Transdermal Drug Delivery Device Based on Microneedle

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***Abstract*—Microneedle (MN) technology, a ground breaking advancement on site of topical drug delivery, offers a low impact, painless, and effective approach of administering medications, biomolecules, and vaccines. By creating micro scale channels across the stratum corneum, MNs enhance the entry of drugs that might not be sufficiently absorbed through conventional routes. MNs are divided into solid, coated, dissolving, hollow, and hydrogel-forming forms based on their composition and design; each type allows for exact control over drug release kinetics and therapeutic targeting. The use of biocompatible and biodegradable polymers, metals, ceramics, and carbohydrate-based materials to increase mechanical strength, safety, and transport efficiency has increased recently due to advancements in materials science. MNs have been widely used in a variety of sectors, including gene therapy, oncology, diabetes treatment, immunization, ophthalmology, dermatology, and cosmetics. New studies combine MNs with photo-thermal agents, biosensors, and nanoparticle carriers for controlled release and diagnostic applications. Optimizing large-scale manufacturing, mechanical stability, drug-loading capacity, and regulatory approval still present difficulties despite notable advancements. However, MN-based systems are still developing as viable next generation drug delivery platforms that are accurate, patient-friendly, and self-administered.**

***Index Terms*—Microneedles, Transdermal drug delivery system, Microchannels, Self-administration, Hollow Microneedle, Poke and Flow,**

I. INTRODUCTION

Micro-needles (MNs) are showing promise in the biomedical area as a successful, minimally invasive technique for a variety of applications, including drug administration, cell transfection, and bio sensing. By downsizing a single needle or a group of needles to micro meter-scale dimensions, MN technology enables the accurate delivery of medications and biomolecules such as proteins, RNA (ribonucleic acid), and DNA (deoxyribonucleic acid) into cells at the appropriate time and location.

A variety of MN design elements, including shape, number of needles per array, height, aspect ratio (base to height), material, and backing block thickness, have a significant impact on the volume that the patch can load and administer. The volume then affects the selection of MN that best accomplishes the desired outcome. Based on their design and drug delivery techniques, MNs can be classified into two main categories: emerging MNs and classic MNs. While evolving MN encompasses dissolving and hydrogel-forming MN, traditional MN includes solid, coated, and hollow MN. Each type of MN has unique advantages and applications based on the specific needs of the study or treatment. (1)

1.1 Transdermal medication administration

Transdermal medication administration is growing in popularity. It increases bioavailability, prolongs drug release, improves physiological and pharmacological response, and reduces unwanted side effects before the medication enters the systemic circulation through the skin. For example, transdermal distribution reduces the necessary dose in testosterone replacement trials by avoiding the hepatic first-pass following oral treatment and addressing the problems with oral and intramuscular delivery. It also increases blood testosterone levels and eliminates the need for frequent injections.

However, the way drugs are transported through the transdermal delivery route, which influences the SC's absorption, is greatly influenced by their chemical properties. Because of this, only few drugs can be used in this way at levels that are significantly therapeutic.(2)

1.2 Drug delivery method using Microneedle

Microneedle (MN) technique delivers drugs minimally invasively through the SC layer and into the underlying layers using small needles. Micro needles, which vary in length from a few micrometres to 2000 μm, are used in these delivery systems. Because of its short length, MN can enter the SC without coming into contact with the nerves in the layers underneath the skin.

Because MNs are less invasive, painless, and offer the convenience of transdermal distribution combined with the efficiency of invasive needles and syringes, they are preferred over conventional drug delivery techniques.

Unlike traditional techniques, MNs do not require professional knowledge or staff because They are intended for patients to self-administer. Additionally, MNs' single-use design reduces the possibility of drug cross-contamination. Hydrogel-forming, dissolving, coated, solid, and hollow Based on their design, there are five different kinds of microneedles. The "poke and patch" approach to solid MN distribution consists of two steps: A transdermal medication patch is used to administer a conventional drug formulation after MN arrays have made holes in the skin. Coated MNs use the "coat and patch" method, which involves coating the microneedle with a medication mixture before applying it to the skin.

