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Review Article

ADVANCEMENTS IN MICRONEEDLE TECHNOLOGY: COMPREHENSIVE INSIGHTS INTO VERSATILE DRUG DELIVERY MECHANISMS

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ABSTRACT

Microneedle-based transdermal medication administration is a revolutionary drug delivery technique that has advantages over parenteral and oral drug delivery systems. They are convenient, painless, safe, and effective. Due to the skin's stratum corneum layer, the majority of drugs only have a limited impact, which constitutes a thickness of about 10 to 15 µm and acts as a barrier for molecules to reach the site of action, allowing just a few molecules to pass through. To overcome this, many researchers have concentrated on using microneedles to bypass the stratum corneum barrier. The main goal of microneedles is to get the drug into the epidermis without disrupting nerve endings. Micron-sized channels created by the skin layer being broken by microneedles transport the medication directly to the epidermis or higher dermis, avoiding the barrier layer and into the systemic circulation. As a result, the microneedle can improve transdermal drug delivery. Microneedles are fabricated in different forms, such as "Solid Microneedles," "Coated Microneedles," "Dissolving or Biodegradable Microneedles," "Hollow Microneedles" and Hydrogel-forming Microneedles, through the use of components including polymers, polysaccharides, silicon, and metals. Micromolding, laser cutting, dip coating, 3D printing and its techniques are just a few of the processes used to make microneedles. Recently, microneedles have become popular for delivering drugs, genes, proteins, RNA and vaccines, demonstrating significant therapeutic effects. A variety of nano-carriers, along with different delivery methods, assist in emphasizing the use of microneedles in the meantime.

Keywords: Microneedles, Drug delivery, Bio-degradable polymers, 3D printing, Nanoparticles, Peptide drug delivery

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INTRODUCTION

It is quite difficult to establish functional delivery strategies for new active medicinal components. Drugs can be administered by different routes such as parenteral, Ocular, Transdermal and other routes such as nasal, pulmonary and buccal routes. Every path has a unique set of benefits and drawbacks. However, oral drug delivery methods have several benefits, including patient compliance, painlessness, increased surface area with rich blood supply for absorption, low cost, ease of drug release in the stomach and intestine, etc. However, there are several drawbacks, such as drug breakdown in the stomach, high First-pass metabolism, low absorption, local discomfort, and environmental changes in the gastrointestinal tract, such as pH and food, that degrade the drug, resulting in absorption fluctuation in the stomach [1, 2]. The parenteral route involves hypodermic needles to deliver the drug and has been well-received throughout the world. It has advantages such as a rapid onset of action, precise medication administration, and continuous drug infusion. It also has drawbacks, such as being unpleasant and painful, posing a risk of opportunistic infections, and requiring only full-skilled operators to administer [3, 4]. In the transdermal route, topical creams are commonly utilized to deliver the drugs to the skin. It has advantages such as avoiding first-pass hepatic metabolism, providing stable drug plasma concentrations for a longer time, and self-administration is possible. Various drawbacks include the epidermis and stratum corneum, which act as a strict barrier to drug delivery, allowing only lipophilic drugs to pass. Similarly, drugs having a hydrophilic structure will not be able to reach the systemic circulation unless they are modified in some way, and only small doses of the drug can be administered [5]. To overcome all these hurdles, several researchers have proposed a revolutionary microneedle-based transdermal drug delivery device. It is considered a Novel technique that involves the utilization of arrays of microscopic needles that are fabricated from Micromolding, Laser Cuttings, and Dip coating techniques. The patch containing micronized needles, when applied onto the skin, creates pores through which the drug can enter the skin. It offers painless administration without reaching nerve terminals or blood vessels, penetrates the living epidermis and stratum corneum, improves patient compliance, is convenient to use and has less microbial contamination. The notion of microneedles was first postulated in the 1970s [6].

This review article on Microneedles thoroughly covers the most recent information obtained from recognized scientific databases such as Scopus, Web of Science, and Springer, among others. The material obtained is up to date, covering from 2015 to 2023, and includes the most recent breakthroughs, studies, and discoveries in the field of Microneedles. The purpose of this section is to compile and synthesize cutting-edge research, advances, and uses of microneedle technology from this time period. It covers topics such as Microneedle design, fabrication, materials, biological applications, drug delivery systems, and therapeutic applications. This review article presents an updated and comprehensive assessment of the advancements in microneedle technology through a comprehensive analysis of these scientific products, which is offered to interested researchers, scientists, and professionals in this rapidly growing industry.

