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Exploring Microneedle Systems for Transdermal Drug Administration

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KEYWORDS

Microneedles; transdermal delivery; microneedle array; stratum corneum; skin

ABSTRACT:

Introduction: Transdermal administration of medication is a preferred method for administering therapeutic medications. It is simple to administer and prevent drug deterioration in the gastrointestinal tract. However, the main obstacle to drug penetration is the stratum corneum. only tiny (<500 Da) and moderately hydrophobic molecules can be administered transdermally. Microneedle (MN) arrays offer a painless substitute to improve transdermal administration and skin permeability. Through the creation of microscopic holes, this technology has the potential to transport a wide range of therapeutic macromolecules to the dermal microcirculation over the skin's surface in a way that is least intrusive to the surface and epidermis. The medication compositions and microneedle design allow for the regulation of dosage, delivery rate, and drug efficacy. This review covers microneedle systems, materials, and manufacturing methods.

Methods: Microneedle arrays can be made in a variety of methods. The most popular methods are micro mouldings, laser ablation, chemical isotropic etching, injection moulding, additive manufacturing, surface/bulk micromachining, and lithography electroforming replication.

Conclusions: Research on the use of microneedles for transdermal medication administration has gained attention since this method of delivery potentially replaces current methods and improves patient accessibility to medications. Four categories exist for microneedles: hydrogel, solid, coated, and dissolving. Ceramics, silicon, metal, polymers, and glass are just a few of the materials used to make them. To impart diverse sizes, forms, and features, various production processes are employed. Clinical experiments using different medications are utilizing microneedles, which are still undergoing evolution.

1. Introduction

Pharmaceutical efficacy depends on both the active drug component and its delivery mechanism to the body. Therefore, it's important to choose the best strategy for drug administration based on the characteristics of the drug. Oral administration is a convenient way for patients to self-administer drugs, but it might be hard to employ for biopharmaceuticals. Injections provide excellent bioavailability and quick medication effect but patient compliance is limited, and administration requires expertise. So, the optimal method of delivering a drug should be as straightforward as taking it orally and have an injection's high bioavailability [1].

Transdermal drug delivery has several benefits, including improved patient adherence, avoiding first-pass metabolism, having a lot of skin surface area to distribute the drug, and rapid dosage termination. However, only a few pharmacological formulations

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with ideal properties have been effectively sold to provide drugs via the epidermis, this is because the stratum corneum resists medication delivery. The issue of it is possible to address inadequate medication delivery by creating micron-sized needles that transfer the medicine gently throughout the stratum corneum [2].

The microneedle device disrupts the skin's surface layer to administer drugs through a topical route via diffusion. A patch with hundreds of microneedles helps administer a therapeutic amount of medication. The needle's dimensions must be optimized and limited to the extent of the epidermis of the skin. Too lengthy and dense needles can injure neurons in the dermal layer, causing pain and irritation. The skin epidermis ranges in thickness from 50 to 100 µm, with palms and soles reaching up to 1500 µm. Microneedles typically have a sharp tip that measures 150-1500 µm in length, 50-250 µm in width, and 1-25 µm in thickness. Microneedle tips can take many different shapes, including pointed, pentagonal, cylindrical, triangular, octagonal, and many others. Microneedle designs vary based on fabrication method, distribution method, needle type, and drug delivery needs [3].

The selection of biomaterial, stringent processing parameters that restrict the kinds of medications that may be employed, and the difficulty in accurately controlling the kinetics and rate of drug release are some of the present obstacles facing the development of MN arrays. Because they are inexpensive and simple to fabricate using micro-moulding techniques, polymer MNs present an appealing alternative for drug delivery that may be produced in large quantities. The effectiveness of transdermal distribution of a variety of hydrophilic compounds, including macromolecules and high-molecular-weight proteins, has recently been shown to be improved by polymer MNs. Water-soluble and biodegradable polymers are among these MNs that provide both the safe degradation or solvent dissolution of MNs and the elimination of the risk of MNs staying in the skin [4].

2. Transdermal drug delivery methods and the structure of the skin

The three sections that make up skin are the outermost layer (epidermis), which contains the stratum corneum, the middle layer (dermis), and the innermost layer (hypodermis). There are various layers in the epidermis. Dead cells make up the top layer, which sheds regularly and is gradually replaced by cells derived from the basal layer. Because collagen and elastin fibre are present in the dermis, which joins the epidermis and hypodermis, it offers strength and elasticity. The connective tissue that links the skin's dermis to underlying structures is called the hypodermis, and it contains adipose tissue for fat storage and defence. The thickness of the epidermal layer is 150–200 µm. Squamous epithelium that has been stratified and keratinized makes up the epidermis. It is composed of four or five layers of epithelial cells, according to where it is located in the body. The stratum corneum, the dead cells that make up the outermost layer of the epidermis (10–20 µm), serves as a strong barrier. It does not have any blood vessels within it.

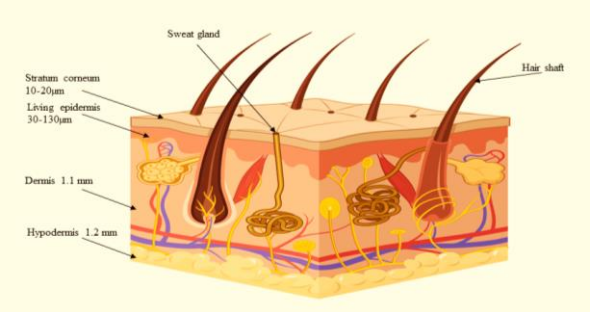

Figure 1: Structure of human skin.

The thickness of the dermis layer is 1.50-3 mm. The fibro-elastic structure known as the dermis, gives the skin its mechanical strength. A vast nerve and vascular network are present in this stratum. It is made up of vessels that carry blood and lymph, nerves, and other elements like the roots of hair and glands that produce sweat. The dermis is made of two layers of connective tissue that compose an interconnected mesh of elastin and collagenous fibres, produced by fibroblasts. Potential injury to the dermal nerve endings is the cause of the discomfort connected with parenteral medication administration. One of the biggest challenges in drug administration via the skin is getting past the intact stratum corneum layer without damaging nerve endings. By passive diffusion, only a small number of highly effective pharmacological molecules with a molecular weight of less than 500 Da and strong lipophilicity can be given directly [5]. Several physical and chemical strategies have been used to increase medication

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absorption via the skin. Chemical methods include dissolving the stratum corneum lipid or making medications more soluble by using penetration enhancers such as surfactants, fatty acids/esters, and solvents. Physical techniques such as iontophoresis, magnetophoresis, sonophoresis, and electroporation have been proven to be effective in establishing channels for a limited number of medications to pass through the skin [2].