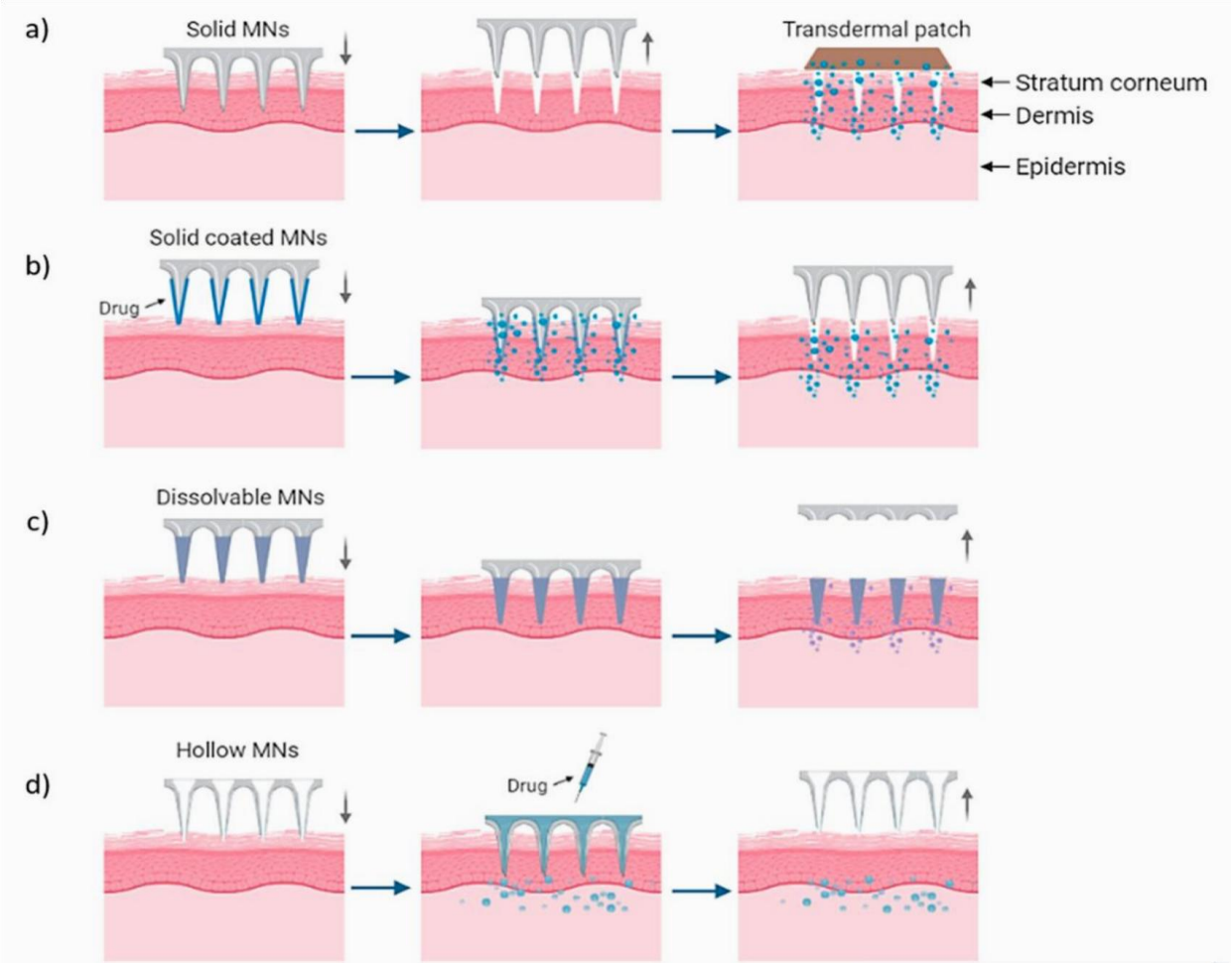
After penetration, the drug is delivered to the skin, enabling the coating to disintegrate. When using a hollow Microneedle, the drug is injected directly into the skin's epidermis or upper dermis layer by filling the microneedle's hollow tip.

This can be characterised as "poke and flow." Hydro gel-forming microneedles, which create swelling by absorbing a lot of water into their polymeric network, and dissolving microneedles, which are primarily composed of biodegradable or dissolving polymers, enable the straightforward one step application process. The "poke and release" method of dissolving and hydrogel-forming MN drugs removes the possibility of unintentionally reusing MN and the need for extra safety precautions for needle disposal.

microneedle’s can be made of silicon, glass, metal, or polymers. MNs are made of ceramics, silicon, glass, and metal. Although their firmness permits skin penetration, their fragility increases the likelihood that they will break inside the layers of skin, resulting in discomfort, oedema, and potentially granulomas. These materials' brittle yet rigid qualities have been compared to the thorns of sea urchins, which are composed of the mineral calcite. Because MN administration accidents and problems are unavoidable, The best materials for MNs should be biocompatible and biodegradable to reduce the impact of accidents, like when the MN tip breaks inside the skin's outermost layers. (2)

II. MICRONEEDLE TYPES

Among the numerous varieties of microneedles that have been created and studied for use in drug delivery are hydrogel, solid, coated, dissolving, and hollow. There are several types of microneedles displayed, each with unique characteristics. Each type of Microneedle administers the drug to the skin in a unique manner. Others have the medicine solution percolated some are dissolved on their surface, some contain the drug solution already, and some are used only to puncture the stratum corneum.



2.1 Solid microneedles:

Solid microneedles are primarily utilized for pre-treatment since they create pores in the skin. The pointed points of the needles penetrate the skin when a medicine patch is applied, forming micron-sized channels that improve penetration by allowing the medication to directly enter the layers of the skin. Once the drug is absorbed by the capillaries, it has a systemic effect. Additionally, it can be utilized locally. Tetramethylammonium hydroxide etching is used to create long, tapered solid silicon microneedles that passively distribute the medication throughout the skin's layers. With an average height of 158µm and a base width of 110.5µm, microneedles were effectively produced.

Next, he produced gold-coated solid silicon microneedles with dimensions of 250 µm in height, 52.8 µm in base width, 4.73 aspect ratio, 24.5° tip angle, and 45 µm in diameter. Increased mechanical strength and bioavailability were the results. Research on polylactic acid microneedles indicates that biodegradable polymer solid microneedles can enhance drug absorption and has the mechanical strength to breach the stratum corneum. Drug penetration has been shown to be enhanced by microneedles with a density of 256 MNs per cm2 and a depth of 800µm. Stainless steel microneedles are also being studied by numerous researchers. Improved captopril and metoprololtartrate distribution was examined after stainless steel MN arrays were installed.

2.2 Microneedles with coatings:

The drug solution or drug dispersion layer envelops the microneedles. The drug is rapidly administered after dissolving from the layer. The amount of medication that can be loaded depends on the size of the needle and the thickness of the coating layer; poly L-lactide (PLLA) microneedle arrays frequently contain comparatively little loaded lidocaine. The loaded lidocaine was shown to release quickly in

phosphate buffer saline and to stay stable for three weeks. Using the same formulation, coated microneedles have also been studied for the administration of several drugs. Co-delivery of several drugs with various qualities was made possible by coating each microneedle with a separate drug and formulation. These simultaneously produced colors that were both water-soluble and water-insoluble. Chen and associates found that the drug delivery efficacy surpassed 90% after adding sulforhodamine B to PLA microneedles. The in vitro experiments on mice validated the continuous medication administration.

2.3 Microneedles that dissolve:

Medication incorporation into the polymer. Once the microneedle is introduced into the skin and dissolves, the medication is released. The application just needs one step because, unlike other cases, the microneedle is not to be removed after insertion.

