages of MN patches. There are a few simple customised techniques for delivering particular compounds into the body in general. The skin can operate as an active immune organ thanks to antigen-presenting cells (APCs), which are immunologically active cells because of low presence of immune cells in muscles than skin, it is more efficient and long-lasting to transfer therapeatic substances through the skin rather than intramuscularly transfer [56-57]. Medication distribution through the skin, however, has not yet realised its full potential due to a lack of resources. Technologies that are minimally intrusive, effective, user-friendly, and ubiquitous drugs. The use of skin administration can eliminate the necessity for intramuscular injections [58]. Traditional needles have a number of drawbacks, including fear of needles (trypanophobia), difficult transport and storage requirements, contamination, the risk of disease transmission, the need for skilled persons to administer immunisation, the risk of accidents, and the discomfort caused by needles [59-60]. Target biomolecules are delivered to the immediate region under the administration site, while bioactive chemicals are sent to faraway locations via the circulatory system Intradermal, subcutaneous, and intramuscular methods might be used in therapeutic settings to administer specific chemicals, factors, and medicines locally [61].

The passive diffusion of medicine into the systemic circulation system is aided by injecting target molecules directly into the muscles and subcutaneous tissue. "The release of target molecules across the epidermal barrier is a key issue in the use of MNs (Indermun et al., 2014). After penetrating the stratum corneum to circumvent the hydrophobic layer and underneath viable keratinocytes, the cutaneous tissue is momentarily disturbed in the transport of target molecules [62]. Passive diffusion is the most common way for target molecules implanted in the epidermis or upper dermis to enter systemic circulation. As a result, MN patches are good candidates for painless hypodermal and dermal injections [63]."

4. CONCLUSION AND RECOMMENDATIONS

Scientific studies on various types of MNs, such as hollow, solid, coated, and dissolvable MNs with a variety of feature sizes for a variety of biomedical applications, including drug administration, biosignal collection, and sample extraction, have recently sparked a spike in scientific studies about MNs. A range of MN production methods, including subtractive and additive approaches, were also developed. This study gives a summary of the working principles of 3D printing technologies, the greatest resolution that can be achieved, supported materials, and benefits as a reference for selecting the best manufacturing process for future MN applications. In addition, the current study includes an overview of the advantages of combining 3D printing with MNs, as well as suitable 3D printing processes for MN production, possible MN applications, and recent advancements. To manage and reduce the impact of life-threatening illnesses on healthcare systems across the world, regular and rigorous health monitoring and large-scale immunisation are necessary.

Traditional methods can fill some of the gaps in routine testing, but they are associated with low patient compliance, high prices, and limited accessibility. Healthcare costs will be decreased dramatically and life quality will be enhanced globally by replacing present procedures with mass-producible, accurate, and cost-effective point-of-need technology. "MNs are low-cost, portable, efficient, precise, and widely available devices that can be used for medicine administration, liquid sample extraction from the body, biosignal collection, and point-of-care diagnostics in a range of shapes and types. In this industry, however, there are still certain challenges to overcome." More study on the materials used to make MNs, for example, is needed to increase their ability to absorb liquids, either to allow for a greater drug load in drug delivery applications or to better sample extraction [64]. Furthermore, most of the reported incidences have been researched using tissues and animals that are identical to the genuine thing. The design and prototyping process can be reduced by eliminating the need for third-party manufacturing firms because recommended MNs with specified size parameters can be developed, altered, and produced directly via 3D printing. 3D printing has a number of difficulties, including slow printing, resolution limits, material limitations, and biocompatibility [65-66]. As a result, future research could focus on developing faster 3D printing technologies while maintaining high resolution. In laser-based approaches, enhancing the properties of the laser beam and nuzzle features in extrusion-based methods can improve the eventual resolution of printed MNs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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