3. Microneedle System and Drug Delivery

To administer the medication topically, the microneedle delivery system briefly disrupts the skin's surface layer, adhering to the diffusion mechanism. Similar to the depth of the epidermis of the human skin, the needle's size must be optimized and limited. In the dermis, excessively long and thick needles can harm the nerves and result in pain and suffering. Overall, the skin's epidermis is between 50 and 100 µm thick, with the palms and soles having patches as thick as 1500 µm. Typically, the length, width, and tip thickness of these microneedles range from 150–1500 µm, with a sharp tip. There exist several shapes for microneedle tips, including but not limited to pointed, pentagonal, cylindrical, triangular, and octagonal shapes. Different microneedle designs exist based on the medications to be administered, the type of microneedle, the delivery technique, and the production process. Depending on the fabrication procedure used to manufacture the microneedle, different microneedles are made from different materials. We then go over a couple of the materials' characteristics [3].

3.1. Mechanism

The diffusion mechanism is responsible for topical medication delivery. Shortly, the skin is interrupted in the microneedle medication delivery system [6]. To administer enough medication to produce the required therapeutic response, thousands of microneedles are arranged in a certain pattern on a small patch that looks like a typical transdermal patch sold in stores. Bypassing the barrier layer, it pierces the stratum corneum. The medication is injected directly onto the skin's surface, or topmost the dermal layer, after which it enters the bloodstream and, upon reaching the site of action, manifests a medicinal effect [7].

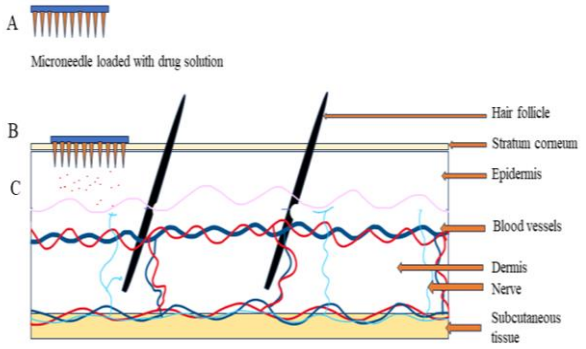

Figure 2: Use of microneedles to provide medication: (A) microneedle loaded with medication dose; (B) microneedle placed inside the skin; (C) drug discharge into the skin.

Previously, to get beyond the stratum corneum's barrier function, the skin was penetrated with a number of solid microneedles. After treating the affected skin area, a medicated patch was applied. The needles were composed of silicon wafers. This method is called "poke and patch." This method was also attempted to non-invasively measure the glucose level by extracting the interstitial fluid [8]. Later studies on microneedle technology focused on creating solid microneedles that were dip-coated with medication solution. Before the drug's release, the skin was punctured. Using a "coat and poke" technique, merely a tiny quantity of medication (around 1 mg) possibly covered over the microneedles, and consistent coating required significant tuning. Following more investigation, the "poke and release" strategy was developed. After being administered, polymers and polysaccharides used to make microneedles either slowly dissolved or broke down. Using a range of easily available carbohydrates and polymers, the "poke and release" method has the benefit of allowing the drug release to be adjusted according to need. Hollow microneedles were created since it was still not possible to provide a significant amount of medication using dissolvable or degradable microneedles, unlike other physical methods. This technique known as "poke and flow," engages in puncturing the skin, thus permitting medication to seep via microneedles that are hollow into the patch's reservoir [9].

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4. Techniques for Transdermal Delivery Using Microneedles

Important factors that impact the effectiveness of MNA-based drug administration are mostly related to the MNA's design (including its size, shape, and manufacturing materials and procedures) as well as the kind of active ingredient that is delivered. "Poke and patch," "poke and flow," "coat and poke," and "poke and release" are some categories into which the various tactics might be divided [10].

4.1. Poke and Patch Solid Microneedle

The "poke and patch" method involved puncturing the skin with solid MNA to generate tiny pores that penetrate to the lowest levels of the epidermis. Because the stratum corneum, the primary barrier to permeability, is broken down, this technique greatly enhances the passive transport of medications through the skin [11]. There are two steps in this approach: Initially, the MNAs are used to puncture the skin and are then extracted; second, the medication is administered in a traditional dose form (cream, patch, or solution), acting as an external drug reservoir. The extended half-life and stronger antibody response of microneedles make them ideal for vaccine administration. Solid microneedles are easier to make than hollow ones, and they have better mechanical qualities and sharper tips. It is also possible to create a solid microneedle using silicon, metals, and polymers, among other materials. Its ease of use in a clinical application and its technological simplicity make it very appealing. This method has several drawbacks and is not without criticism. A primary disadvantage is that the micropores are only open for a brief period, which could result in an early cessation of the active substance's delivery [12].

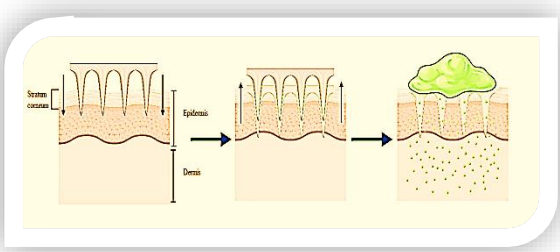

Figure 3: Diagrammatic representation of the poke and patch method with a solid microneedle array.

4.2. Coat and Poke using Coated Microneedle

The "coat and poke" techniques are an additional method for using solid MNA. This method entails coating the surface of the solid microneedles with a formulation that contains a medicine or vaccination [13]. Following MNA insertion, this technique permits medication diffusion from the coating layer into the deep layers of the epidermis. According to the coating layer's thickness, it usually carries a lesser quantity of the medication. It is essential to be able to consistently coat a controlled drug layer onto MNs to successfully administer medication using a coated MN.

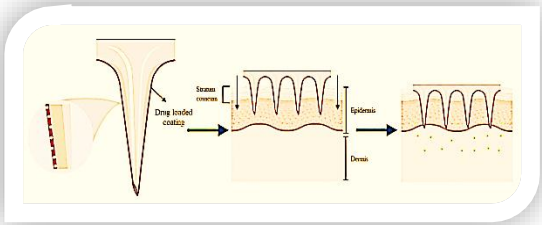

Figure 4: Diagrammatic representation of the coat and poke method.