Skin anatomy and microneedle drug delivery

The skin is the largest organ and covers about 15% of body weight. It has a total surface area of around 20 square feet. The skin shields us from the detrimental effects of ultraviolet light. It also serves as a barrier against thermal, mechanical, and physical as well as frightening substances that allow for the sensations of touch, heat, and cold and help regulate body temperature. Fig. 1 illustrates the three layers that make up the skin. (1) The top layer of skin, called the epidermis, has a barrier known as the "Stratum Corneum" that prevents the administration of drugs transdermally. It is composed of living cells without a circulatory network 150–200 µm in thickness. Passive diffusion through interstitial fluid satisfies this layer's nutritional needs [7]. (2) Dermis-The innermost layer of the skin is made up of connective tissue from a mesh of collagen and elastin fibers, which provides strength and elasticity to the skin. (3) Hypodermis-also known as the subcutaneous layer, forms the middlemost layer of the skin, which is located just beneath the dermis and provides cushioning, insulation and support to the tissues [8]. Few potent pharmacological substances with high

lipophilicity and low molecular weights (less than 500 Da) can be supplied directly through passive diffusion since the topmost layer of the epidermis is made mostly of dead cells [9–11]. Researchers are developing microneedle-based transdermal drug delivery systems to enhance the pharmacokinetic and pharmacodynamic properties of currently available medicines. As a result, Microneedles were created in response to the requirement for a low-cost, repeatable technique of delivering medications to the epidermal layer without harming nerve cells or raising the possibility of microbial penetration.

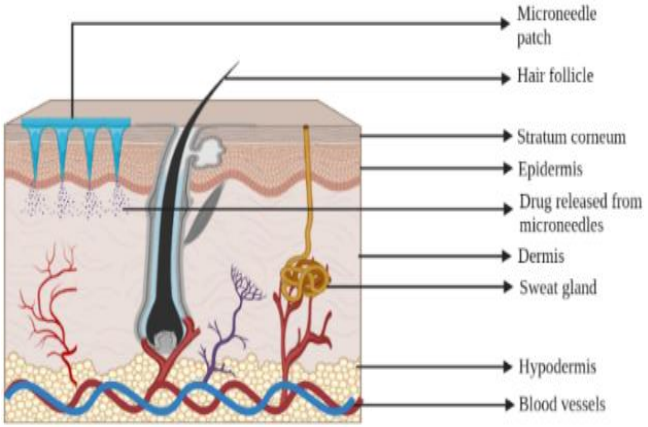

Fig. 1: Anatomy of skin [12, 13]

Microneedle

Microneedle is a transdermal device with small micron-sized projections, which is similar to that of hypodermic needles that can range in length from 100 to 1000 µm and 600 µm in height. They can pierce the stratum corneum [14, 15]. It consists of a drug-coated array of micro-structured projections. For transdermal drug delivery, microneedles can be fabricated within a patch. They are manufactured by using different materials such as silicon, silicon dioxide, polymers, glass, and other materials, as shown below in table 1. They are able to pierce through the skin and create holes that allow the medication to disperse and enter the systemic circulation. Drugs such as biopharmaceuticals, genes, proteins and vaccines are delivered using microneedle-based drug delivery [16]. Microneedles were designed to pierce the epidermis up to a depth of 70–200 mm. Because the microneedles are small and short, they do not reach the nerves of the dermis layer, allowing for painless application [17]. As a result, microneedles are more successful in improving medication transport over the skin than conventional transdermal delivery methods.

Table 1: Types of polymers used in microneedle drug delivery

Metals	Polymers			References
	Biodegradable polymers	Non-biodegradable	Natural polymers	
Titanium	Polylactic Acid (PLA)	Polyvinyl Acetate Cellulose	Carboxymethyl	[14]
Stainless Steel	Polyglycolic Acid (PGA)	Polyetherimide	Amylopectin	[15]
Aluminium oxide	Polycarbonate	Alginic Acid Starch	Thermoplastic	[16]
Silica glass	Polyvinyl Pyrrolidine	Carbopol	Dextran	[17]
Palladium	Poly (lactide-co-glycoside) (PLGA)	Polystyrene	Galactose	[18]

Table 2: Types of microneedle drug delivery

Types of microneedles	Description	References
Solid Microneedle	These are small micron-sized arrays. The sharp ends of the microneedle tips form pores on the skin's surface during insertion and removal. The composition may be applied to the skin to cause gentle diffusion of the drug through the pores into the skin. Then, it enters the systemic circulation and produces a therapeutic effect.	[18]
Coated Microneedles	These are identical to solid microneedles in appearance. The drug solution or drug dispersion layer surrounds the microneedle tips in coated microneedles. This type of microneedle works on the 'Coat and Poke' principle.	[9]
Biodegradable Microneedles	These microneedles have several advantages over rigid or coated microneedles, such as ease of manufacture, simplicity, and high drug delivery capacity. Here, the drug delivery is based on the poke-and-release approach. Basically, water-soluble compounds such as Biodegradable polymers or sugars are used to make these types of microneedles.	[19]
Hollow Microneedles	Hollow microneedles are filled with the drug dispersion or drug solution. Similar to hypodermic injection. They have holes at the tips. The medication is deposited straight into the epidermis or higher dermis layer after being inserted into the skin, which can deliver various volumes of fluids into the skin at various pressure-driven flow rates.	[20]
Hydrogel-forming microneedles	This microneedle is a recent innovation. Microneedles are produced from super-swelling polymers. Polymer needle tips swell by absorbing bodily fluid, allowing the drug to be released. They concurrently generate channels; this enables the drug from the reservoir to be introduced into the microcirculation. Upon removal, they leave minimal or no polymer residue on the skin.	[21]