The drug's release within the skin is regulated and broken down by the polymer. The polymer's bio-acceptance and propensity to dissolve into the skin make it one of the best options for long-term treatment. To improve patient compliance, it is contained in dissolving microneedles composed of biodegradable polymers.

A crucial but challenging component of creating dissolving microneedles is efficient needle drug distribution. Mixing polymers and drugs is therefore a crucial step in this production process. Chen and his colleagues developed tip-dissolving microneedles that showed rapid and efficient drug delivery without irritating the skin. Complete insertion is difficult, and microneedle disintegration takes time.

Created mechanically strong, fast-separating microneedles that were applied to solid microneedles. A delivery effectiveness of roughly 90% was noted in 30 seconds. To prevent drug diffusion across the entire microneedle, bubbles were introduced to the dissolving microneedles.

Approximately 80% of the medicine delivery efficiency in the 1920s was attained by them. Sharp produced detachable arrowhead microneedles. When injected into the skin, the blunt metal shafts that held the tips of the drug encapsulated polymer dissolve or split within seconds. These changes to dissolving microneedles demonstrated the potential for controlled release kinetics and quick drug delivery.

2.4 The hollow microneedles

The drug solution or dispersion is poured into the empty spaces of the hollow microneedles. Their tips are punctured. The medication is injected straight into the upper dermal or epidermis layer of the skin. Its main uses are in high molecular weight materials including proteins, oligonucleotides, and vaccines. The release pressure and drug flow rate can be altered if the medication is to be supplied by quick bolus injection. These microneedles can give a large dose of the drug because more medication may fit inside the needle's empty space. It is crucial in this situation to keep the flow rate constant. The flow velocity will increase with a larger microneedle bore, but the strength and sharpness will decrease. Hollow microneedles with an external diameter of 100 μm and a length of 500–600 μm are made and aligned on a silicon substrate. Sometimes, to make the microneedle stronger, it is coated with metal, but this can make the needles sharp. At a pressure differential of 2KPa, a flow rate of 0.93μls−1 was obtained. Madden and colleagues used hydrofluoric acid etching to create fused silica hollow microneedles. These microneedles circumvented the limitations of the hypodermic needle by automatically injecting a very small quantity of immunisation into the skin. It's interesting to note that Suzuki and associates created hollow microneedles that demonstrated better skin penetration and resembled mosquito activity.

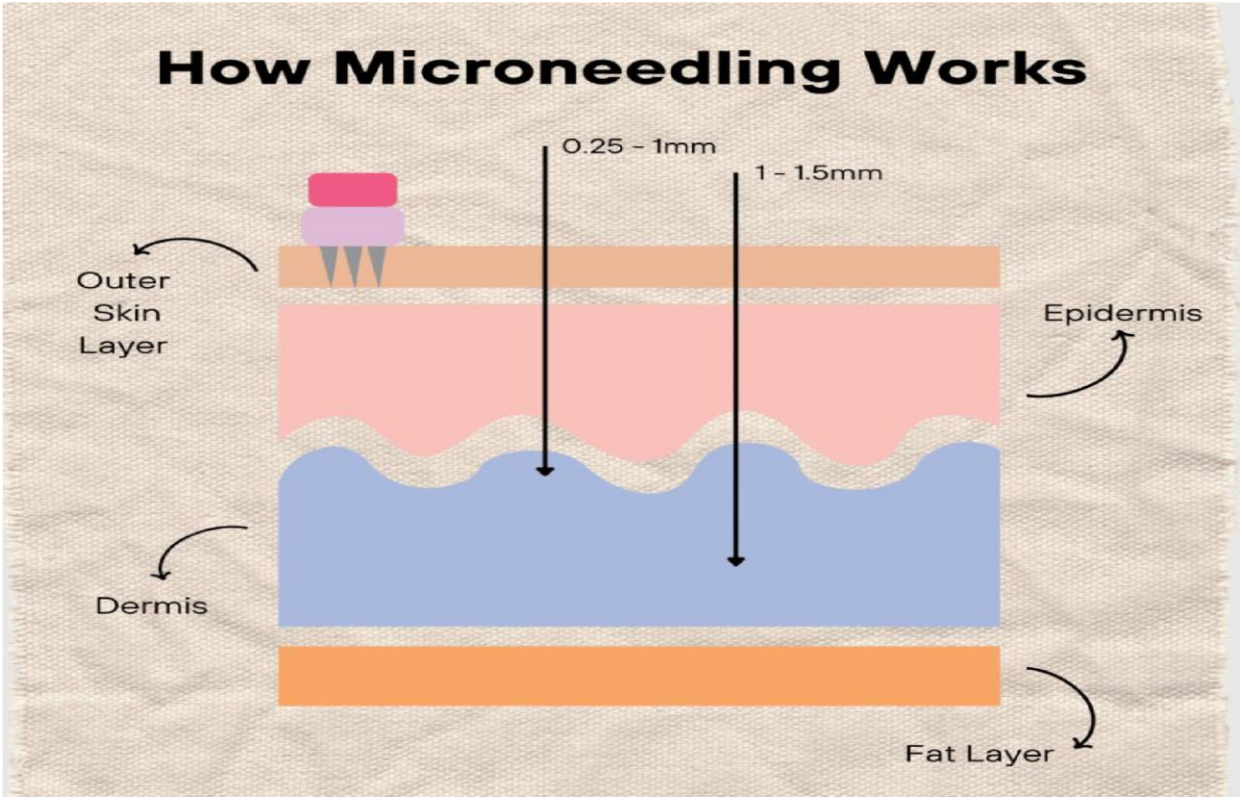
2.5 Microneedles with hydrogel formation:

The creation of this type of microneedle is a fairly recent innovation. These microneedles are composed of highly swelling polymers, whose hydrophilic nature enables their three dimensional network to absorb large volumes of water. When the interstitial fluid is inserted into the skin, triggers the expansion of these polymers, forming microchannels between the transdermal patch and the capillary system. Such microneedles primarily function to disrupt the barrier of the skin before drug delivery and act as a rate-regulation layer as they expand. Their design—both in terms of size and shape—is adaptable. Hydrogel-forming microneedles have been explored for the transdermal drug delivery of metformin to reduce gastrointestinal negative effects associated with oral route intake. These microneedles possess unique advantages, including ease of sterilization and complete removal from the skin. Studies have

demonstrated that constructing microneedles in this way improves drug permeation and bioavailability. Furthermore, swellable microneedles for drug delivery are fabricated using cross-linked polymer materials [3]

III. TRANSDERMAL DRUG DELIVERY USING MICRONEEDLES

The ability of microneedles to deliver therapeutic molecules into the skin with minimal invasiveness is the main driving force behind their development. Different strategies for using microneedles for TDD have been motivated by this objective. The majority of research has concentrated on using solid microneedles composed of silicon or metal to create tiny holes in the skin. The "poke and patch" method is used to apply a transdermal patch, or its prototype, to the skin's surface. After these microchannels are formed. Then, when an electric field is provided, drug movement can happen either by diffusion or by iontophoresis. Another approach, known as “coat and poke,” involves inserting microneedles into the skin after surface layer them with the desired drug all of the drug intended for delivery is contained directly on the microneedle itself, with no external d rug reservoir on the epidermis. "Dip and scrape" is a variation of this method. Involves immersing the drug solution's microneedles and then gently dragging them across the skin so that the medication is deposited within the small abrasions formed by the needles. Furthermore, hollow microneedle designs—functionally closer to traditional injections than patches—have also been explored. Although they are more complex to manufacture and apply, hollow microneedles enable active fluid transport through their lumen into the skin, allowing for much faster and controllable delivery rates. The existing research on transdermal administration of medications, vaccines, proteins, and genetic materials using microneedles is summarized below, emphasizing studies focused on therapeutic administration. However, conference papers from the micro fabrication field that discuss advanced needle production technologies without assessing their drug delivery efficiency are not included in this review. Similarly, the considerable but unpublished industrial efforts related to developing microneedles for transdermal drug delivery have been excluded. [4].



IV. MICRONEEDLE MATERIAL SELECTION

Depending on the intended use, the microneedles should be made of biocompatible and decomposable materials. It should be strong enough mechanically to pierce skin without causing damage. Metals and polymers are among the many materials used to make microneedles. Metals, polymers, and inorganic materials are the three primary types of materials. [5] Because of its many advantages, including their high drug-entrapment capacity, affordable of production, and superior biocompatibility, polymeric microneedles are highly prized in biomedical research" Nanomaterial and piezoelectric polymer-based drug delivery methods are receiving more interest from researchers. Electrical energy can be converted from mechanical energy and vice versa by these substances. As will be covered in more detail in this article, piezoelectric materials are used to precisely deliver medications to particular organs or cells. [6].

4.1 Inorganic Materials

Polymeric microneedles are widely valued in biomedical research because to their various benefits, such as their high drug-loading capacity, inexpensive cost of production, and outstanding biocompatibility. Drug delivery techniques based on piezoelectric polymers and nanomaterials are attracting increased attention from researchers. These substances have the ability to change mechanical energy into electrical energy and vice versa. As will be covered in more detail in this article, piezoelectric materials are used to precisely administer medications to particular organs or cells. Microneedles are frequently made from ceramic materials such calcium sulfate, zirconia, and alumina. Microneedles are made from biodegradable bio ceramic materials because of their precise drug-release properties and remarkable mechanical endurance .Microneedles are made by micromolding ceramic materials. Alumina, which has the formula for the chemical the main ceramic material that has been thoroughly studied for the creation of microneedles is Al 2 O 3. Because of its remarkable porosity and chemical resistance, alumina can be used in controlled-release formulation applications. Because of their remarkable mechanical properties and ability to load drugs, calcium phosphate dihydrate and calcium sulphate dihydrate are used as materials for microneedles. Microneedles are also made from ormocer, a composite material made of both organic and inorganic materials. By changing the synthesis techniques and component concentrations, the hybrid material can change its characteristics. [7]

4.2 Materials Made of Polymers

The best materials for making microneedles are polymers because of their low cost, capacity to expand and dissolve, compatibility with living organisms, and possibility for spontaneous disintegration.

. They are widely used in the production of hydrogel-based and dissolvable microneedles. There have also been reports of other polymer-based microneedles, such as coated, solid, and hollow types. The most common polymers used to make microneedles are poly L-lactic acid (PLLA), acid (PLGA), polylactic-co-glycolic poly (methyl methacrylate) (PMMA), polyvinyl pyrrolidine (PVP), polyvinyl alcohol (PVA), polycaprolactone (PCL), lose (CMC), and carboxymethylcellu polyethylene glycol (PEG). Because of their low rigidity, some polymers can tolerate the safe insertion of microneedles. To solve this problem, materials with exceptional mechanical strength are employed. [8]

4.3 Metallic Materials

Microneedles have long been made from metallic materials such as palladium, titanium, stainless steel, nickel, and alloys. Metals have remarkable mechanical properties, such as remarkable resistance to fracture, and are highly biocompatible... The earliest known metallic microneedle was made of stainless steel and had a Young's modulus of 180 GPa.

For transdermal drug delivery, titanium microneedles have been created and are being used in addition to stainless steel. The production of these materials is very complex, and it has been discovered that some metal microneedles cause inflammatory responses.

4.4 Carbohydrates

Microneedles have historically been made from metallic materials such as palladium, titanium, stainless steel, nickel, and other alloys.