4.3. Hydrogel-Forming and Dissolving Microneedles for Poke and Release

Various materials that are compostable and dissolve in water can be used. To create a dissolving MNA, which allows for the loading and release of medications as the MNA dissolves following insertion [14,15]. Expertise in technology is needed for the creation and manufacturing of a dissolvable MN array. But complete insertion, which is frequently challenging to achieve, is also necessary for this form of MN, and its dissolution is delayed. By regulating the pace at which the formulation dissolves utilized as the MNA matrix, dissolving microneedles can sustain regulated drug release for an extended period, which is an improvement over the "poke and patch" method. Because the MNA can puncture the skin and is left in place until complete breakdown, another benefit is that the medication administration procedure is reduced to just one step [16,17]. Dissolving MNA prevents the production of sharps waste, lowering management costs and lowering the risk of needlestick injuries. However, the disadvantages include a possible decreased capacity to puncture the stratum corneum and restricted drug loading.

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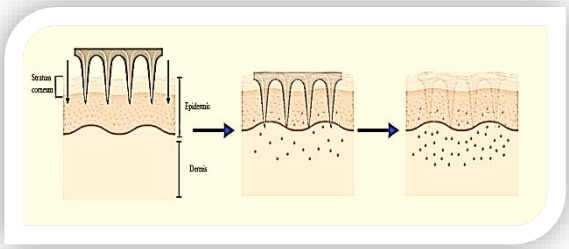

Figure 5: Schematic illustration of the poke and release approach.

These devices are intended to create continuous, unlocked tiny pores between cutaneous capillaries by absorbing skin interstitial fluid upon installation. With this technique, less effective drugs kept in an attached patch-style drug reservoir can be released [18,19].

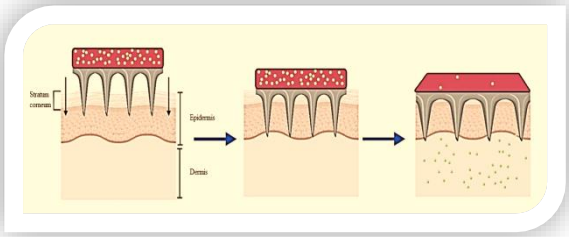

Figure 6: Schematic illustration of hydrogel-forming or swelling MNA.

4.4. Poke and Flow using Hollow Microneedle

The "poke and flow" methods were developed to get around the drawbacks of hypodermic injections by injecting a medication solution under the skin [20,21]. The hollow microneedle is made up of a void or unfilled chamber that can be utilized for preserving or inserting drugs. A larger dose is used with the hollow microneedle and amount of medication solution handling capacity than the solid microneedle. Moreover, a hollow microneedle can introduce the medication into the dermis or viable epidermis, which is appropriate for high molecular weight chemicals. In this approach, microneedles function similarly to hypodermic needles, which are used to inject medication formulations following skin perforation. Because of their micrometric scale, the manufacturing process is challenging and costly. In contrast, due to the lower size of these needles, the average patient accepts this procedure more than traditional injections.

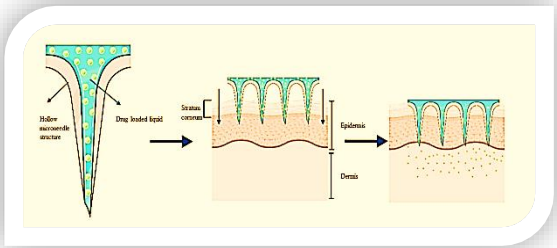

Figure 7: Illustration of the poke and release method schematically

5. MNA Fabrication

5.1. Materials

Depending on the design or components of the patch, microneedles can be made of a variety of materials, including metal and polymer. In general, the materials used to make microneedles should be strong enough to penetrate the skin. Non-dissolving microneedles are biocompatible, inert, and powerful enough to penetrate skin without triggering an immunological reaction. On the other hand, water-soluble and biocompatible matrices should typically be present in coated and dissolving microneedles. Furthermore, it should break down or dissolve in the body without causing toxicity. During the microneedle patch manufacturing, storage, and shipping processes, the matrices and medicines must be compatible. The features of the several materials that are utilized to make microneedles are listed below [22].

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Table 1: Materials used to prepare microneedles

Metals	Synthetic polymers		Natural polymers
	Biodegradable polymer	Non-Biodegradable polymer	
Silicon [71]	Polylactic acid (PLA) [75]	Polyvinyl acetate (PVA)	Thermoplastic starch [78]
Stainless steel [72]	Polyglycolic acid (PGA) [75]	Alginic acid	Carboxymethylcellulose [78]
Titanium [73]	Polylactide-co-glycolic acid [75] (PLGA)	Gantrez AN-139, a copolymer of methyl vinyl ether and maleic anhydride (PMVE/MA)	Amylopectin [78]
Mesoporous silicon [74]	Polycarbonate [76], Polyvinylpyrrolidone (PVP) [77]	Carbopol 971 P-NF, polyetherimide	Dextran, galactose [78], Chondroitin sulfate, maltose [79]

Silicon: Since silicon has sufficient mechanical strength for skin insertion, solid and coated microneedles are frequently made from it [23]. Deep reactive ion etching and photolithography can be used to precisely make silicon microneedles with small, sharp points that are less than 100 μm in length [24]. Nevertheless, the procedure is costly, the equipment is pricey, and the production rate is poor. There can be safety issues if the silicon microneedle breaks off from the skin and remains in the tissue. Lately, silicon has been utilized for reverse master moulds instead of solid microneedles.

Metal: Metal materials have strong mechanical and tensile strength; therefore, they can readily penetrate through the skin. They're utilized to make solid, coated, and hollow microneedles. Microneedles are often made of stainless steel [25] or titanium (Ti) [26]. While stainless steel is commonly utilized in microneedle manufacture, compared to Ti alloy, it deteriorates more quickly. Despite being greater in price, titanium alloys are tougher structurally than stainless steel.

Polymer: Microneedles must be made from soluble in water, biodegradable, and skin-insertion-durable polymers [27]. The preferred technique for creating polymer microneedles is solvent casting. By using this method, the microneedle structure is used to make an inverse mould, onto which a polymer mixture is poured, given time to cure, and then removed from the mould. Solvent casting is a technique applied for manufacturing hydrogel or dissolving microneedles using a variety of polymers, such as hyaluronic acid, CMC, polyvinyl pyrrolidone, and poly (lactic-co-glycolic acid) (PLGA). Typically, dissolvable, hydrogel-forming, solid, coated, and hollow MN arrays are constructed with polymers. [28].

