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MICRONEEDLE IN TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Many benefits, including avoiding hepatic first-pass metabolism, maintaining a constant plasma concentration, safety, and compliance over oral or parenteral pathways, come with drug delivery via the skin. The largest obstacle to transdermal delivery, however, is the fact that only a small number of strong medications with optimal physicochemical characteristics can pass through skin barriers, intracellularly penetrate, and attain therapeutic concentration through this mechanism. Considerable work has gone into creating strategies to improve the drugs' transdermal penetration. One of the macroscale physical enhancement techniques that significantly broadens the range of medications available for transdermal and intradermal administration is the use of microneedle. Microneedles typically range in length from 0.1 to 1 mm.. This review covers the components, manufacturing processes, characterization methods, and transdermal delivery applications of microneedle are discussed.One can create solid, coated, hollow, or dissolvable micro needles using a range of materials, including silicon, stainless steel, and polymers. There has been much discussion about their implications for transdermal drug delivery. Ongoing delivery, effectiveness, affordable fabrication, and large-scale manufacturing are still problems, though. This review covers the various characterization techniques as well as the gaps in microneedle manufacturing technology. Additionally covered in this review are their possible effects on applications related to cosmetics, disease diagnostics, drug delivery, and vaccine delivery.

Keywords: Transdermal Drug Delivery, Microneedles, Drug Delivery System.

I. INTRODUCTION

This approach is non-invasive, comfortable, and designed to treat respiratory disorders or certain drugs that have been shown to pass through the blood–air barrier [6]. When patients who require multiple doses (three to four times per day) self-administer and overdose, there are certain disadvantages and risks [7]. The goal of reducing patient risk has led to efforts to identify optimal material matrices and tuneable release kinetics to further boost the potency and dose efficacy of these types of drugs [8,9,10,11, 12]. Finally, the transdermal drug delivery (TDD) route focuses on supplying drugs through the layers of the skin, which are discussed in more detail in the ensuing sections. A use case for TDD is as

Drug delivery system

It is common practice to use medicine to extend life and improve health. Tablets, injectables, capsules, and implantable devices have replaced the once-preferred method of delivering medication: chewing medicinal leaves. Drug delivery systems have advanced significantly as a result of these developments . Drugs that target the afflicted area and minimize harm to healthy cells have become increasingly effective over time in treating particular illnesses . Patients who experience discomfort from their symptoms may benefit from better drug transport and absorption. There are numerous ways to administer medications to the human body, including oral, parenteral, transdermal, and inhalation [3]. When used in moderation, the oral route is the most tried-and-true and patient-friendly approach. Oral drugs could have adverse effects. aIt is common practice to use medicine to extend life and improve health. Tablets, injectables, capsules, and implantable devices have replaced the once-preferred method of delivering medication: chewing medicinal leaves. With a controlled dosage, the oral route is the most established and patient-friendly approach. Long-term use of oral medications can result in side effects due to their effects on vital organs such as the liver and kidneys. Humans can receive hydrophobic drugs parenterally via intramuscular, subcutaneous, or intravenous injections . Parenteral administration is one of the best options for drug delivery in an emergency because it is a rapid delivery method. When used in moderation, the oral route is the most tried-and-true and patient-friendly approach. Oral drugs could have adverse effects. However, many patients do not prefer the parenteral route because it can often be quite painful. The purpose of the inhalation method is to deliver the medication straight to the lungs This method is painless, comfortable, and intended to treat conditions related to the respiratory systems or specific medications that have been demonstrated to work through the blood–air barrier . However, there are

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certain drawbacks and hazards when patients who need multiple doses (three to four times per day) self-administer and overdose . Researchers have been searching for the best material matrices and tuneable release kinetics to increase the potency and dose effectiveness of these types of medications in an effort to reduce patient risk . Finally, and perhaps most importantly, the transdermal drug delivery (TDD) route focuses on delivering medications through the layers of the skin, which are discussed in more detail in the following sections. One use for TDD is to replace oral medication delivery in patient populations that frequently have difficulty swallowing it, such as the elderly and neonatal populations. TDD may also provide proteins, peptides, and macromolecules with a more efficient means of evading the digestive system and achieving increased bioavailability. Additionally, TDD provides a method of continuous delivery and may not.

Transdermal drug delivery

The initial step in transdermal drug delivery is to apply the medication directly to the skin. The drug enters the stratum carenum after passing through the dermis and epidermis .The drug is prepared for absorption when it reaches the dermal layer . The goal of this method is to get the drug molecules into the bloodstream by controlling the rate of skin diffusion .