These metals have exceptional mechanical strength, including high fracture resistance, and excellent biocompatibility. The first known metallic microneedle was composed of stainless steel and had a young's modulus of roughly 180 GPa. For transdermal drug delivery, titanium-based

microneedles have also been developed and used in addition to stainless steel. Nevertheless, it has been demonstrated that certain metal microneedles cause inflammatory reactions, and their manufacturing process is often highly complex, though certain metals allow easier processing. Adjusting the fabrication parameters can modify properties such as optical transparency and electromechanical coupling efficiency. Additionally, polymer classes like polyamides, polyurea, fluoropolymers, polysaccharides, polyesters, and polypeptides are known to exhibit piezoelectric behavior. Natural biopolymers such as collagen, silk, and cellulose also demonstrate piezoelectric characteristics. [9]

V. MECHANISM OF MICRONEEDLE DRUG DELIVERY

5.1. Skin barrier penetration

The main physical barrier to transdermal drug distribution is the stratum corneum (SC), the outermost dermal layer. Only very small molecules are able to passively diffuse across it. By puncturing the horny layer and creating micro-channels into the viable layer of epidermis or superficial dermis, the array of microscopic projections known as microneedles—which are typically between 100 and 1000 μm long—can dramatically reduce the barrier to permeation. These tiny needles are minimally invasive because they often avoid deeper nerve endings and important blood arteries, which may lessen discomfort.

5.2. Creation of micro-channels & direct delivery

For instance, in coated MNs, the drug coating dissolves after insertion; in dissolvable/biodegradable MNs, the needle itself dissolves releasing the drug; and in hollow MNs, fluid drug formulations can be directly infused. Once the micro-channels are formed, the drug (which may be coated on the microneedle, encapsulated in the needle itself, or delivered through hollow microneedles) has access to the viable skin layers (either the dermis or epidermis).

5.3. Drug diffusion and uptake into skin layers / systemic circulation

Once microneedles create tiny channels in the skin and the drug is released, it begins to move through the interstitial fluid within the epidermis and dermis. From there, the medication can either enter nearby capillaries or lymphatic vessels for systemic circulation, or remain concentrated in the targeted area for local treatment.

The overall diffusion process typically involves several stages — the drug being released from the microneedle, settling into the viable layers of the skin, spreading both outward and downward through the surrounding tissue, and finally being absorbed either into the bloodstream or lymphatic system (for systemic delivery) or interacting with local cells (for localized therapy).

Since the drug is absorbed directly through the skin's capillaries, this method helps bypass the body's first-pass metabolism that occurs in the liver and successfully penetrates the skin's tough outer barrier, the stratum corneum.

5.4. Controlled release / enhanced delivery

Many MN systems use design elements, such as multilayer structures, slow-dissolving polymers, coatings with controlled dissolution, or incorporating nanoparticles,to modify drug release.

Drug stability, targeted distribution, and controlled release upon penetration are further improved when MNs are combined with nanoparticles (or nano-carriers). [10]

VI. RECENT DEVELOPMENTS IN MN RESEARCH

The creation and use of MN transdermal medication delivery systems depend heavily on manufacturing technology. Depending on the qualities of the medication and the substrate material, different manufacturing procedures are chosen. Mold-based and mold-free technologies are used in MN production, with additive manufacturing becoming a popular choice for polymer MN manufacture. Precision and mechanical performance are still difficult to achieve, but three-dimensional printing has benefits for creating MNs with intricate shapes and several uses. In order to create MNs suited for certain uses, researchers have created and refined a number of fabrication procedures, which frequently call for a combination of approaches. [11]

Hydrogel microneedles have demonstrated remarkable mechanical flexibility and biocompatibility for biomedical applications since their launch in 2012.

They enable drug delivery thanks to their enormous loading capacity and adjustable rates of release. . (12) Water-soluble polymers like hyaluronic acid (HA), polyvinylpyrrolidone (PVP), and polyvinyl alcohol (PVA) are used in dissolving microneedle (DMN) systems that contain nanoparticles or micro-particles. Commonly used as excipients. Within the microneedle matrix often integrated with materials like liposomes or metallic nanoparticles the drug is encapsulated in controlled-release carriers such as microspheres or nanoparticles to allow sustained and gradual release. For instance, bilayer dissolving microneedles containing PLGA nanoparticles have been developed to deliver ovalbumin efficiently to ocular scleral tissue over an extended period. Similarly, insulin-loaded porous silicate microneedles have shown significant hypoglycemic effects in animal models. Other formulations include PLGA microneedles coated with tetracycline and silica micro-particles carrying cytokines to promote periodontal tissue regeneration. Moreover, PVP/PVA-based dissolving microneedles embedded with methotrexate nano-crystals have successfully delivered the drug transdermally for up to 72 hours, while microparticle-loaded microneedles have localized amphotericin B within skin layers for nearly a week.

In treatments such as those for alopecia, combining lipid-based carriers like liposomes with microneedle delivery systems has proven to enhance both drug absorption and stability, highlighting the synergistic potential of these advanced formulations. [13]

VII. PRESENT ISSUES AND VIEWPOINTS

Microneedles (MNs) face both exciting and challenging problems as they move from research labs to industry. To do this, significant challenges and problems must be promptly rectified. This means overcoming obstacles and ensuring viability in relevant markets. The proactive approaches needed to resolve these issues will ultimately decide MNs' and their commercial applications' future. (14) One of DMNs' problems, which leads to medication waste, is their incapacity to completely penetrate the skin. Additionally, the skin penetration of DMNs composed of various biomaterials varies noticeably. Pure PVA microneedles lack the mechanical stability required to penetrate the stratum corneum, whereas pure silk fibroin microneedle patches frequently shatter at the base. [15]