Glass: Most hollow glass microneedles are created by wet etching or using a micropipette extractor [29]. Its durability is sufficient for implantation into the skin. Sterilization is easy because the material is stable at high pressures and temperatures and is biocompatible. However, it fractures easily; specifically, granulomas or inflammation may arise if the microneedle tip breaks and remains in the skin tissue.

Ceramic: Alumina, calcium phosphate, and calcium sulphate are examples of ceramic materials that have been studied for their potential use in the production of microneedles due to their biocompatibility and excellent mechanical strength. [30].

Carbohydrate: By using the hot melt process, carbohydrate microneedles are created using silicon and metal microneedle templates [31]. These are affordable alternatives for other microneedle materials, and more significantly, they pose no health risks to people [32]. The typical sugar used to make microneedles is maltose.

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They provide several drawbacks in addition to their advantages.

5.2. MN Manufacturing Method

Microneedle arrays can be made in a variety of methods. The most popular methods are micro mouldings, laser ablation, chemical isotropic etching, injection moulding, additive manufacturing, surface/bulk micromachining, and lithography electroforming replication.

Micro-Moulding:

The technique of micro-moulding entails copying the master mould. A solution including a polymer and active medicinal ingredients is used to cast the mould [33]. For mass production, micro-moulding is regarded as an economical technique [69]. For the manufacture of MN, micro-moulding is frequently employed with polymer material. When it comes to micro-moulding processes, the PDMS has many benefits, including inexpensive, convenient usage, stable temperature and minimal surface energy [34,70]. The difficulties in controlling the drug loading capacity the polymer's mechanical properties, and penetration depth are the limitations of this approach.

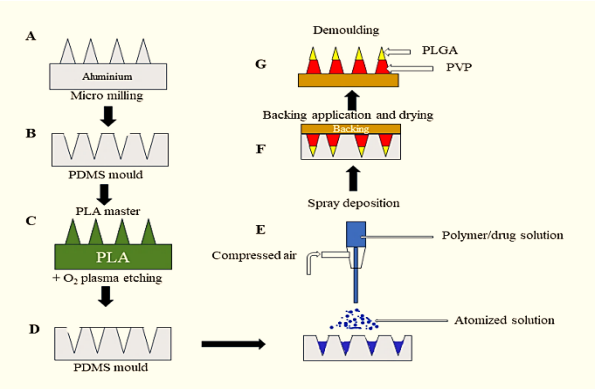

Figure 8: The method used to fabricate multilayer MNs is (A) micro-milling aluminium masters. (B) PDMS mould replication from the master. (C) Using oxygen plasma for tip sharpening and micro-moulding to fabricate PLA master. (D) Duplication of the PLA master PDMS mould. (E) Fill the mould cavity with a drug-containing polymer solution by spray deposition. Polymer solutions are deposited one after the other to produce multilayer MN. (F) To solidify the polymer, after covering the mould with the yellow supporting substance, allow it to air dry. Demoulded solidified multilayer MN array is removed from the mould (G). PLGA and PVP layers are represented by green and red, respectively.

Laser Ablation:

Laser ablation is a technique that uses a concentrated optical laser beam to extract an object from a substrate to produce microneedle arrays. For numerous purposes, multiple substances have been treated at the micro and nanoscale using lasers [35-42]. Numerous kinds of lasers have been researched for microneedle array production. CO^2 [43,44], UV excimer, and femtosecond laser machines are a few of these. The production of MNs is considered to be quick and efficient when using the laser ablation approach. Reaching the material sheet's burn point takes the laser beam between 10 and 100 nanoseconds [45]. You could also shape any metal using a laser. The mechanical and structural characteristics of MN are altered by this process, which is linked to heat reactions near the cutting edge. This could cause fatigue resistance or other unfavourable effects in MNs, like cracking. The substrate is subjected to minimal heat loads during the non-contact laser ablation procedure. Nevertheless, in comparison to other kinds of equipment, the laser is more expensive [46]. For large-scale manufacturing, the laser ablation approach is not appropriate [47].

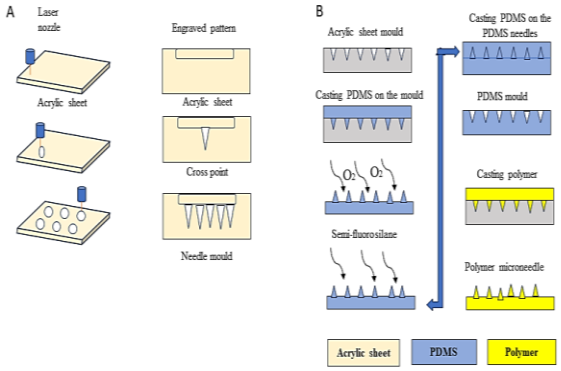

Figure 9: Manufacturing of the MN mould: (A) The suggested cross-over lines (COL) technique was employed to construct the MN acrylic mould using a CO_2 laser cutter. (B) Polydimethylsiloxane (PDMS) MN moulds, which may be utilized to create a range of

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polymer-based MNs, were made using the acrylic mould.

Lithography:

The master design for the geometric shapes is transferred onto a substrate's surface using the lithography technique [48-53]. Because photolithography has several applications in the microelectronics area, pattern transfer is the primary use for it [54]. In other techniques, such as microelectronic and micromachining, lithography is the first step towards fabricating an MN. For lithography, the photoresist needs to be precisely treated. Approximately 30–35% of the cost of producing integrated circuits is attributed to this technology. It is possible to create products from a variety of materials, such as glass, metal, ceramics, and polymers. by lithography [55]. In addition, it creates smooth vertical sidewalls and exact geometries. However, this method required a sophisticated space (cleanroom) and lengthy manufacturing times [56].