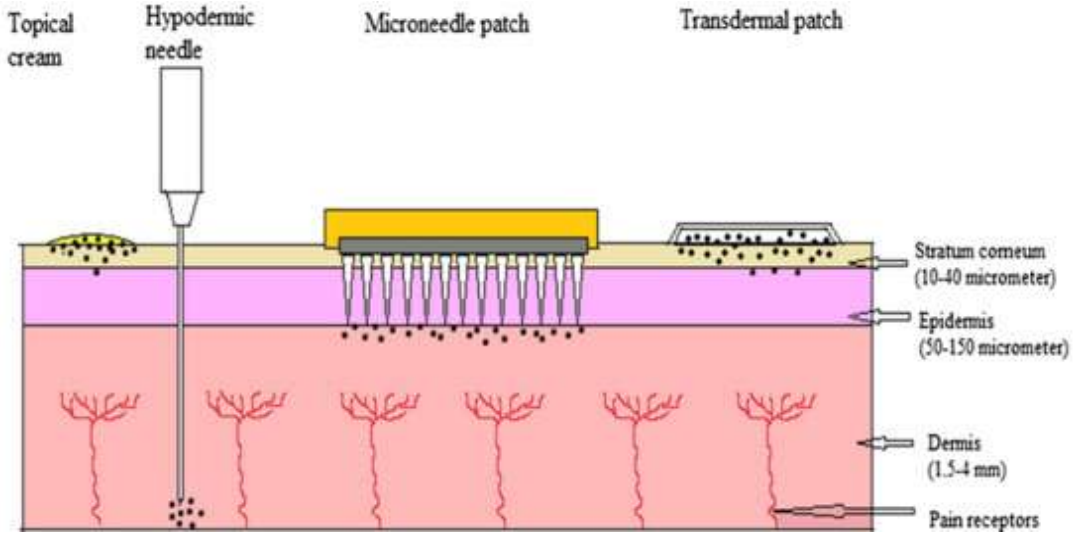

Figure 1: Various transdermal drug delivery system types [16].

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Prausnitz and Langer have classified the development of transdermal drug administration into four generations, as shown in The first patch-based devices used natural dispersion to provide a little amount of medication. The focus of the second generation was on using chemical precursors to activate medication delivery. The third generation includes technologies including microneedles, electroporation, and thermal ablation that may precisely target the medication upon penetrating the stratum corneum.

The fourth generation precisely controls the release of pharmaceuticals by fusing sensing modalities with drug delivery microneedles. Transdermal drug delivery (TDD) has several advantages over other drug delivery methods. TDD is able to accurately and dependably give the medication to the patient at the correct dosage.

Blood in a well manage fashion .Additionally, the transdermal route lowers the risk of adverse drug reactions by preventing medications from getting into important organs like the liver and kidneys . It is also possible to administer proteins, peptides, and macromolecules that typically have poor bioavailability when taken orally through the transdermal drug delivery system . The low bioavailability of many oral medications addresses this issue. Michal Goodman compared the two methods of delivering different domains and found that transdermal delivery had a higher safety profile than oral preparations. Transdermal drug delivery may also require patient-specific formulations and custom manufacturing, which could lead to a slightly more expensive course of treatment . Perhaps the biggest challenge is that TDD is currently only available in extremely effective

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medications that have perfect physicochemical characteristics but are not commercially viable. These include compounds like nicotine, nitroglycerine, and estradiol that can pass through skin barriers, passively diffuse, and intercellularly permeate to reach therapeutic concentrations . The main barrier to limiting drug flux into the skin is the outermost, biphasic stratum corneum, which has both hydrophilic and hydrophobic regions and is 10 to 20 micrometers thick. lot of work has gone into improving the transdermal penetration of the medications through the stratum corneum with the use of a chemical or physical enhancer . By physically altering or rupturing the stratum corneum, most medications are applied through the skin. It is possible for medications to infiltrate the skin after they pass through the stratum corneum and come into touch with the interstitial fluids. The administration of hydrophilic medicines in this way is therefore feasible, or as a backup, sweat glands might be utilized. Patients using transdermal delivery to treat vein collapses caused by frequent injections, needle fear, and extended administration times can all be helped with microneedles. One helpful workaround to prevent these problems is to utilize microneedles.

Microneedles for transdermal drug delivery

MN technology aims to provide an active transdermal medicine delivery system in place of conventional syringe injections. Stratum corneum penetration allows the MN array to administer the medication in a minimally invasive manner . These arrays consist of tiny needles with a height ranging from 25 to 2000 μm. MNs have been employed in many different contexts, such as medication and vaccine delivery, aesthetic operations, and illness diagnosis. This review paper provides additional examples of the diverse forms, materials, and structural arrangements of MNs, as well as the various manufacturing processes. You may see some of the current commercial MN devices in Figure 3. Thirty percent of the latest scientific literature on “transdermal delivery technology” of Minnesota research, according to Donnelly et al.Environmental factors include skin physiology, physiochemical characteristics, and ambient circumstances can affect the MN drug delivery route. These consist of the temperature and relative humidity in the neighborhood of the application region. Excessive water and other salts in sweat can alter the osmotic gradient and interfere with drug release kinetics, whereas too little (low humidity) will delay the release of medications to the epidermal layers. Excessive sweat can hinder the microneedle patch’s ability to adhere to the skin during transdermal drug delivery, further delaying the elution of medications through the skin. Likewise, extremely low or extremely high pH ranges surrounding the skin area may cause the medicine to permeabilize less into the state corneum and beyond.By defattening the stratus corneum, which serves as a barrier to transdermal absorption, excessive application of lipid coatings to the skin can facilitate this process.As a result of increased diffusivity and vasodilation of skin vessels, increasing skin temperature can improve drug penetration .