To use microneedles for transdermal drug delivery, a variety of drug delivery techniques have been used, as shown in the [fig. 2][18-20]. These include the following

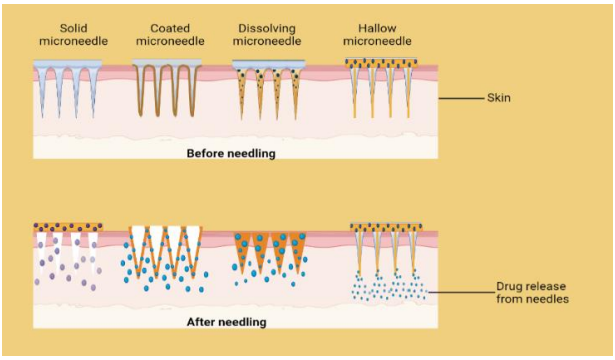

Fig. 2: Different types of microneedles [18-20]

Table 3: Types of microneedle drug delivery approaches, there are 4 drug delivery approaches, as shown in [fig. 3] [22]

Type of approach	Description	References
Poke and Patch approach.	This type of approach requires a two-step application. The microneedle patch is applied on top of the skin surface. Following the removal of the Patch, a patch containing the drug formulation can be applied to the skin's surface, allowing the drug formulation to diffuse into the skin and have a pharmacological effect.	[23]
Coat and Poke approach	The drug solution or drug dispersion layer is coated onto the microneedle tips. Furthermore, removing it leaves holes in the skin. Drug delivery is quick, via which the medication can permeate from the coated surface to the deeper layers of the epidermis.	[24]
Poke and Release approach	In this type of approach, when the microneedle patch is inserted into the skin, the drug that is loaded onto the microneedle tips dissolves gradually. In the end, the microneedles will be completely dissolved. This approach features the medication being released slowly from the microneedle in a controlled manner. As a result, the drug is released, and a therapeutic response is achieved and leaves no residue on the skin.	[23, 24]
Poke and Flow approach	In this type of approach, Drugs can be delivered directly into the skin through the perforations. Here, the flow of the solvent is through a microneedle bore at higher volumes. The pace of drug distribution can be controlled. As a result, the medication is released. This form of discharge can be seen in hollow microneedles.	[25]

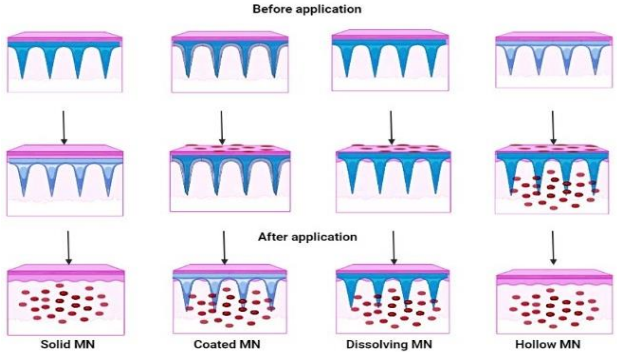

Fig. 3: Different types of microneedle drug delivery approaches [22-25]

Table 4: Various methods for the preparation of microneedles

Methods	Description	References
Micromolding and melt casting method	Using this technique, a microneedle mold is initially crafted from a silicon wafer. This wafer is then oxidized at1000 °C. Subsequently, the liquid polymer solution is filled into the pre-arranged molds, and any air gaps are eliminated either by vacuum or centrifugation. After this process, the molds are dried in an oven. The microneedles are removed after they have cooled, as shown in [fig. 4].	[26]
Laser cutting	Laser cutting is a method in which an infrared laser is used to cut metallic sheets into the shape of microneedles, with the help of software called "AutoCAD" is used to create the microneedle geometry, as well as the shape and orientation of arrays. The laser beam subsequently eliminates the metal sheet in accordance with the design, resulting in the formation of microneedles, as shown in [fig. 5]. Typically, this process is utilized to make metallic microneedles. Stainless steel is the most used material.	[27]
Laser Ablation	Laser ablation, similar to laser cutting, is employed to produce solid metal arrays. Not only stainless steel but also metals like tantalum can be manufactured using this method. After three such pulses, this bulge transforms into a needle approximately 10 µm in height. Further applications of twisted light pulses can refine the microneedles, achieving a tip diameter of under 0.3 µm	[28]
Dip coating	Dip coating is the easiest method for coating microneedles. In this method, the microneedles are first dipped in drug solution and then withdrawn, resulting in the development of a liquid coating on the surface of the microneedle; after that, the liquid layer is allowed to dry, resulting in a solid film covering on the microneedle tips without any contamination. To administer hydrophilic and hydrophobic medicines, the dip coating approach has been used. Dip coating has the disadvantages of being a slow process and the possibility of deterioration [fig. 6].	[28]