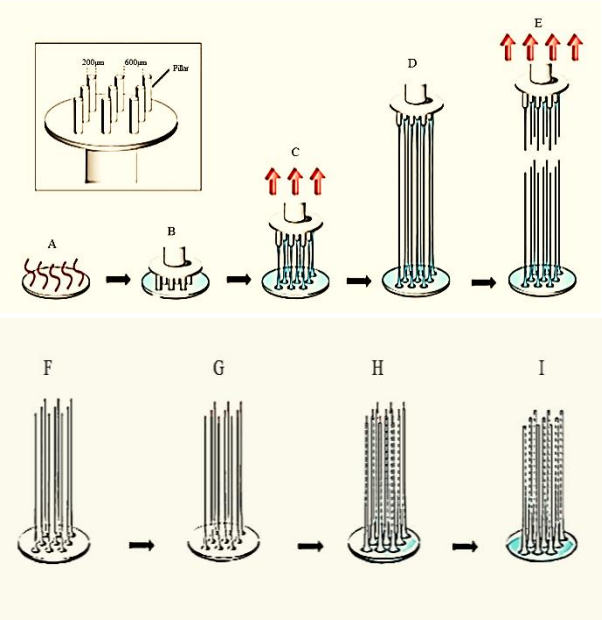

Figure 10: Using lithography, a 3D UHAR MN is created. An illustration system for sketching lithography with patterned pillars is displayed in the inset. 200mm diameter and 3mm length stainless drills served as columns and were arranged in a three-by-three array on a PDMS frame. (A) After cooling, spin coating was used on the SU-8 2050 photosensitive. (B) Lithography was carried out using drawing after the photoresist made contact with the patterned pillar. (C) The drawing resulted in the substrate and pillar appearing as an extended conical bridge. (D) A stiff structure was produced by curing the intended UHAR microneedle mould. (E) A solid MN mould was created by the split of the three-dimensional microstructure bridge. (F) The solid MN moulds undergo chemical layering. (G) Using a drawing system, electroless material was applied to the upper part of the MN mould. (H) Conducting solid microneedle moulds with nickel electroplating. (I) Following the removal of the photosensitive MN mould and electroless assurance, the hollow metallic MN array was created.

Injection Moulding:

Another technique for fabricating MN is injection moulding. The below figure illustrates how injection moulding and the hot embossing technique are used to fabricate MNs. The MNs were utilised for several insertions without blunting the needle, demonstrating their ability to tolerate strong forces. Hydrophilic compounds with a high molecular weight could be delivered via these needles. This method allows MNs to be produced in large quantities at a reasonable cost. Micro-injection moulding offers high insertion flow rates, precise dosing, and excellent repeatability when used to separate the moulding and polymer melt injection processes. [57]. The injection moulding technique has a limitation in regulating small shot sizes because of the common screw size (15-150 mm) and greater initial equipment costs [58].

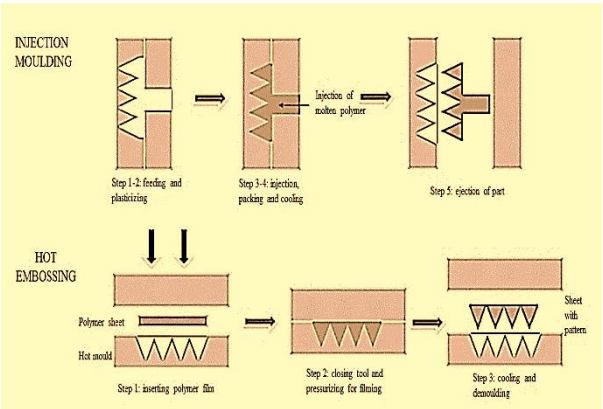

Figure 11. Step-and-repeat hot embossing and regular injection moulding.

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Additive Manufacturing:

The production of MN arrays by producing additively, or three-dimensional moulding, has garnered significant attention in recent years. Layer by layer, the desired material is deposited by a 3D printer to create an object. Recent years have seen a sharp increase in the use of 3D printing technology in tissue engineering implants within the biomedical device business [59-67]. One benefit of manufacturing an MN array with 3D printers is the ability to modify design parameters and shorten processing times [68].

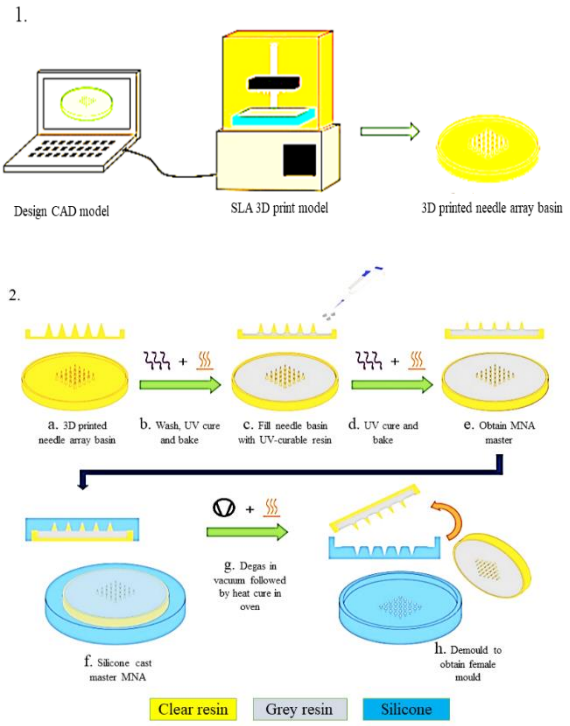

Figure 12: An outline of the fabrication process known as "Print and Fill" (1) A Form 2 SLA printer is used to 3D print the needle array basin design after it is designed. (2) Production of MNA master moulds First, a 3D printed needle array basin is taken; then, it is washed, UV-cured, and baked; then, it is filed with UV-curable resin; finally, it is subjected to a subsequent UV drying and heating; finally, microneedle array master is obtained; then, silicone is cast over MNA master; finally, the silicone mould is degassed and then heated in an oven; finally, it is demoulded to produce a usable MN mould.

Conclusion

Transdermal medication administration using microneedles, is gaining popularity in research due to their ability to improve patient access to medications by substituting traditional methods of administration. There are categories for microneedles like solid, coated, dissolving, or hydrogel compositions. They are constructed from a variety of materials, such as ceramics, silicon, metal, polymers, and glass. To impart unique shapes, sizes, and characteristics, various production processes are employed. Through clinical trials, microneedles are still evolving and using different medications. This approach has generally yielded positive outcomes in experiments. This approach has the potential to offer therapeutic benefits in various fields. In the field of transdermal medication administration, MNA has grown to be a resource with significant presence and potential. Their enormous potential resides in their capacity to interfere with the less intrusive method, maintaining the skin's barrier function rather than alternative techniques. It's nearly painless to insert these devices because they don't go through the skin's nerve terminations. However, research has indicated that MNA produces significantly less anxiety than other techniques, including injections, which may lead to higher compliance rates, particularly in the paediatric population. We have compiled the research conducted in this field by numerous research groups in this review. Different processes have been used to produce MNs with varying designs. Not all of them, though, can result in the intended improvement in the delivery of the target molecule. Drug transport may be impacted by a wide range of factors, including proportions of length, weight, appearance, material type, patch size, and length of application about MNs. Researchers have put up various suggestions to explain how these factors affect skin permeability. From basic skin patches to point-of-care instruments, MNs have revolutionized the field of transdermal pharmaceutical administration.