Although polymeric microneedles may be biocompatible, if materials build up in the body, they could be harmful to the immune system and liver. It is essential to strengthen their insertion skills to avoid bending and breaking. Combining different polymeric materials can improve flexibility and structural integrity, which is crucial for delicate tissues. The goal of upcoming developments in polymeric microneedle technology is to enhance manufacturing and processing procedures. Despite the uses of transdermal products today, there is still a lot of space for advancement and commercialization that addresses cost-effectiveness and production issues. In the creation of smart products, polymeric microneedle devices are viewed as revolutionary, with the potential to improve living conditions. [16]

VIII. GENERATION OF MICRO-NEEDLE

First-generation transdermal delivery methods have been increasingly used in clinical settings to provide small, lipophilic, low-dose drugs (17). This generation of ointments, creams, sprays, gels, and patches needs to be lipophilic, have a low molecular weight, and work well at low dosages. These elements limit the number of drugs that can be applied topically. For example, lipophilic drugs can reach the capillary bed by slowly passing through the stratum corneum (18). First-generation TDD aims to enhance the formulation process so that the medication can passively permeate the skin. Chemical permeation enhancers, particulate carrier systems like The second generation of noninvasive TDD systems (TDDS) includes emulsions and nanocarriers, electrically assisted techniques like electrophoresis, and external stimuli assisted techniques like magnetophoresis. (19).

Clinical products have been developed through the use of chemical enhancers and iontophoresis in second-generation TDDS (17b). The goal of the second generation of transdermal drug delivery is to make the skin more permeable. So that drugs can pass through it by temporarily compromising the stratum conium's ability to function. This generation uses many improvements that don't damage the dermis. Three techniques are used in this generation: Navigational ultrasound, iontophoresis, and traditional chemical augmentation (20)

Noncavitational ultrasound is the other member of the second generation of transdermal drug delivery. Schmidt and Fellinger (1954) demonstrated that hydrocortisone ointment could be able to cross a vascular barrier using ultrasonic technology in 1950. An ultrasonic device for lidocaine-based local cutaneous anesthetic was authorised in 2004 by the US Food and Drug Administration (21). By changing the molecular packing or removing lipids, amphiphilic substances, solvents, and surfactants disturb the intracellular lipids of the stratum corneum. Hydrophilic macromolecules cannot be delivered by conventional chemical enhancers, but they can transfer small molecules. Adding a cleavable chemical group, such as carbonates or esters, is another tactic to boost the drug's lipophilicity. One advantage of this technique is that it doesn't inflame the skin(18b). Iontophoresis is the process of using electrical energy to promote an electrically charged compound's penetration (22)

Third-generation delivery methods precisely target the stratum corneum, the barrier layer of the skin, such as microneedles, thermal ablation, and electroporation. (17b). The goal of transporting proteins, macromolecules, and vaccines through the stratum corneum layer is this generation of transdermal medication delivery. This technique involves administering the medication more quickly without harming the skin's deeper layers(18b). Electroporation breaks the skin lipid bilayer by applying brief, high-voltage pulses. This disruption process creates routes for the delivery of DNA, peptides, vaccinations, and small-molecule medications (23). When ultrasonic energy is applied, cavitational bubbles are created (Leighton, 2012). Cavitational bubbles can improve transdermal drug distribution and allow more focused effects.

A microscale conduit formed by thermal ablation in It is possible to administer drugs or vaccinations through the stratum corneum. In an attempt to improve skin permeability, microdermabrasion removes the stratum corneum and other skin layers. (18c) For instance, skin microdermabrasion has been used to deliver insulin, lidocaine, and 5-fluorouracil (24).

Microneedle application increased the local concentration of red blood cells (RBCs) for up to 24 hours, depending on the needle lengths, time, and force utilized. Microneedles can deliver macromolecules such as proteins, peptides, growth hormones, insulin, and immunobiologicals (25).

IX. APPLICATION OF MICRO-NEEDLE IN DIFFERENT DISES

9.1 CANCER THERAPY: A variety of anticancer agents have been explored for delivery through microneedle-based systems. Researchers have developed hyaluronic acid–based dissolving microneedle arrays incorporating drugs such as doxorubicin along with gold nanocages, enabling a combined chemo-photothermal therapeutic effect for the treatment of superficial tumors. In another study, Wang and colleagues designed self-degrading microneedles by encapsulating glucose oxidase and anti-PD-1 antibodies within pH-responsive dextran nanoparticles for targeted melanoma therapy. Similarly, Bhatnagar et al. looked into using microneedles to deliver gemcitabine and tamoxifen locally in order to lessen systemic side effects during the treatment of breast cancer. Solid microneedles loaded with 5-fluorouracil showed markedly increased skin permeability for the treatment of basal cell carcinoma—roughly 4.5 times higher than that achieved with conventional topical formulations. These studies collectively highlight the growing potential of microneedle technology as a minimally invasive platform for effective, localized cancer therapy (26).

9.2 Delivery of OCCULAR Drugs:

Coated microneedles offer a less invasive approach for delivering drugs to both the eye's anterior and posterior segments via intracorneal or intrascleral pathways. For instance, pilocarpine administered into the corneal stroma via coated microneedles has shown nearly a hundredfold improvement in bioavailability compared to conventional topical eye drops. Moreover, hollow microneedles can be employed to introduce therapeutic fluids into the suprachoroidal spaceallowing the medication to go circumferentially around the eye and possibly target areas like the macula close to the limbus. . In another application, methotrexate has been delivered using biodegradable polymerbased implantable microneedles for the treatment of primary vitreoretinal lymphoma (27).

9.3 VACCINES: Because microneedle-based vaccination can efficiently target antigen-presenting cells, such as dermal dendritic cells and epidermal Langerhans cells, it has demonstrated enhanced immunogenic responses. Promising results were found in early research on the delivery of vaccines using microneedle devices. In-vivo studies have been conducted on a number of vaccinations, including those for influenza, measles, poliovirus, rotavirus, adenovirus, botulism, tetanus, anthrax, hepatitis B and C, HIV-1, chikungunya, diphtheria, herpes simplex, human papillomavirus, rabies, plague, TB, West Nile, and others. virus, and others, in both human subjects and animal models such as non-human primates. These studies collectively support the potential of microneedle technology as an efficient and less invasive platform for immunization (28).