Accurate microneedle metering and dosage loading are crucial when delivering sensitive medications like insulin and chemotherapy. Due to their ability to avoid digestion and first-pass metabolism, microneedle patches often require a lower dosage to achieve comparable therapeutic effects than oral ingestion . Microneedles have fast bloodstream absorption compared to oral administration, which makes them useful for treating localized illnesses with significantly less medication loading.When it comes to carrying larger dosages than solid microneedles, hollow microneedles can act as drug reservoirs. Using inkjet and spray atomization processes, solid microneedles composed of ceramic or metal materials can be coated with very accurate drug formulations . The type of drug, intended course of therapy, and patient profile all have a significant impact on how much medication is loaded into a microneedle. Because of their ability to manage drug loading techniques and manufacturing processes, MNs provide an extremely precise delivery mechanism . Nonetheless, factors such as skin physiology, surrounding environmental factors, and method of application to skin surfaces can affect how well a medication dissolves in skin interfaces.

Types of microneedles-

Any one of the five microneedle design types—hydrogel, solid, coated, hollow, and dissolving—can serve as the foundation for a microneedle drug delivery method.expandable microneedles. The types of minuscule needles depicted in the figure illustrate their medication release pattern of microneedle.

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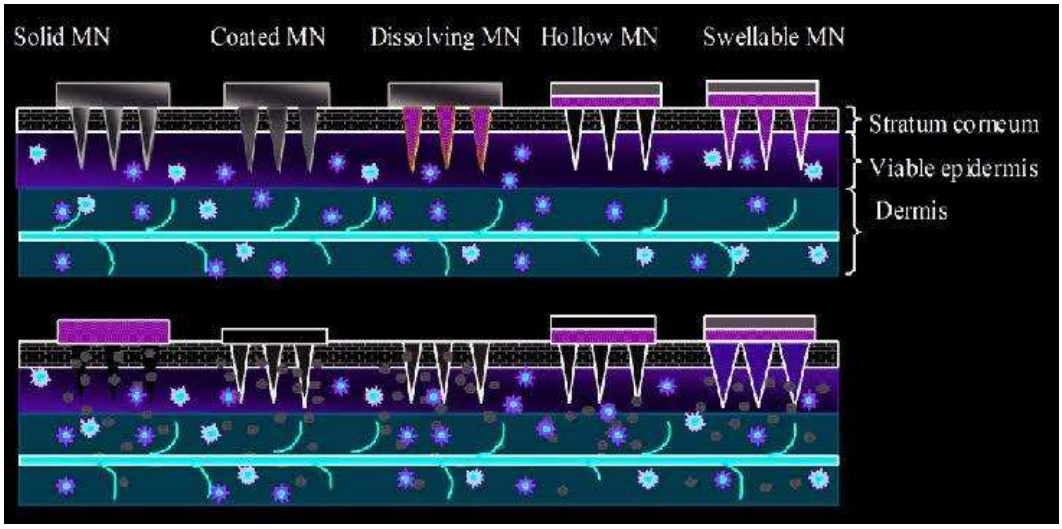

Figure 2: Microneedles- inert part of transdermal drug delivery systems.

1. Solid microniddles

The goal of this kind of microneedle structure is to pierce the stratum corneum and enhance kinetic transport and medication administration to the dermis. Throughout the skin15. Considering intramuscular Distribution, the solid microneedle works better for Vaccination administration since it generates a more durable Increased antibody response. In contrast to hollow Solid microneedles are simpler to use than Produce, possess exceptional mechanical qualities, and Sharper advice . Also, the solid microneedle has the potential to be Composed of a range of substances, such as metals and silicon And polymers.

2. Hollow microneedles

The hollow microneedle has a hollow, empty core or chamber that is used to inject or hold medication fluid. The hollow microneedle has a higher dose/amount capacity. Compared to the solid microneedle, of medication solution. A void Moreover, medication delivery by microneedles can reach living epidermis. The optimum choice for mixtures with a high molecular weight is dermis. Additionally, it controls the release of drugs over Period, thereby enabling the use of liquid vaccines. Formulas. Hollow microneedles function as a medication. Delivery mechanism that acts as a channel for the dispersion of drugs .Depending on a non-pressurized medication, into the dermis Reservoir, as opposed to eluting solid microneedles Medication that mostly uses the Tuneable Osmotic Gradient It is possible to obtain release kinetics by employing hollow Creation and formulation of microneedle materials Parameters. Pharmaceuticals with higher concentrations may result in drug profiles with burst release, while pharmaceuticals placed into matrices may create steady-state drug release that lasts days to weeks, according on the purpose of the application. Hollow It is possible to design microneedles similarly to hypodermic needles.to make it possible to modify the flow rate and pressure. Other aspects of the procedure, like the aspect ratio of the microneedle It is possible to adjust (height to base diameter ratio) to obtain Time-varying delivery, gradual infusion, or quick release rate. The hollow microneedle has shown to be an effective tool. in numerous vaccinations and vaccines throughout the years. But since it is weaker and needs more attention, Regarding the construction and application of the needle, this kind of The solid needle garnered more attention than the microneedle. Furthermore, throughout the injection procedure, the hollow microneedle encounters technical problems such leaks and clogging.