References

1. Lee IC, He JS, Tsai MT, Lin KC. Fabrication of a novel partially dissolving polymer microneedle patch for transdermal drug delivery. J Mater Chem B. 2015;3(2):276–85.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 2115-2127 | ISSN:2251-6727

2. Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug delivery system. Journal of Pharmacy and Pharmacology. 2011 Dec 8;64(1):11–29.
3. Damiri F, Kommineni N, Ebhodaghe SO, Bulusu R, Jyothi VGSS, Sayed AA, et al. Microneedle-Based Natural Polysaccharide for Drug Delivery Systems (DDS): Progress and Challenges. Pharmaceuticals. 2022 Feb 3;15(2):190.
4. Lee IC, He JS, Tsai MT, Lin KC. Fabrication of a novel partially dissolving polymer microneedle patch for transdermal drug delivery. J Mater Chem B. 2015;3(2):276–85.
5. Matteucci M et al. A compact and disposable transdermal drug delivery system. Microelectron Eng 2008; 85: 1066–1073.
6. Wermeling, D.P.; Banks, S.L.; Hudson, D.A.; Gill, H.S.; Gupta, J.; Prausnitz, M.R.; Stinchcomb, A.L. Microneedles permit transdermal delivery of a skin-impermeant medication to humans. Proc. Natl. Acad. Sci. USA 2008, 105, 2058–2063.
7. Alkilani, A.; McCrudden, M.T.; Donnelly, R. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the Stratum Corneum. Pharmaceutics 2015, 7, 438–470.
8. Wang PM et al. Minimally invasive extraction of dermal interstitial fluid for glucose monitoring using microneedles. Diabetes Technol Ther 2005; 7: 131–141
9. Milewski M et al. Current aspects of formulation efforts and pore lifetime related to microneedle treatment of skin. Expert Opin Drug Deliv 2010; 7: 617–629.
10. Prausnitz, M.R. Engineering Microneedle Patches for Vaccination and Drug Delivery to Skin. Annu. Rev. Chem. Biomol. Eng. 2017, 8, 177–200.
11. Li, W.-Z.; Huo, M.-R.; Zhou, J.-P.; Zhou, Y.-Q.; Hao, B.-H.; Liu, T.; Zhang, Y. Super-Short Solid Silicon Microneedles for Transdermal Drug Delivery Applications. Int. J. Pharm. 2010, 389, 122–129.
12. Gupta, J.; Gill, H.S.; Andrews, S.N.; Prausnitz, M.R. Kinetics of Skin Resealing after Insertion of Microneedles in Human Subjects. J. Control. Release 2011, 154, 148–155.
13. Chen, Y.; Chen, B.Z.; Wang, Q.L.; Jin, X.; Guo, X.D. Fabrication of Coated Polymer Microneedles for Transdermal Drug Delivery. J. Control. Release 2017, 265, 14–21.
14. Rodgers, A.M.; McCrudden, M.T.C.; Vincente-Perez, E.M.; Dubois, A.V.; Ingram, R.J.; Larrañeta, E.; Kissenpfennig, A.; Donnelly, R.F. Design and Characterisation of a Dissolving Microneedle Patch for Intradermal Vaccination with Heat-Inactivated Bacteria: A Proof of Concept Study. Int. J. Pharm. 2018, 549, 87–95.
15. Lee, W.-J.; Han, M.-R.; Kim, J.-S.; Park, J.-H. A Tearable Dissolving Microneedle System for Shortening Application Time. Expert Opin. Drug Deliv. 2019, 16, 199–206.
16. Ito, Y.; Yoshimitsu, J.-I.; Shiroyama, K.; Sugioka, N.; Takada, K. Self-Dissolving Microneedles for the Percutaneous Absorption of EPO in Mice. J. Drug Target 2006, 14, 255–261.
17. Hong, X.; Wei, L.; Wu, F.; Wu, Z.; Chen, L.; Liu, Z.; Yuan, W. Dissolving and Biodegradable Microneedle Technologies for Transdermal Sustained Delivery of Drug and Vaccine. Drug Des. Devel. Ther. 2013, 7, 945–952.
18. Singh, T.R.R.; Garland, M.J.; Migalska, K.; Salvador, E.C.; Shaikh, R.; McCarthy, H.O.; Woolfson, A.D.; Donnelly, R.F. Influence of a Pore-Forming Agent on Swelling, Network Parameters, and Permeability of Poly(Ethylene Glycol)-Crosslinked Poly(Methyl Vinyl Ether-Co-Maleic Acid) Hydrogels: Application in Transdermal Delivery Systems. J. Appl. Polym. Sci. 2012, 125, 2680–2694.
19. Donnelly, R.F.; Singh, T.R.R.; Garland, M.J.; Migalska, K.; Majithiya, R.; McCrudden, C.M.; Kole, P.L.; Mahmood, T.M.T.; McCarthy, H.O.; Woolfson, A.D. Hydrogel-Forming Microneedle Arrays for Enhanced Transdermal Drug Delivery. Adv. Funct. Mater. 2012, 22, 4879–4890.
20. Norman, J.J.; Choi, S.-O.; Tong, N.T.; Aiyar, A.R.; Patel, S.R.; Prausnitz, M.R.; Allen, M.G. Hollow Microneedles for Intradermal Injection Fabricated by Sacrificial Micromolding and Selective Electrodeposition. Biomed. Microdevices 2013, 15, 203–210.
21. Martanto, W.; Moore, J.S.; Kashlan, O.; Kamath, R.; Wang, P.M.; O'Neal, J.M.; Prausnitz, M.R.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 2115-2127 | ISSN:2251-6727

Microinfusion Using Hollow Microneedles. Pharm. Res. 2006, 23, 104–113.