9.4 INSULIN DELIVERY: raditional insulin administration techniques often fail to replicate the body's natural insulin secretion patterns. Such inconsistent or inadequate insulin delivery can lead to severe complications—under-dosing may cause kidney damage and vision loss, while overdosing can trigger hyperglycemia-related seizures, loss of consciousness, or even fatal outcomes. In contrast, microneedle-based insulin delivery offers a more precise and controlled approach, ensuring that insulin release more closely aligns with the patient's physiological needs (29)

9.5 PEPTIDE AND PROTEIN DELIVERY: Coated microneedles are used to deliver proteins such as ovalbumin and serum albumin. Because peptides don't penetrate the skin well, less medications can be administered through alternative methods. The drug's bioavailability is increased by cyclosporin A-containing dissolving microneedles. In order to treat haemophilia A and diabetic insipidus, coated microneedles were used to deliver desmopressin. The findings demonstrated better medication delivery within 15 minutes of putting desmopressin acetate-coated microneedles into a hairless guinea pig (30).

9.6 VITAMIN DELIVERY: A coated microneedle array filled with PLGA nanoparticles demonstrated five times better delivery performance than alternative transdermal methods for vitamin D supplementation. Similarly, a positive in-vitro outcome was obtained when vitamin K was placed onto dissolving microneedles. (31)

9.7 Delivery of lidocaine: Microneedle systems For the delivery of lidocaine, such as coated and hollow types are frequently used. This technique serves as an effective and less intimidating alternative for patients with needle anxiety, especially among children. Researchers have also designed biodegradable microneedles containing lidocaine to achieve localized anesthetic effects, demonstrating that the formulation rapidly dissolves within the skin, typically within 15 minutes of application (32)

9.8 MICRONEEDLES IN DERMATOLOGY AND COSMETICS: Microneedles are frequently utilized to treat various skin conditions in the fields of dermatology and cosmetics. The distribution of lysine-threonine-threonine-lysine-serine (KTTKS) was studied utilizing solid disposable microneedles; the findings demonstrated improved drug delivery with microneedles. Showed how solid microneedles may be used to administer eflornithine hydrochloride more effectively for the treatment of facial hirsutism. Because they Microneedle rollers are now commonly used to treat psoriasis because they can treat extensive skin areas and improve drug administration to extensive areas of skin. Microneedles are being used more and more in the fields of dermatology and cosmetics to treat periorbital hypermelanosis, melasma, acne vulgaris, androgenic alopecia, alopecia areata, wrinkles, scars, and skin imperfections
(33)

9.9 GENE THERAPY
These days, a range of low molecular weight drugs, such as proteins, peptides, oligonucleotides, DNA, and other inactivated viruses, are transdermally delivered using microneedles. Furthermore, several studies using influenza, Bacillus CalmetteGuérin (BCG), and other vaccines have shown how promising the microneedle method of vaccine delivery into the skin is. Gene therapy has recently made use of siRNA and microneedles. Furthermore, it has been documented that microneedles may reliably and successfully deliver nucleic acids to the skin to treat a range of wounds, cancers, genetic skin disorders, and hyperproliferative illnesses (34)

9.10 Microneedle in diabetes: Exogenous insulin must be injected several times a day to continuously control blood glucose levels. For the steady and reliable delivery of insulin into the bloodstream, transdermal patches are an attractive dosing technique. Insulin patches help deliver insulin in a noninvasive, painless, and patient-friendly manner. Patients can remove the patches with ease, even if they have hyperinsulinemia. It has recently been established that nanoheaters integrated into insulin patches efficiently release insulin and have similar in vivo activity in mice compared to s.c. insulin injection.

Insulin-charged microneedles produced a hypoglycemic effect that was nearly equivalent to inject insulin subcutaneously. The study indicates that insulin charged microneedles composed of HA provide a substantial alternative method of delivering insulin to the bloodstream through the skin without running the danger of seriously damaging the epidermis. In response to hyperglycemia, the drug-loaded polymeric vesicles efficiently released insulin and encapsulated glucose oxidase (GOx). In reaction to rising glucose levels, GOx may dramatically speed up the rate of insulin release, causing hypoglycemia similar to that brought on by subcutaneous injection or with insulin-charged microneedles. Thus, using microneedles to administer insulin transdermally may be very helpful in the management of diabetes (35)

9.11 Microneedle in Scars treatment: Numerous studies demonstrate MN's effectiveness in treating scars. Ten patients with atrophic face scars from acne had their histological alterations caused by MN assessed in a pilot research. Skin biopsies were taken both before and after derma roller therapy Collagen types I, III, and VII synthesis had statistically significantly risen by the conclusion of treatment, whereas total elastin had decreased ($p < 0.05$). Each patient had some discomfort and oedema at the treatment location, but these symptoms subsided within a day. Other than that, no side effects were noted. Patients reported improvements in scar appearance of 51%–60%, 40%–50% for skin texture, and 80%–85% for overall satisfaction following six therapy sessions spread over three months ($p = 0.001$) (36)