3. Dissolving microneedle

The dissolving microneedles Intended to release the incorporated drug after dissolving Itself in the skin within minutes without generating Sharp waste (Arya et al., 2017). These consist of sugars that release the encapsulated medication in a matter of minutes, including dextrin, galactose, trehalose, and maltose (Ogundele, 2017). Dissolving polymeric microneedles are typically created using water-soluble polymers like methyl cellulose, PVP (Ito et al., 2006; Kolli and Banga, 2008; Sullivan et al., 2008), polyvinyl alcohol, sodium alginate, HPMC (McGrath et al., 2013), or co-polymers like poly (methyl vinyl ether co-maleic acid) (Garland et al., 2012) and for controlled release using PLGA over hours to months (Park et al., 2006). In general, dissolving

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microneedles are made to break through the skin, form drug channels, dissolve other substances, and allow them to enter the skin. Additionally, It can be shaped into the desired according to Rejinold (2015), prior to insertion. Since its initial use, maltose has been widely acknowledged as a safe material for the production of microneedles., there is the disadvantage with the use of maltose microneedles; it absorbs water under high humidity condition and therefore it leads to bending and insertion of microneedles gets difficult (Ogundele, 2017). Dissolved microneedle arrays have been used to deliver a wide range of compounds, from hydrophilic, low molecular weight drugs to larger biopharmaceutical molecules, demonstrating the ability of such a platform to enhance the TDD.

4. Coated microneedles

A solid-type MN that has been drug-coated is called a coated MN. The coated layer often contains less of the drug23, depending on its thickness. The efficacy of medication delivery utilizing a coated MN depends on the capacity to reliably coat MNs with a regulated drug layer. Proteins and DNA can be delivered non-invasively using a coated MN. Although the coated MN offers the benefit of rapidly delivering the medication to the skin, additional patients could become infected by the drug residue at the needle's tip. Lastly, the outcomes of the coated MN vaccine delivery method were comparable to those of intradermal and intramuscular vaccination delivery methods.

5. Dissolving microneedle

Dissolvable MN, which debuted in 2005, is a promising MiTechnique based on its attributes. These characteristics include a one-step medication application that facilitates the convenience of drug administration and the quick release of macromolecules25.Because of the improvement in the use of dissolvable MNs after "poke-and-release," this method is thought to be better than others. Quick loading of the dissolvable MN tip is made possible by a two-step casting method. The drug load readily releases and diffuses when the dissolvable MN is put into the skin since the needle tip dissolves. The ideal materials for making dissolvable MN are those that dissolve in water. Similarly, the production of dissolvable MN is best served by the micro-mold fabrication approach. Designing and producing a dissolvable MN array requires technical know-how. But this This kind of MN requires both a delay in dissolution and full insertion, which is frequently challenging to accomplish.

II. MN MANUFACTURING METHODS

The fabrication of the MN arrays can be done in multiple ways. Surface/bulk micromachining, chemical isotropic etching, injection molding, laser ablation, micro-molding, additive manufacturing, and lithography-electroforming-replication are the most widely used techniques (Table 1).

1 Laser ablation:

Laser ablation is a technique that uses a concentrated optical laser beam to remove material from a substrate in order to produce MN arrays. Several materials, ranging in size from micro to nanoscale, have been processed by lasers for a variety of purpose. A variety of laser types have been investigated for MN array production. Among them are the femtosecond laser machine, CO2 [(Figure 11), and UV excimer.

The laser ablation method is believed to be a rapid and effective way to produce MNs. material sheet's burn point is approached by the laser beam in ten to one hundred nanoseconds. Any metal could also be shaped using a laser. This process is linked to changes in MN structure and mechanical properties as a result of heat impacts near the cutting surface.

This could cause MNs to experience un favourable outcomes including fatigue resistance or cracking. Low heat loads are applied to the substrate during the non-contact laser ablation process. But in contrast to other kinds of machinery, the laser is more expensive. Large-scale production is not a suitable use for the laser ablation process.