22. Aldawood FK, Andar A, Desai S. A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications. Polymers (Basel). 2021 Aug 22;13(16):2815.
23. Hoang MT, Ita KB, Bair DA. Solid microneedles for transdermal delivery of amantadine hydrochloride and pramipexole dihydrochloride. Pharmaceutics. 2015 Dec;7(4):379-96.
24. Donnelly RF, Singh TR, Tunney MM, Morrow DI, McCarron PA, O'Mahony C, Woolfson AD. Microneedle arrays allow lower microbial penetration than hypodermic needles in vitro. Pharmaceutical research. 2009 Nov;26:2513-22.
25. Gupta J, Gill HS, Andrews SN, Prausnitz MR. Kinetics of skin resealing after insertion of microneedles in human subjects. Journal of controlled release. 2011 Sep 5;154(2):148-55.
26. McCarthy PT, Otto KJ, Rao MP. Robust penetrating microelectrodes for neural interfaces realized by titanium micromachining. Biomedical microdevices. 2011 Jun;13:503-15.
27. Prausnitz MR. Engineering microneedle patches for vaccination and drug delivery to skin. Annual review of chemical and biomolecular engineering. 2017 Jun 7;8:177-200.
28. Donnelly, R.F.; Morrow, D.I.J.; McCrudden, M.T.C.; Alkilani, A.Z.; Vicente-Pérez, E.M.; O'Mahony, C.; González-Vázquez, P.; McCarron, P.; Woolfson, A.D. Hydrogel-Forming and Dissolving Microneedles for Enhanced Delivery of Photosensitizers and Precursors. Photochem. Photobiol. 2014, 90, 641–647.
29. Dharadhar S, Majumdar A, Dhoble S, Patravale V. Microneedles for transdermal drug delivery: a systematic review. Drug development and industrial pharmacy. 2019 Feb 1;45(2):188-201.
30. Ita K. Ceramic microneedles and hollow microneedles for transdermal drug delivery: Two decades of research. Journal of Drug Delivery Science and Technology. 2018 Apr 1;44:314-22.
31. Donnelly, R.F.; Morrow, D.I.J.; Singh, T.R.R.; Migalska, K.; McCarron, P.A.; O'Mahony, C.; Woolfson, A.D. Processing difficulties and instability of carbohydrate microneedle arrays. Drug Dev. Ind. Pharm. 2009, 35, 1242–1254.
32. Miyano, T.; Tobinaga, Y.; Kanno, T.; Matsuzaki, Y.; Takeda, H.; Wakui, M.; Hanada, K. Sugar Micro Needles as Transdermic Drug Delivery System. Biomed. Microdevices 2005, 7, 185–188.
33. Donnelly, A.D.W.R.F.; Singh, T.R.R.; Morrow, D.I.J. Microneedle-Mediated Transdermal and Intradermal Drug Delivery; John Wiley & Sons: Hoboken, NJ, USA, 2012.
34. Armani, D.; Liu, C.; Alum, N. Re-configu le fluid circuits by PDMS Elastomer Micromachinig. In Proceedings of the IEEE International Conference on Micro Electro Mechanical Systems, Orlando, FL, USA, 21 January 1999; pp. 222–227.
35. Adarkwa, E.; Desai, S. Scalable Droplet Based Manufacturing Using In-Flight Laser Evaporation. J. Nanoeng. Nanomanuf. 2016, 6, 87–92.
36. Yang, M.; Xu, Z.; Desai, S.; Kumar, D.; Sankar, J. Fabrication of Micro Single Chamber Solid Oxide Fuel Cell Using Photolithography and Pulsed Laser Deposition. J. Fuel Cell Sci. Technol. 2015, 12, 021004.
37. Desai, S.; Esho, T.; Kaware, R. Experimental investigation of controlled microdroplet evaporation toward scalable micro/nanomanufacturing. IIE Trans. 2012, 44, 155–16
38. Esho, T.; Desai, S. Laser based microdroplet evaporation towards scalable micro and nano manufacturing. In Proceedings of the 2012 Industrial and Systems Engineering Research Conference, Orlando, FL, USA, 19–23 May 2012; pp. 1750–1757.
39. Parupelli, S.K.; Desai, S. Understanding Hybrid Additive Manufacturing of Functional Devices. Am. J. Eng. Appl. Sci. 2017, 10, 264–271.
40. Desai, S.; Craps, M.; Esho, T. Direct writing of nanomaterials for flexible thin-film transistors (fTFTs). Int. J. Adv. Manuf. Technol. 2012, 64, 537–543.
41. Ahmed, M.; El-Naggar, M.E.; Aldalbahi, A.; El-Newehy, M.H.; Menazea, A. Methylene blue degradation under visible light of metallic nanoparticles scattered into graphene oxide using laser ablation technique in aqueous solutions. J. Mol. Liq. 2020, 315, 113794.
42. Ismail, A.M.; El-Newehy, M.H.; El-Naggar, M.E.; Moydeen, A.M.; Menazea, A.A. Enhancement the Electrical Conductivity of the Synthesized

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 2115-2127 | ISSN:2251-6727

Polyvinylidene Fluoride/Polyvinyl Chloride Composite Doped with Palladium Nanoparticles via Laser Ablation; Elsevier: Amsterdam, The Netherlands, 2020; Volume 9, pp. 11178–11188.