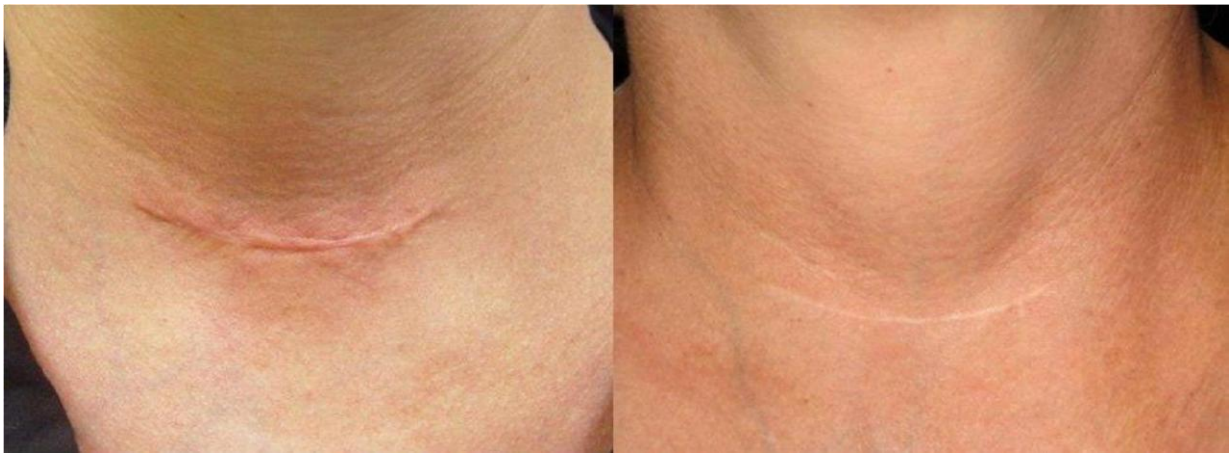
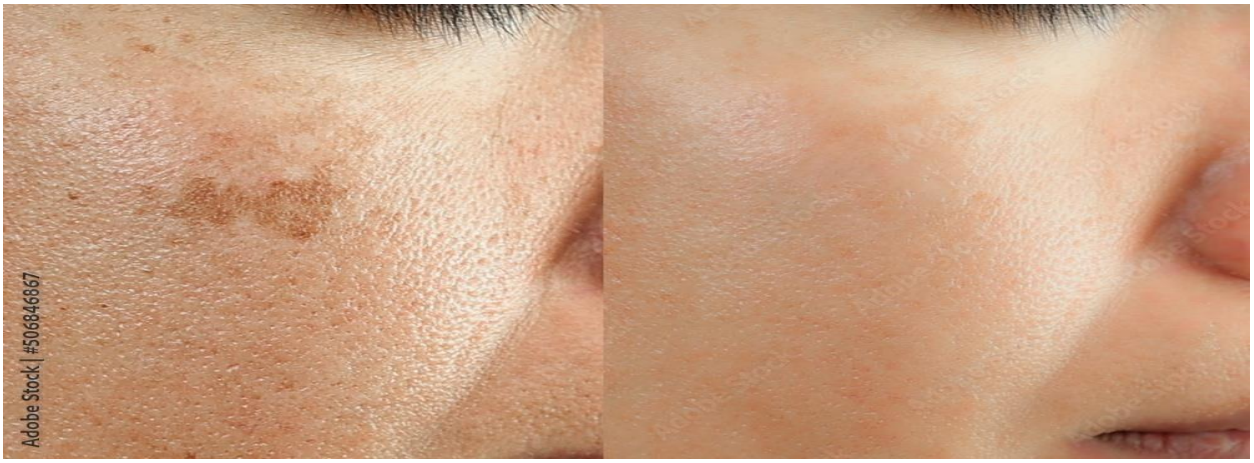


Fig: scars treatment

9.12 microneedle in melasma: In the management of melasma, microneedle-assisted TDDS has demonstrated more effective results compared to the use of topical skin-lightening agents alone. In a clinical study by Budamakuntla et al., involving 60 participants Treatments for moderate to severe melasma were given at 0, 4, and 8 weeks. The study compared topical tranexamic acid with tranexamic acid microinjections and microneedling. After a three-month follow-up period, the mean Melasma Area and Severity Index (MASI) score increased by 44.41% in the microneedling group ($p < 0.001$) and by 35.72% in the microinjection group ($p < 0.01$). Furthermore, compared to 26% in the microinjection group, 41% of patients treated with microneedling saw an improvement of 50% or more. Both treatment methods were well tolerated, with only mild and transient side effects such as erythema, burning sensations, and minor discomfort reported **(37)**



9.13 vitiligo The effectiveness of microneedling as an adjunct therapy for vitiligo remains uncertain. A study investigating repigmentation outcomes in patients with bilateral symmetrical vitiligo that was resistant to treatment were compared between using topical 0.005% latanoprost solution alone and in combination with Dermaroller and narrowband UVB therapy. Results showed that only 8.8% of the treated patches achieved more than 50% repigmentation, with 17 patients in each group exhibiting some degree of repigmentation (accounting for 37.8% of the treated areas). However, the difference in repigmentation between the treatment groups was not statistically significant. (38)

X. ADVANTAGES

ADVANTAGES	DISADVANTAGES
Enhanced comfort and manageability	Expensive
Consistent infusion	Localized discomfort
steady blood levels	Low limits of permeability
Managing oneself	No quick release of drugs
Termination flexibility	Difference in the barrier
Enhanced adherence to treatment	Limitations on molecular size

XI. CONCLUSION

Within conclusion by bridging the gap between traditional transdermal delivery systems and invasive injection techniques, microneedle technology offers a novel, patient-compliant approach to targeted and long-term medication administration. The transition from solid to dissolving and hydrogel-forming MNs has enhanced drug-loading efficiency, safety, and biocompatibility. Their adaptability highlights their multifarious clinical promise in a variety of therapeutic domains, such as cancer therapy, diabetes, arthritis, immunization, and dermatological applications. Precision and individualized care are further improved by recent advancements in smart MNs, which incorporate sensors, nanoparticles, and stimuli-responsive polymers. To expedite regulatory approval and commercialization, future research must concentrate on large-scale, economical production, enhanced mechanical robustness, and standardized clinical validation. All things considered, microneedles have great potential as a ground-breaking instrument in contemporary biomedical engineering, combining therapeutic effectiveness with patient comfort and technical advancement.

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