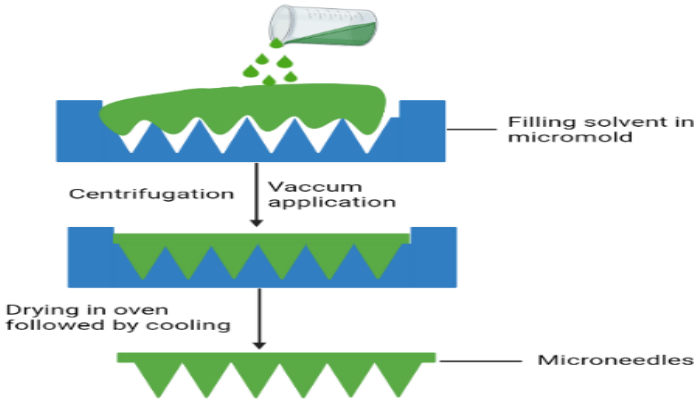

Fig. 4: Micromolding method [26]

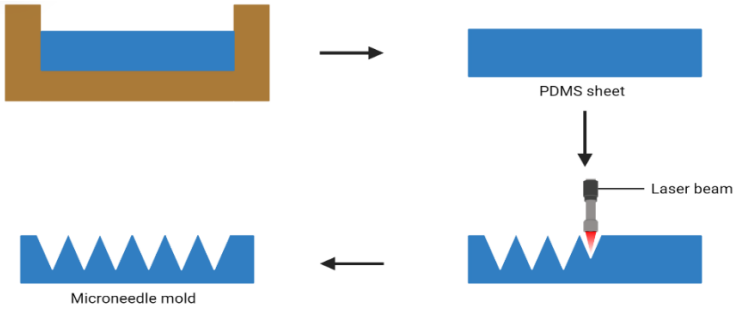

Fig. 5: Laser cutting method [27]

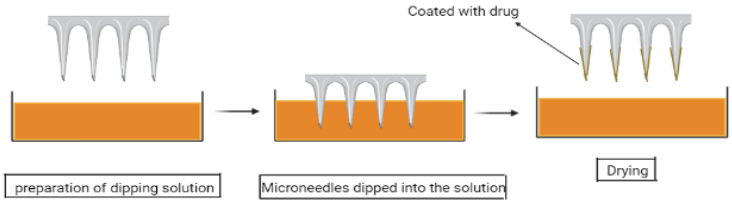

Fig. 6: Dip coating method [28]

Table 5: Drugs used in microneedles for transdermal drug delivery

S. No.	Compounds	Type of microneedles	Applications	Diameter of microneedles	References
1.	Sulforhodamine B	Coated MNs	MNs height and coating solution viscosity substantially impact drug loading and delivery effectiveness. Increasing coating solution viscosity and MN height may result in better drug loading. However, when the coating solution's viscosity increased, the MNs sharpness reduced, making it more difficult for them to penetrate the skin and reducing the efficiency of medication delivery.	(5 × 5 arrays, heights 550, 650, and 750 µm)	[26]
2.	Bleomycin	Coated MNs	By using bleomycin-coated MNs instead of intralesional injection, a more concentrated medication dose can be administered.	Pyramid shape	[27]
3.	Gentamicin	Dissolving microneedle	Polymer microneedles had a mechanical strength that allowed them to pierce the epidermis. Additionally, these polymer MNs provide the medication with a prolonged release.	Pyramid-shaped (500 µm height 19 x 19 needles)	[28]
4.	Donepezil	Hydrogel-forming MN	The type of polymer utilized to manufacture MNs affects the rate at which MNs dissolve and their penetration. When comparing Gantrez® with PVP, it was discovered that Gantrez® had a higher rate of skin penetration, whereas PVP MNs had a higher rate of disintegration.	Conical shape (600 µm in length, 300 µm in width, and 150 mm between needles)	[29]
5.	Diclofenac sodium	Hydrogel-forming MNs	The mechanical strength of MNs is increased when chitosan and PVA are combined during their manufacture, and a prolonged drug release profile is made possible.	(2.4 mm long, 780–800 µm in base diameter, and 210 µm at the tip diameter)	[29]

Advantages of 3D printing

3D printing of microneedles

Two alternative MN designs were made, a pyramid and a cone with square and circular cross-sections, using the proper engineering tools. All MNs have a 1 mm length., and the pyramid and Base cross-sections of the cone were 1x1 mm and 1 mm, respectively. The MNs were manufactured as patches of 48 MNs each, bonded to a solid 15x15x1 mm substrate. Formlabs' Form 2 stereolithography (SLA) printer, which has high-resolution capabilities, was used to create the arrays. The mechanical properties of the MN arrays were improved by 60 min of exposure to UV light at 400 °C after being cleaned in isopropyl alcohol to get rid of extra resin [30].

Three-dimensional printed microneedles

Microneedles manufactured in three dimensions (3D) are an exciting advancement in the biomedical and medication delivery industries. Because they provide a minimally intrusive technique for medication delivery, immunization, and diagnostic applications, microneedles, which are small needles typically ranging from hundreds of micrometers to a few millimeters in length, have the potential to revolutionize several medical operations 3D printing technology in microneedles, and its diagrammatic representation is shown in fig. 7.