43. Tu, K.T.; Chung, C.K. Fabrication of biodegradable polymer microneedle array via CO2 laser ablation. In Proceedings of the 10th IEEE International Conference on Nano/Micro Engineered and Molecular Systems, Xi'an, China, 7–11 April 2015; pp. 494–497.
44. Nejad, H.R.; Sadeqi, A.; Kiaee, G.; Sonkusale, S. Low-cost and cleanroom-free fabrication of microneedles. Microsyst. Nanoeng. 2018, 4, 17073.
45. Jeggy, C. Micro-Injection Moulding: From Process to Modelling; Presses Univ. de Louvain: Louvain-la-Neuve, Belgium, 2004.
46. Yuan, W.; Hong, X.; Wu, Z.; Chen, L.; Liu, Z.; Wu, F.; Wei, L.L. Dissolving and biodegradable microneedle technologies for transdermal sustained delivery of drug and vaccine. Drug Des. Dev. Ther. 2013, 7, 945–952.
47. Lutton, R.; Larrañeta, E.; Kearney, M.-C.; Boyd, P.; Woolfson, A.; Donnelly, R.F. A novel scalable manufacturing process for the production of hydrogel-forming microneedle arrays. Int. J. Pharm. 2015, 494, 417–429.
48. Donnelly, R.F.; Raghu, T.; Singh, R.; Woolfson, D. Microneedle-based drug delivery systems: Microfabrication, drug delivery, and safety. Drug Deliv. 2010, 17, 187–207.
49. Gaikwad, A.; Desai, S. Understanding Material Deformation in Nanoimprint of Gold using Molecular Dynamics Simulations. Am. J. Eng. Appl. Sci. 2018, 11, 837–844.
50. Gaikwad, A.; Odujole, J.; Desai, S. Atomistic investigation of process parameter variations on material deformation behavior in nanoimprint lithography of gold. Precis. Eng. 2020, 64, 7–19.
51. Odujole, J.I.; Desai, S. Molecular dynamics investigation of material deformation behavior of PMMA in nanoimprint lithography. AIP Adv. 2020, 10, 095102.
52. Odujole, J.; Desai, S. Atomistic Investigation of Material Deformation Behavior of Polystyrene in Nanoimprint Lithography. Surfaces 2020, 3, 649–663.
53. Gaikwad, A.; Desai, S. Molecular Dynamics Investigation of the Deformation Mechanism of Gold with Variations in Mold Profiles during Nanoimprinting. Materials 2021, 14, 2548.
54. Madou, M.J. Fundamentals of Microfabrication: The Science of Miniaturization; CRC Press: Boca Raton, FL, USA, 2002.
55. Tran, K.T.; Nguyen, T.D. Lithography-based methods to manufacture biomaterials at small scales. J. Sci. Adv. Mater. Devices 2017, 2, 1–14.
56. Nejad, H.R.; Sadeqi, A.; Kiaee, G.; Sonkusale, S. Low-cost and cleanroom-free fabrication of microneedles. Microsyst. Nanoeng. 2018, 4, 17073.
57. Demir, Y.K.; Akan, Z.; Kerimoglu, O. Characterization of Polymeric Microneedle Arrays for Transdermal Drug Delivery. PLoS ONE 2013, 8, e77289.
58. Juster, H.; van der Aar, B.; de Brouwer, H. A review on microfabrication of thermoplastic polymer-based microneedle arrays. Polym. Eng. Sci. 2019, 59, 877–890.
59. Parupelli, S.K.; Desai, S. A Comprehensive Review of Additive Manufacturing (3D Printing): Processes, Applications and Future Potential. Am. J. Appl. Sci. 2019, 16, 244–272.
60. Aldawood, F.K.; Desai, S.; Chang, S. Additive Manufacturing of Compensator Devices for Radiation Therapy. In Proceedings of the 2012 IISE Annual Conference, Virtual Conference, 1–3 November 2020.
61. Desai, S.; Bidanda, B. Reverse Engineering: A Review & Evaluation of Contact Based Systems. In Rapid Prototyping; Kluwer Academic Publishers: New York, NY, USA, 2006; pp. 107–131.
62. Adarkwa, E.; Desai, S.; Ohodnicki, J.; Roy, A.; Lee, B.; Kumta, P.N. Amorphous calcium phosphate blended polymer coatings for biomedical implants. In Proceedings of the 2014 Industrial and Systems Engineering Research Conference, Montréal, QC, Canada, 31 May–3 June 2014; pp. 132–138.
63. Altubaishe, B.; Clarke, J.; McWilliams, C.; Desai, S. Comparative Analysis of Risk Management Strategies for Additive Manufacturing Supply Chains. Am. J. Appl. Sci. 2019, 16, 273–282
64. Haeberle, G.; Desai, S. Investigating Rapid Thermoform Tooling Via Additive Manufacturing (3d Printing). Am. J. Appl. Sci. 2019, 16, 238–243.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 2115-2127 | ISSN:2251-6727

65. Mckenzie, J.; Parupelli, S.; Martin, D.; Desai, S. Additive Manufacturing of Multiphase Materials for Electronics. In Proceedings of the 2017 Industrial and Systems Engineering Conference, Pittsburgh, PA, USA, 20–23 May 2017.
66. Desai, S.; Yang, M.; Xu, Z.; Sankar, J. Direct Write Manufacturing of Solid Oxide Fuel Cells for Green Energy. J. Environ. Res. Dev. 2014, 8, 477.
67. Parupelli, S.K.; Desai, S. Hybrid additive manufacturing (3D printing) and characterization of functionally gradient materials via in situ laser curing. Int. J. Adv. Manuf. Technol. 2020, 110, 543–556.
68. Johnson, A.R.; Procopio, A.T. Low cost additive manufacturing of microneedle masters. 3D Print. Med. 2019, 5, 2.
69. Griffiths, C.A. Micro Injection Moulding: Tooling and Process Factors; Cardiff University: Cardiff, UK, 2008.
70. Park, J.-H.; Allen, M.G.; Prausnitz, M.R. Biodegradable polymer microneedles Fabrication, mechanics andtransdermal drug delivery. J. Control. Release 2005, 104, 51–66.
71. Ashraf MW et al. Design, fabrication and analysis of silicon hollow microneedles for transdermal drug delivery system for treatment of hemodynamic dysfunctions. Cardiovasc Eng 2010; 10: 91–108.
72. Chen H et al. Iontophoresis-driven penetration of nanovesicles through microneedle-induced skin micro channels for enhancing transdermal delivery of insulin. J Control Release 2010; 139: 63–72.
73. Widera G et al. Effect of delivery parameters on immunization to ovalbumin following intracutaneous administration by a coated microneedle array patch system. Vaccine 2006; 24: 1653–1664.
74. Ji Jet al. Microfabricated microneedle with porous tip for drug delivery. J Micromech Microeng 2005; 16: 958– 964.
75. Park JH et al. Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery. J Control Release 2005; 104: 51–66.
76. Jin CY et al. Mass producible and biocompatible microneedle patch and functional verification of its usefulness for transdermal drug delivery. Biomed Microdevices 2009; 11: 1195– 1203.
77. Sullivan SP et al. Dissolving polymer microneedle patches for influenza vaccination. Nat Med 2010; 16: 915– 920
78. Donnelly RF et al. Design, optimization and characterisation of polymeric microneedle arrays prepared by a novel laser-based micromoulding technique. Pharm Res 2011; 28: 41–57.
79. You SK et al. Effect of applying modes of the polymer microneedle roller on the permeation of L-ascorbic acid in rats. J Drug Target 2010; 18: 15–20.