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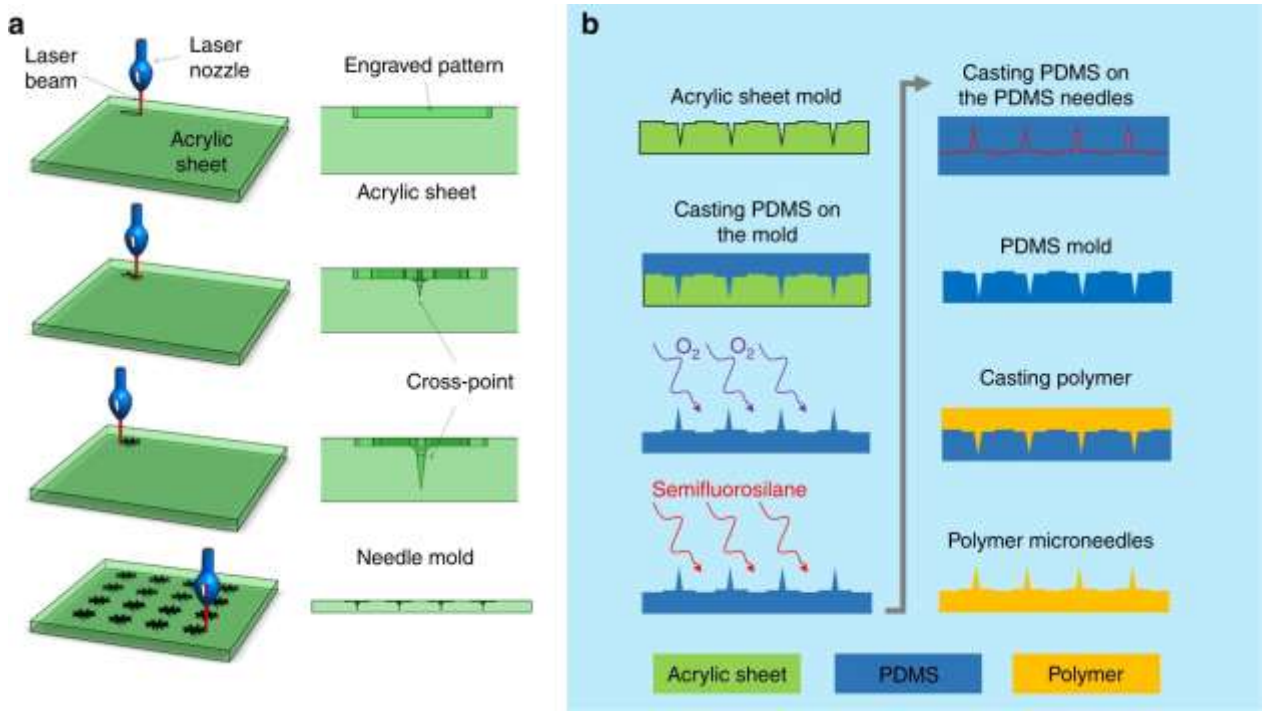

Figure 2: MN mold fabrication: (a) The suggested cross-over lines (COL) technique was employed to create the MN acrylic mold with a CO2 laser The acrylic mold was used to build a polydimethylsiloxane (PDMS) MNs mold, which may be used to make a variety of polymer-based MNs. Reproduced with permission from Springer Nature (2018), Low-cost and cleanroom-free production of MNs, by Hojatollah Rezaei Nejad et al.

2. Lithography

The master pattern of the geometric shapes is transferred onto a substrate's surface using the lithography technique. Because photolithography has several applications in the realm of microelectronics, it is mostly utilized for pattern transfer. Lithography is the initial stage in the fabrication of an MN in other techniques, such as microelectronic and micromachining. The photoresist must be precisely processed for lithography. Approximately 30–35% of the cost of producing integrated circuits is attributed to this technology. Glass, metal, ceramics, and plastics are just a few of the materials that can be produced using lithography. Moreover, it creates smooth vertical sidewalls and exact geometries (Figure 3). However, this method necessitates a longer production period and a sophisticated facility (cleanroom).

Using lithography, create a three-dimensional UHAR MN. A drawing system with patterned pillars for drawing lithography is displayed in the inset. 200 mm diameter and 3 mm length stainless drills were placed in a 3 × 3 array on a PDMS frame to serve as pillars. (a) Spin coating and cooling were applied to the SU-8 2050 photoresist. B) Drawing lithography was carried out following contact between the photoresist and the patterned pillar..(c) The drawing produced the appearance of a longer, conical bridge between the pillar and substrate. (d) To create a stiff structure, the intended UHAR microneedle mold was cured. (e) A solid MN mold was created by the 3D microstructure bridge's separation. (f) The solid MN molds' chemical deposition. (g) Electroless material was applied to the upper part of the MN mold by a drawing mechanism. (h) Electroplating solid MN molds with nickel. (i) After the photoresist MN mold and electroless protection were removed, the hollow metallic MN array was produced . Published by John Wiley and Sons in 2010, this image is reprinted with permission from Kwang Lee et al.'s Drawing Lithography: Three-Dimensional Fabrication of an Ultrahigh-Aspect-Ratio.