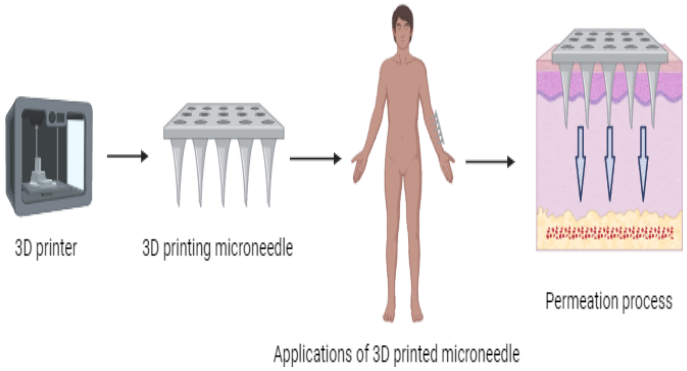

Fig. 7: The 3D-printed microneedles for transdermal drug delivery [31]

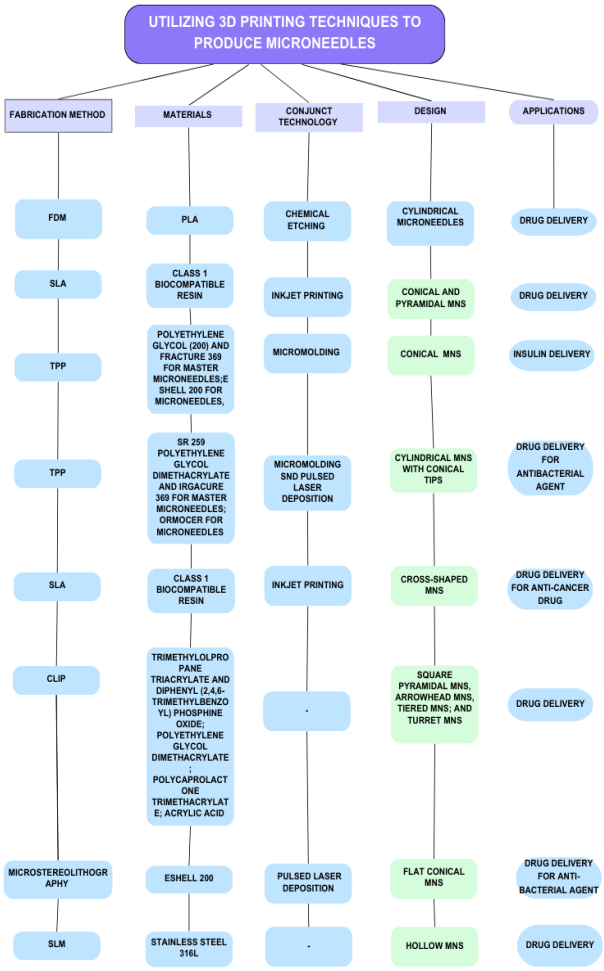

Fig. 8: 3D printing in microneedles [31, 28]

Utilizing 3D printing techniques to produce microneedles

In this article, the fabrication of MNs will be described by classifying 3D printing techniques into three types according to the ISO/ASTM 52900 standard for additive manufacturing. The idea behind each method will be discussed, along with several examples of manufactured MNs. Has examples of MNs created using SLM, CLIP, and micro stereolithography, as well as examples created using FDM, SLA, and TPP 3D printing processes [27, 28].

Evaluation of microneedles

Mechanical properties

A microneedle needs to be strong enough to stay intact while within the skin yet sharp and narrow enough to penetrate the skin easily. Two essential factors for a secure and effective microneedle design are the insertion force and the force at which the microneedle loses structural integrity. The ratio of these two forces is known as the "safety factor." The ratio should be as high as possible [32].

Margin of safety

Some of the researchers described the margin of safety as the ratio of the force required to pierce the stratum corneum to the force at which microneedles broke [33]. They used automated tools to check the margin of safety for silicon microneedles. The compressive failure force was measured using an indurated station with microneedles inserted between the punch and the load cell. For sample silicon microneedle arrays, a sufficient margin of safety was discovered.

Measurement of fracture force

Researchers employed an axial load test station to determine the force required to cause a mechanical break in a microneedle. The microneedle was pressed against a flat Aluminium surface at a speed of 0.01 mm/s until it achieved a predetermined displacement of 500 mm [34]. Adhesive tape was wrapped around the needle's base to secure the microneedles to the test surface. The manner of the microneedle's breakage was observed through an attached microscope to identify the type of failure. By analyzing the force and displacement data, the fracture force was quantitatively determined.

Studies on *in vitro* skin permeation

A diffusion cell device is used to measure the drug's skin penetration. Pig ear skin, which is placed in the experiment between the donor and recipient compartments, is typically used. The cumulative permeation characteristics of untreated and microneedled skin are researched [35].

