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Review article

Exploring micro needles applications in rheumatoid arthritis: efficacy, safety, and patient benefits

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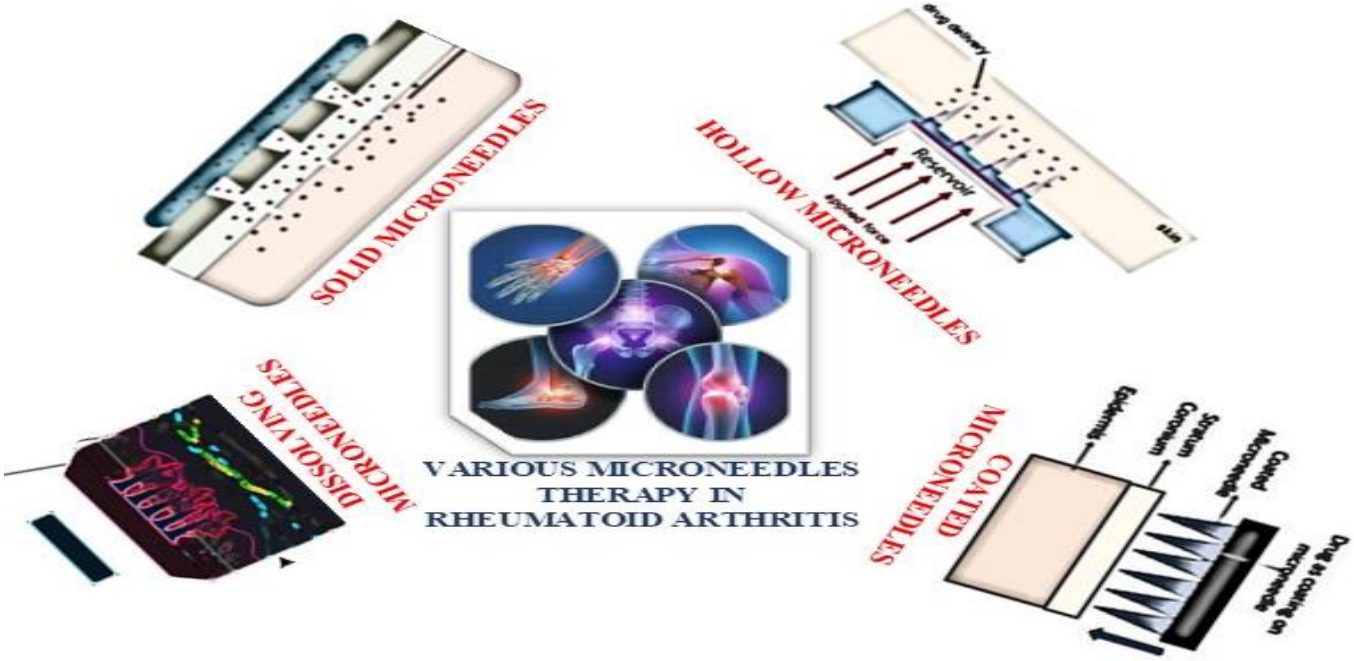
ABSTRACT

The most significant organ in the body, the skin is also where many drugs are administered. Many benefits, including averting first-pass liver metabolism, maintaining a steady levels of plasma, safety, as well as complying over oral or parenteral methods, come with drug delivery via the skin. A few of the microscale physical improvements that significantly broadens the range of medications available for through the skin and intradermal application is the use of microneedles. Microneedles are delineate to pierce the stratum corneum, the topmost layer of the skin, deprive of giving rise to considerable exertion or tissue destruction. They are consistently tens to hundreds of micrometres in size. An array of goods, for instance silicon, polymers, and stainless steel, has been utilized to create solid, coated, hollow, and dissolvable microneedles. Meanwhile, because of their superior biocompatibility, reduced preparation expense, and strong mechanical qualities, biodegradable polymers have steadily emerged as the material of choice for creating MNs. The technique of creating microneedle arrays enhances safety, effectiveness, and bioavailability to enable medication delivery via the skin. The autoimmune disease known as rheumatoid arthritis (RA) is marked by chronic synovitis, reduced joint function, inflammation, proliferation of synovial cells, formation of pannus, and consequent loss of cartilage as well as bone.



Microneedles have proven to be an incredibly effective therapeutic tool in the delivery of medications, genes, proteins, RNA, and vaccinations in recent years. The many kinds of MNs, the materials utilised to make them, and their characteristics in terms of administering treatments for rheumatoid arthritis are all covered in the current review.

Keywords: Microneedle, Transdermal, Skin, Patient compliance, Efficacy, Therapeutic effect.

INTRODUCTION

Many techniques have been used to give medications in order to improve health and extend life. The initial stage of cutaneous drug administration involves the immediate application of the medicament onto the skin. The drug passes through both the epidermis as well as dermis before entering the stratum corneum. The medication is prepared for uptake when it touches the dermal sheet. By controlling skin diffusion, the drug molecules are supposed to enter the circulation by this method. The introduction of microneedles has caused a radical change in the medication delivery system environment [1].