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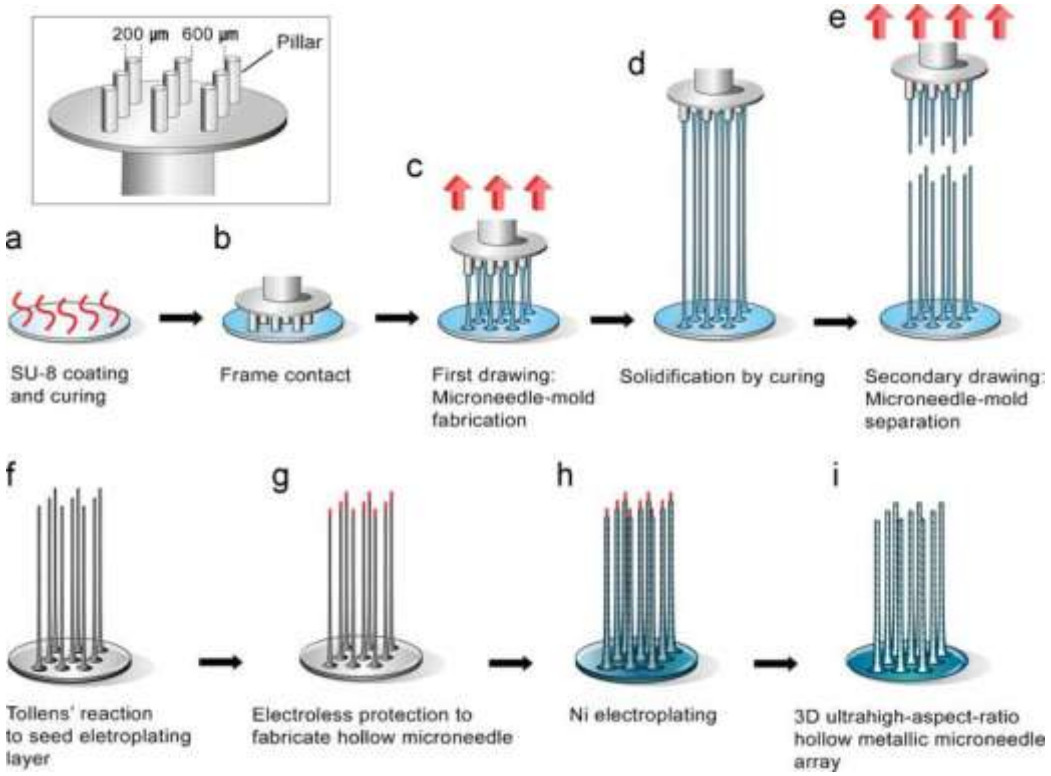

Figure 3:

3. Micro-Molding:

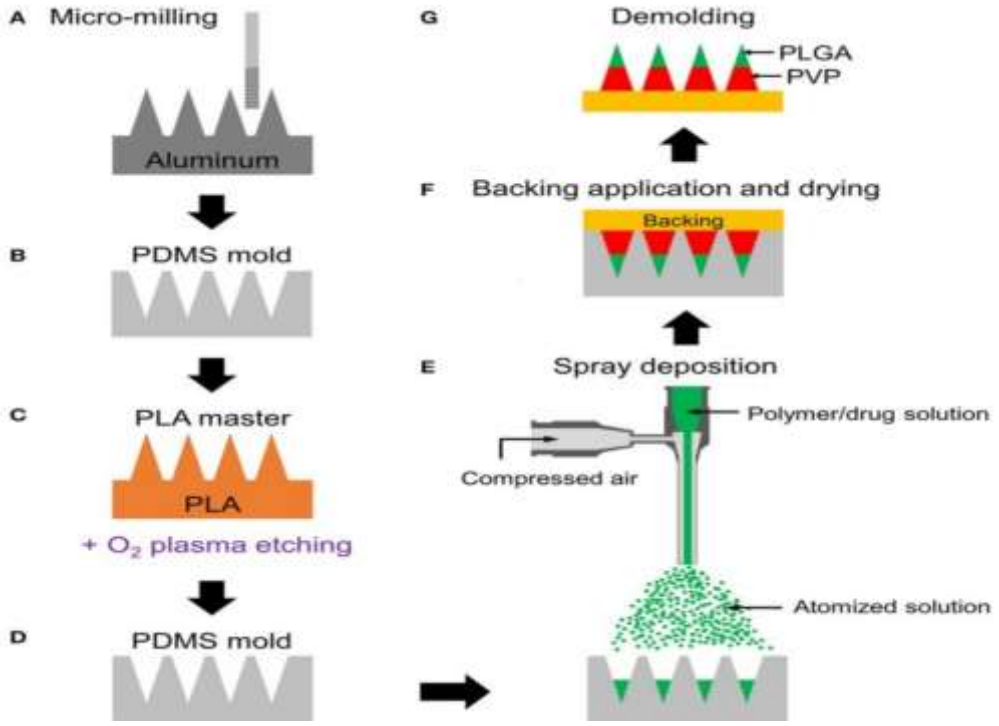

Figure 4:

The technique of micro-molding entails copying the master mold. A polymer-and active medicinal ingredient-containing solution is used to cast the mold . For mass production, micro-molding is regarded as an economical technique. When it comes to micro-molding techniques, the PDMS has a number of benefits, including low cost, convenience of usage, low surface energy, and thermal stability. The challenges of regulating the drug load capacity, mechanical behavior of the polymer, and penetration depth are the constraints of this approach.