Clinical trials and safety

Numerous preliminary clinical trials experiment on microneedles have been performed and proved to be effective in many ways, but only a few have been successful. In 2001, an attempt was made to study microneedles in human subjects. The objective was to determine whether silicon microneedles are less painful than 26-gauge hypodermic needles. The microneedles were inserted into the forearms of the 12 healthy males and females who agreed to participate in the research. According to the study's findings, microneedles caused less discomfort than hypodermic needles produced [36].

Applications of microneedles

Microneedle delivery systems have gained popularity for administering a range of biopharmaceutical medications, including oligonucleotides and peptide drugs vaccines, and anti-cancer drugs such as Gemcitabine and paclitaxel in the treatment of ovarian and breast cancer [37]; diagnosis of various diseases, and delivery of insulin in diabetic patients [38]. As well as they are also used in many cosmeceutical industries.

Oligonucleotide delivery

Oligonucleotides are known as short DNA or RNA molecules. Delivering oligonucleotides to their intracellular action sites is challenging. To address this, a variety of strategies were used to improve the delivery. By using microneedles, an attempt has been made to deliver oligonucleotide drugs; the poke-with-patch method was explored to deliver oligonucleotides using solid microneedles made of titanium or stainless steel. In comparison to intact skin, more medication was observed to reach the site of action. Iontophoresis, in combination with microneedle therapy, produced better results than iontophoresis alone [39].

Vaccine delivery

A biological preparation is a vaccination. It provides immunity against a particular ailment. It is obtained from toxins or surface-active proteins of disease-causing microorganisms. They are available in two forms: killed and live-attenuated or weakened forms. The effectiveness of the microneedle technique in vaccine therapy has been established [40]. There was an effort to develop a microneedle patch for administering the influenza vaccine. Using hollow microneedles to deliver the medication requires a smaller dose than an intramuscular injection.

Cosmetics

Microneedles play a vital role in the cosmetics industry, mainly to improve the appearance and heal scares and blemishes. The microneedle method was used to administer various cosmetic active substances such as ascorbic acid, eflornithine, and retinyl retinoate [41]. Some of the approved Microneedles products in cosmeceuticals are Derma rollers, which are used to prevent wrinkles and enhance skin texture [42].

Cancer therapy

Cancer is one of the deadliest diseases in the world, and many people have died because of inadequate treatment. Some of the breast cancer drugs, such as Paclitaxel and Gemcitabine, can be delivered by using microneedles [43]. Microneedle delivery systems of various types have already been employed to treat superficial cancer. A recent advancement merged NIR-responsive PEGylated gold nanorod (GNR-PEG) with poly(L-lactide) microneedles, termed GNRPEG microneedles and DTX-loaded MPEG-PDLLA micelles to treat human epidermoid cancer. The term GNR-PEG MN refers to this combined approach. Created by attaching GNR-PEG to the PLLA microneedle surface, showcased not only efficient skin penetration but also effective heat transfer capabilities. This enabled the tumor sites to reach temperatures near 50 °C, effective for tumor eradication.

Diagnosis of diseases

In recent years, a variety of microneedles have been employed for diagnosing a range of diseases, including cancer, cardiovascular disorders, atherosclerosis, diabetes and thrombosis. This is due to their ability to penetrate the skin and gather biomarkers from blood vessels or skin interstitial fluid through capillary action. To begin with, the interstitial fluid found in the skin is a valuable reservoir of biomarkers essential for diagnosing diseases; compared to traditional methods, the microneedle patch offers the advantages of painlessness, easy application, and the ability to extract skin interstitial fluid in a short time [44].

Treatment for diabetes

Diabetes affects the majority of people these days. Because the beta cells in the pancreas do not secrete enough insulin. Insulin is a peptide hormone, which means it's made up of many amino acids. To combat this, a novel technique known as hydrogel-forming microneedle drug delivery is developed to administer the drug, like metformin hydrochloride, straight into the bloodstream. The drug is released in a controlled manner here, resulting in a longer action time. Microneedles insulin can be more effectively administered than the hypodermic needle [45].

Challenges

A lot of research is being done to see how MN affects transdermal drug delivery. There is an extensive amount of potential for enhancing transdermal drug administration with these micron-sized needles. Yet, before these needles can be utilized in clinical environments, numerous hurdles, such as skin irritation, microbial

contamination, and therapeutically appropriate drug doses, need to be addressed. Additionally, there is a constrained range of compatible biomaterials, a need for more mechanical strength, subpar drug delivery control, and a restriction on drug loading dose. The medications that are most likely to be given in therapeutically relevant quantities are potent pharmaceuticals that require low dosages and vaccinations. Another issue is the distribution of macromolecules, which are biotechnology products. Because of their high molecular weights and hydrophilicity, these molecules are difficult to distribute across the skin [46].