A prevalent, systemic, chronic autoimmune illness that causes inflammation and consequent joint discomfort is called rheumatoid arthritis (RA). The pathological characteristics associated with this disease include deterioration of the cartilage, bone, and joints, as well as synovial inflammatory hyperplasia. Usually, this results in pain, stiffness, and edema in the joints. The condition may worsen joint damage and potentially result in disability as it progresses, which would have a major negative impact on people's health [2]. Non-steroidal anti-inflammatory medicines (NSAIDs), glucocorticoids, and disease-modifying antirheumatic medications are the mainstays of therapeutic RA treatment. Dissolving microneedles (DMNs) are epidermal formulations with the previously mentioned properties that are made of biodegradable polymers with water-soluble properties. As opposed to conventional transdermal transport, they may boost superficial or systemic application by sending the medicinal product to the tissues through the emergence of transient small pore sizes in the dermis, which breaks down the skin's barrier. Transdermal transport compositions, such as DMNs and AP, serve as the foundation for mixed regimens. Simultaneous multi-drug administration can be accomplished by combining the two into an individual composition, which will decrease the amount of dosage required and enhance the patient's tolerance and pharmacological impact [3] The macromolecular medication is loaded inside DMN syringe points, which disintegrate fast when introduced into the layer of skin and efficiently provide the medication. With just one dose of the combined composition, a synergistic as well as detoxifying twin pharmacological effect is produced. Microneedles (MNs), the newest type of TDDS, have the ability to perforate the stratum corneum, creating recoverable microchannels that allow medication to travel through the skin obstacle [4].

Microneedle History

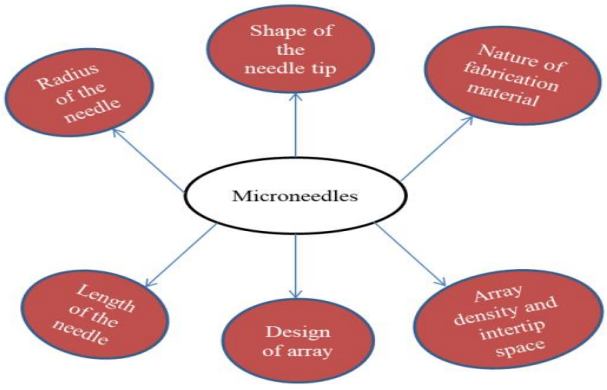
The idea of microneedles has evolved throughout time, moving from the application of massive needles to contemporary designs. In 1905, Dr. Ernst Kromayer, a German dermatologist, healed skin disorders like wrinkles and excessive pigmentation with motor-powered tooth burs of various sizes. The first recorded usage of microneedles occurred in 1921, when Chambers inserted a needle into an egg's nucleus. Injection medication delivery hooked the stratum corneum initiated to get interest in the 1960s. In 1998, a prototype transdermal microneedle was pitched and made from silicon wafers using photolithography and ion etching [5].

To create microneedles, an assortment of components including glass, ceramics, metal, and polymers were used. Some fabrication techniques and materials are being investigated for transdermal drug delivery (TDD) after a microneedle matrix was employed in 2004 to breaches holes in the skin. There are several varieties of MNs, encompassing solid, coated, hollow, dissolvable, and hydrogel-forming MNs. Additionally, a variety of production techniques include photolithography, micro-injection moulding, laser ablation, etc.

Fabrication of Microneedles

Microelectromechanical systems (MEMS) can be used to create microneedles. Three steps make up the fundamental process: etching, patterning, and depositing. The creation of thin films, ranging in thickness from a few nanometers to roughly 100 micrometres, is referred to as deposition. Laying, an outline onto a film is called patterning. Wet as well as dry etching are both distinct kinds of etching. Etching is the technique of cutting into the exposed areas of a material's surface to produce a design using a strong acid or mordant. The choice of manufacturing or fabrication technique is influenced by the design, geometry, as well as substance of the microneedle [6].

Figure 1: Selection material for preparation of microneedles



Micro-electromechanical Systems (MEMS)

Using MEMS techniques, solid as well as hollow MNs along with molds for dissolving MNs have been generated entirely from an appropriate substrate. Three carefully regulated steps make up the production process: material deposition, patterning, and etching.

The first step involves either chemical (CVD) or physical vapour deposition (PVD) to build a film on a substrate that has a thickness of a few nanometers to 100 µm. Atoms are immediately transferred from the source to the substrate perpetually the gas stage in the PVD procedure, fabricating the sheet. Film is formed during the CVD process as a result of an interaction of chemicals on the substrate surface.

Photolithography is the remarkably widely used type of lithography. This procedure is construct on the examination that certain substances, including metals, embellish blurred when conquered to UV light (λ = 193-236 nm), while glass remains clear. Moreover, photolithography makes it possible to manufacture MN moulds. In this instance, a stiff silicone mold along a positive image is fabricated, and the selected components is subsequently relevant to a negative mold constructed of poly (dimethyl siloxane) (PDMS) [7].