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The multilayer MN fabrication method is schematically shown as follows: (A) Aluminum master fabrication by micro-milling. (B) Duplicating the master PDMS mold. (C) Using oxygen plasma to sharpen the tip and micromold the PLA master. (D) PDMS mold replication using the PLA master. € Fill the mold cavity by spray-depositing a drug-containing polymer solution. Polymer solutions are sequentially deposited to produce multilayer MN. (F) Applying the yellow backing material to the mold and letting it dry at room temperature to solidify the polymer. (G) Removing the multilayer MN array that has solidified from the mold. PLGA and PVP layers are shown by green and red, respectively. Reproduced with permission from Frontiers in Bioengineering and Science, Min Jung Kim et al., Fabrication of Circular Obelisk-Type Multilayer MNs Using Micro-Milling and Spray Deposition

4. Injection molding:

Another technique for fabricating MN is injection molding. Figure 14 illustrates the method of creating MNs by employing the heat embossing technique and injection molding. Lhernould et al. created a 4 × 4 hollow polymer MN array [150] using polycarbonate (PC) material. The MNs proved to be strong enough to tolerate repeated insertions without dulling the needle. To create a solid MN, another study employed a micro-injection molding technique . Delivering hydrophilic compounds with a high molecular weight is possible using these needles. By molding plastic material, Sammoura et al. created a polymeric MN . A fresh chicken leg and beef liver were effectively punctured with the needles, and around 0.04 µL of liquid was extracted from each tissue. The suggested technique enables mass manufacture.

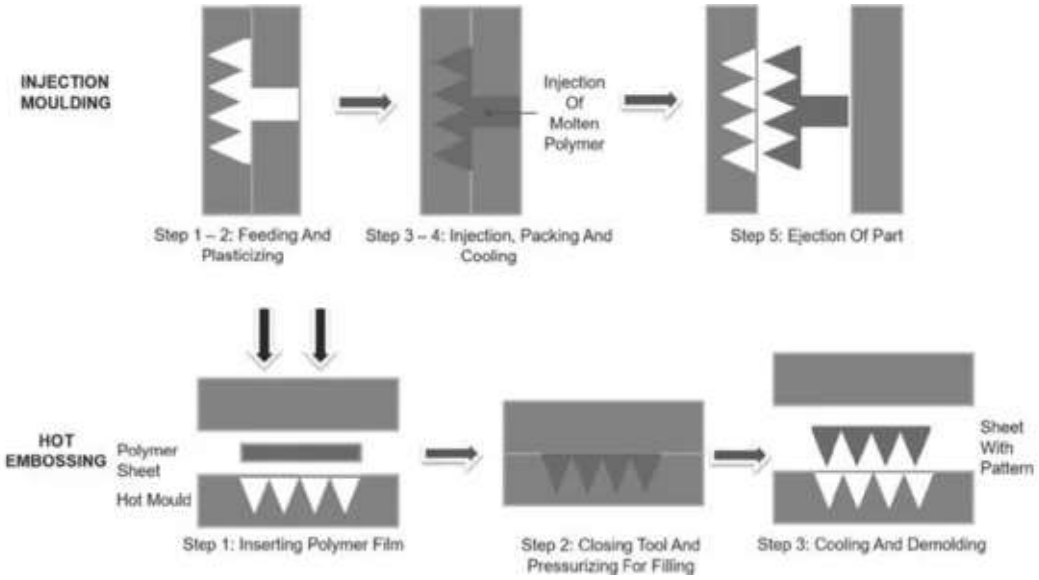

Figure 5: Standard injection molding and step-and-repeat hot embossing process steps.

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High injection flow rates, accurate dosing, and outstanding repeatability are other benefits of micro-injection molding when separating the plasticization and polymer melt injection processes. Controlling the small shot size is a limitation of the injection molding technique because of the common screw size, which is roughly 15–150 mm, and the higher initial equipment cost .

5. Additive manufacturing:

The production of MN arrays through additive manufacturing, or 3D printing, has garnered significant attention in recent years. By layering on the desired material, a 3D printer constructs an object. 3D printing technologies for tissue engineering implants have been rapidly expanding in the biomedical device industry in recent years. Using a commercial 3D printer, Johnson et al. created the first MN master in 2019. To create an MN mold, Krieger et al. proposed a two-step process known as "print and fill" . A different study created MN patches using

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a stereolithography method. The flexibility of design parameters and shortened processing lead times are benefits of manufacturing an MN array with 3D printers.