Recent advancements in microneedles

The treatment of osteoarthritis

Bionic MNs with multiple functions enable sustainable drug delivery to various body parts over an extended duration. When rats with knee osteoarthritis were treated using MNs filled with glucocorticoid, there was a significant decrease in swelling and inflammation in their knee joints fig. 9 [47, 48]. Meloxicam has low water solubility. Like other NSAIDs, it can cause gastrointestinal side effects, leading to decreased adherence among patients. Moreover, since osteoarthritis (OA) is a long-term condition, medications for this treatment are typically consumed over extended periods. The results showed that MNs provided advantages, including rapid drug release (achieving 91.72% in less than 30 min), effective skin administration (79.18%), minimal skin irritation, a significant increase in relative bioavailability (reaching 122.3%), and strong anti-inflammatory and pain-relieving properties. As a means of delivering drugs through the skin, MNs can address the challenges of low oral uptake for certain drugs and reduced patient adherence. Nonetheless, there have been limited reports on MNs being used to treat osteoarthritis [49–51].

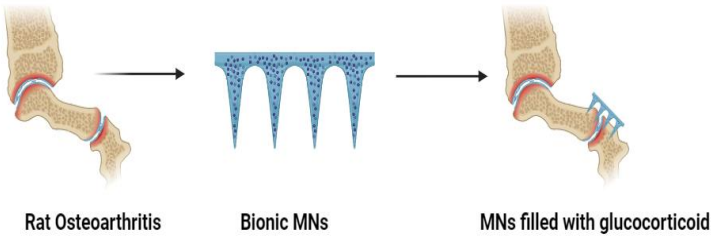

Fig. 9: Bionic MNs filled with glucocorticoid, there was a significant decrease in swelling and inflammation in their knee joints [3]

The treatment of rheumatoid arthritis

Besides meloxicam for osteoarthritis, several other medications, including methotrexate [52, 53], artemether [54, 55], alkaloids [56, 57], capsaicin [58], Etanercept (EN) [59], have been integrated with MNs technology to treat rheumatoid arthritis. Therefore, MN transdermal delivery presents a potential administration method for arthritis treatment. This method is utilized to control the pace of drug release, reduce the necessary dosage, and lower the chances of drug-related side effects using a minimally invasive delivery approach. The IPS facilitated the conversion of the micrometer-sized crystalline lipophilic drug into a nanometre-sized amorphous form suitable for transdermal diffusion fig. 10. Additionally, it constructed the DMN structure for transdermal administration [60].

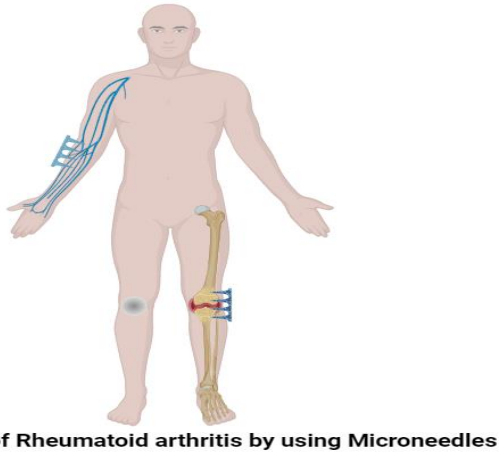

Fig. 10: Mechanism of Rheumatoid arthritis by using microneedles [60]

The treatment of dermatology dermatosis

Traditional patches often feature a basic microstructure and deliver drugs at a slower rate, limiting their therapeutic impact and broader medical use. In contrast, MNs possess porous microstructures. They can employ polymeric materials with multifunctional antibacterial properties to encase skin regeneration or the process of skin tissue renewal factors or medications, facilitating either controlled or sustained the discharge of a drug. For instance, chitosan polymers stand out as a distinct natural polysaccharide alkaline, renowned for its biodegradability, non-toxic nature, biocompatibility, inherent antibacterial properties and hemostatic features [61, 62]. For example, this approach finds extensive use in the development of multifunctional smart micron array patches designed for wound healing. The integration of microneedles in the drug delivery system not only tackles the problem of low transdermal efficiency when applying UK5099 externally but also overcomes the issues of short drug retention time and the requirement for repeated injections that come with subcutaneous administration of exosomes [63].

The treatment of cancer

Microneedles (MNs) have been utilized for the minimally invasive delivery of anticancer drugs (chemotherapy) and also for conveying agents used in photothermal therapy (PTT) and photodynamic therapy (PDT)) to locations of skin tumors, resulting in enhanced

therapeutic effectiveness. Cryomicroneedles, when employed for cell delivery, can maintain the viability and proliferative capacity of the delivered cells. Biocompatible Cryomicroneedles can enable minimally invasive cell delivery for various cell therapies [64, 65]. Additionally, the integration of microneedle-based percutaneous delivery with cancer immunotherapy offers an enticing avenue for enhancing the effectiveness of cancer treatment. The combination of chemotherapy and photothermal therapy holds significant possibility for enhancing the efficacy of treatment cancer, with the added benefit of preventing cancer recurrence due to lingering cancer cells developed, microneedles composed of layered polyvinylpyrrolidone (PVP) and coated with chitosan, carrying Adriamycin, along with polyvinyl alcohol (PVA) enriched with AuMSS. The approach facilitated the transfer of AuMSS and Adriamycin nanorods (referred to as Doxorubicin encapsulated in microcapsules) to cancer cells. The Doxorubicin encapsulated in microcapsules in the patch was proven to be a simple and easily expandable delivery tool, leading to enhanced therapeutic outcomes in tumors when combined with photothermal therapy and chemotherapy [66].

Diabetes treatment

Insulin is an endogenous hormone synthesized by the islet cells of the pancreas, serving to regulate glucose levels in the bloodstream. People with diabetes, whether they have type 1 diabetes (where the body cannot produce insulin) or type 2 diabetes (where the body doesn't respond adequately to insulin), often require long-term insulin injections [67, 68]. However, maintaining precise control of blood sugar levels with insulin can be challenging. An incorrect dosage can result in the risk of hypoglycemia, which, in case of severe, could potentially result in seizure, unconsciousness, or even death. Consequently, individuals with diabetes must continuously monitor their blood glucose levels during insulin therapy. The distribution of insulin through microneedles represents one of the most sophisticated and significant applications of this technology. In 2015, the research team led by Zhen Gu introduced the idea and initial model of the "Smart Insulin patch" and subsequently created the Zenomics company to progress its clinical development efforts further [69]. Utilizing microneedles smaller than 1 mm in size can diminish the discomfort associated with injections and enhance the overall quality of life for patients. Metformin, employed as a hypoglycemic agent, is incorporated into detachable microneedles made from polyvinyl and sucrose (PVA/Suc). These microneedles release the medication when exposed to near-infrared (NIR) irradiation as required [70].

The vaccine delivery

Microneedles applied in the delivery of vaccines represent a well-established field of research, making it a more developed area of study. Notably, Microneedle-based vaccines can be stored at room temperature and transported in a solid state. They can be customized for packaging or encapsulating different immunization types, including DNA vaccines, subunit antigens, and inactivated or live virus vaccines [71]. In the study conducted by Kim *et al.* [72], they administered Middle East respiratory syndrome coronavirus(MERS-CoV) and severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) administering vaccines to mice through the traditional subcutaneous needle injection method as well as through percutaneous delivery using dissolved microneedles arrays (MNA). They conducted a comprehensive preclinical analysis of the immunogenicity of the Middle East respiratory syndrome coronavirus (MERS-CoV) production of antibodies within two weeks. Individuals who received the Middle East respiratory syndrome coronavirus(MERS-CoV) vaccine generated antibodies that could neutralize the virus for a minimum of one year, and a similar trend was observed for those immunized against severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) [73, 74]. Furthermore, the MNA delivery method for these vaccines elicited a more robust immune response compared to traditional hypodermic needle injections. This implies that microneedle array holds promise as an effective strategy for immunization against coronavirus infections [75].

Other applications

Initially, microneedles were primarily used to enhance the efficiency of transdermal drug delivery. However, the use of microneedles has since broadened to encompass a wide range of other fields within the biomedical domain. Significant studies have demonstrated the diverse biomedical applications of MNs. Specifically, hollow microneedles and porous microneedles have found extensive use in biosensor research, yielding promising outcomes in various applications [76].

Table 6: The significant investigations into the biomedical applications and the most recent advancements in the field of microneedles (MNs)

Biomedical application (Diseases)	Latest research (drugs)	References
Osteoarthritis	Meloxicam, Glucocorticoid	[77]
Rheumatoid arthritis	Methotrexate, Alkaloids, Artemether, Capsaicin, Etanercept (EN)	[78]
Dermatosis	Small molecule drug UK5099, keratin and Exosomes	[79]
Cancer	Transporting ovalbumin-pulsed dendritic cells to target subcutaneous melanoma tumors, delivered rapamycin to treat skin tumors and vascular anomalies.	[77, 80]
Diabetes	Delivery of Exendin-4 (Ex4) and glucose oxidase (Gox) Insulin delivery	[79, 78]
MERS, SARS	Vaccines for MERS-CoV and SARS-CoV-2	[80]

CONCLUSION

Microneedles are a relatively novel method of drug delivery. The microneedles are more effective than the current transdermal drug delivery systems. Microneedles have several advantages, such as patient compliance, painless medication delivery, bypass-pass metabolism, and direct local drug administration; in this review, we go over the materials that are required for the systematic development of microneedles. We also explored the types of drug delivery approaches with their suitable methods for the preparation of Microneedles and their application in Cancer, Diabetes, Cosmetics, Vaccine delivery, and other applications. Microneedles appear to be a potential technique of drug delivery, and more studies and improvements in this field could improve the importance of Microneedle drug delivery.

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AUTHORS CONTRIBUTIONS

Lokeswar Sekar-Literature review, Data curation and Writing, original draft; Raagul Seenivasan-Literature review, Data curation and Writing, original draft; M Vivek Reddy-Conceptualization, Critical Evaluation; K Dileep Varma-Literature review, Data curation; Syed Suhaib Ahmed-Literature review, Data curation; Jey Kumar Pachiyappan-Review and editing, Supervision, Evaluation, Visualization; GNK Ganesh-Review and editing, Supervision, Evaluation, Visualization, Proofreading.

CONFLICT OF INTERESTS

Declared none

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