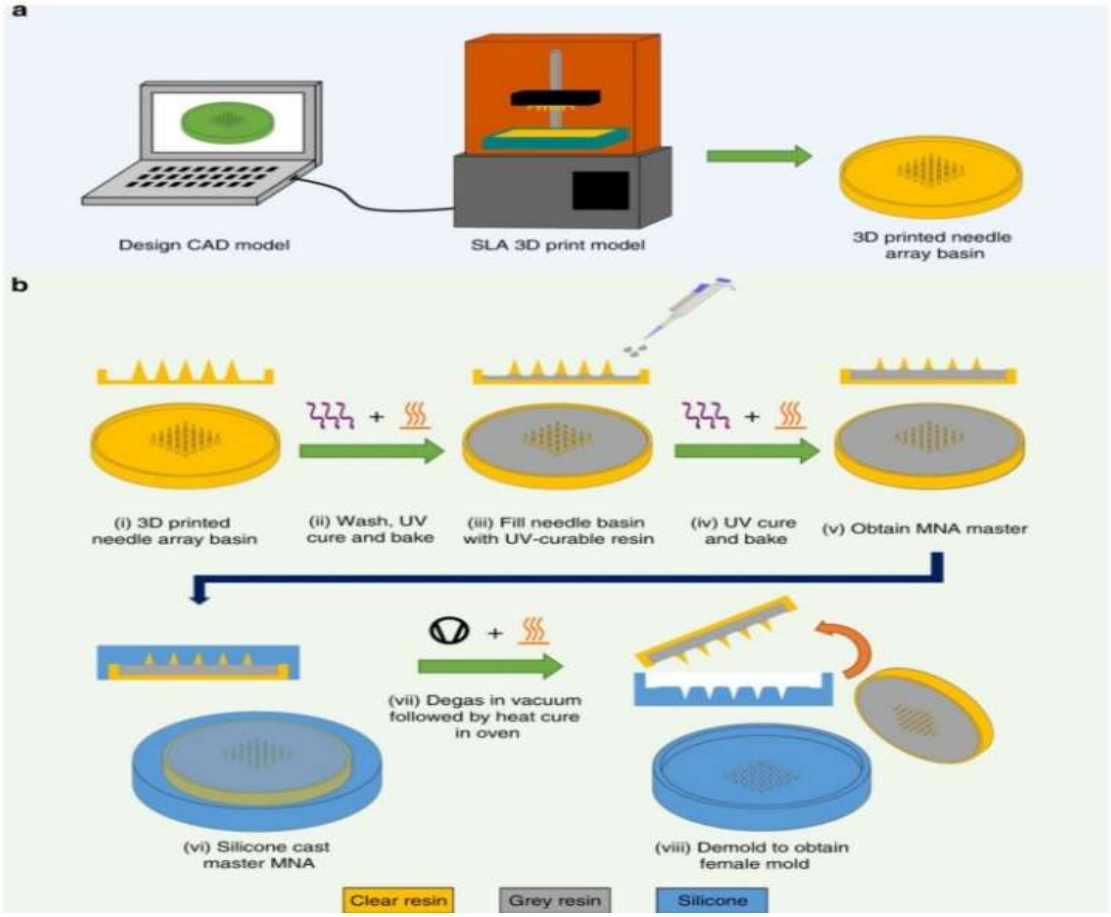

Figure 6:

An outline of the "Print and Fill" method of production (a) The design of the needle array basin is printed in three dimensions using a Form 2 SLA printer. (a) The MNA master mold construction technique The steps involved are as follows: (i) take a 3D printed needle array basin; (ii) wash the printed needle array basin, then follow with UV curing and baking; (iii) file the needle array basin with UV-curable resin; (iv) repeat UV curing and baking; (v) obtain MNA master; (vi) silicone cast the MNA master; (vii) degas the silicone mold and heat cure it in an oven; (viii) demold to obtain a usable MN mold [63]. Excerpted with permission from Kevin J. Krieger et al.'s 2019 publication, Springer Nature, on a straightforward and adaptable process for creating high-aspect ratio MN molds using inexpensive 3D printing.

III. CONCLUSION

The technology of transdermal medication delivery is not outdated, and it has evolved beyond adhesive patches. Because of recent developments in Technology and the capacity to administer the medication to the action location without cause skin rupture Transdermal approach, membrane, is turning into a Commonly used method of administering drugs. But the advancement of DDS is also becoming more and more costly. The more recent APIs Are much more energetic, thus they must be given in a regulated fashion. Utilizing the The transdermal route has a solid reputation. Since the nineteenth century. In addition to the present Commercial forms, novel medications are being Designed as transdermal devices due to The benefits that come with manage Route. Transdermal medication delivery modificati Systems can improve the bio-availability of poorly absorbed medications that cause their market value to rise quickly. One of the areas of the pharmaceutical industry that is expanding the fastest right now is transdermal drug delivery systems. Drug delivery system advancements have progressively resulted in steady distribution, improved efficacy, and rate-controlled delivery with fewer adverse effects. The effective development of novel techniques that can improve the permeability of pharmaceuticals via

the skin is anticipated to boost the biomedical application of transdermal rate-controlled drug delivery (TDDS) and its future growth.

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