In order to create a design on the materials superficially, the visible superficially of the substrate are etched away employing a powerful acid or corrosive substance. Wet as well as dry etching are the two different manifestations of etching. By immersing the substrate in the chemical liquid during the wet etching process, extra material is eliminated, resulting in metallic as well as silicon MN arrays. On the other side, a vapour phase or plasma etcher is familiar to accomplish the dry etching approach.

An interaction between the gas with the substrate is made possible in the RIE procedure by the gas's excitation towards a reactive phase. By adjusting the gas pressure, the number of ions that affect the level of isotropy can be changed. Ions can be accelerated by the electric field, which also increases the etching's direction. In the IBM method, the material that is etched is physically removed by accelerating inert ions from a source. While RIE can produce anatomy, it has a poor etching outlay and finds it difficult to preserve an optimal width-to-height proportion. The procedure noted as the Bosch procedure, or deep reactive ion etching (DRIE), works well to create off-plane MNs [8].

Laser Cutting

Metal MNs can be produced via electroplating or electroless plating metal upon positive alternative negative MN moulds, 3D laser cutting, and laser ablation. Using an infrared laser, stainless steel or titanium sheets shaped like MNs are sliced to create arrays of solid MNs. Some computer-aided design (CAD) software is employed to produce the desired shape, geometry, plus dimensions of MNs. MNs undergo cleaning in steaming water as well as bending upright at a 90-degree angle from their lowest level once the laser beam has taken on the predetermined shape of the needle. After then, burrs are removed, MNs are thinned out, and the tips are refined by electropolishing, cleaning, and drying them next to compressed air [7, 8].

Laser Ablation

It approaches to material processing, which includes metal processing, is top-down. Solid metal arrays are fabricated when light pulses cause the intended form to bulge on a sheet of metal. Nevertheless, the creation of ion and electron plasma is unsuitable for the creation of structured materials considering as high-intensity laser pulses. Thus, Omatsu presented a new, efficient, and time-saving fabrication technique for producing metal MNs based on optical vortices that are circularly polarized as well as nonzero overall angular momentum, as illustrated. The creation of tantalum MNs with small tip radii and a vertical height of over 10 µm was reported by the authors. Evens et al. presented a brand-new technique in 2020 for creating solid polymer MNs via laser-ablated steel molds. Additionally, this mold was used in the injection molding procedure to create the polymer MNs. This low-cost production approach allows for the variation of MN height and the acquisition of acute tip radii [7].

Micromolding Method (Solvent Casting)

Typically, dissolving MNs are made by flowing the liquid mixture into an MN mould that has already been constructed. Generally, a silicon wafer is employed as a foundation to create the mold. The wafer is subsequently oxidized at 1000°C. Wafer coating is done by CVD, while lithography techniques are employed to form a needle geometry and then RIE. After filling the molds with a liquid polymeric solution, air pockets are extracted utilizing vacuum or centrifuge. The MNs are taken away from the molds initially they have calmed and then dehydrated in the oven. Very easy and economical generation of MN at room temperature is one of this method's benefits. Furthermore, it is reported that synthesis of biodegradable polymer microneedles (MNs) with a suitable configuration and enough courage to pierce skin, utilizing natural as well as synthetic materials. It is interesting to note that ceramic MNs have also been produced via micro-molding [9].

Atomized Spraying Method

The insufficient capacity to generate dissolving MNs in massive amount with the appropriate morphology and physical attributes is addressed by this technique. It is also possible to reduce the issues caused by the viscosity as well as surface tension of the liquid when filling the MN molds. Polymers (PVA, PVP, CMC, HPMC, Sodium alginate) along with sugars (trehalose, fructose, plus raffinose) can be used to make dissolving MN. To summarise, an

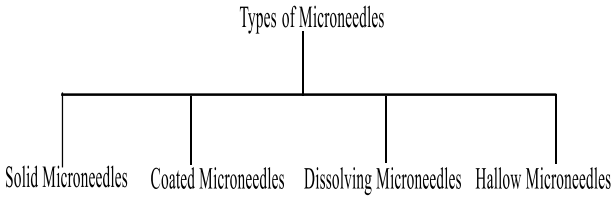
atomized sprinkle is engendered by a nozzle that is linked to a liquid composition with a source of air. After filling PDMS molds, the mixture is allowed to air dry for two hours. This technique can also result in laminate-layered in addition horizontally-layered dissolving MN [10].

Droplet-Born Air Blowing Method (DAB)

Because MN is manufactured in a hot and humid environment, conventional techniques of producing MN have resulted in drug inactivity. Among the sketching lithography techniques, DAB is an approach, which was put forth by Kim et al [11]. This process, which uses air pushing to form polymer droplet-like particles into MNs, allows for manufacture in temperate climates without the need for heat or UV light. In a nutshell the process commences with the top as well as lower layers being discharged with the solution that has been prepared. Next, the higher plate is lowered to facilitate droplet contact. The viscous solution lengthens as the upper plate moves upward. The droplet is subsequently eliminated from a substrate along with blown with air to remove any residual water and harden it into the appropriate configuration [12, 13].

Type of Microneedles

Figure 2: Types of Microneedles

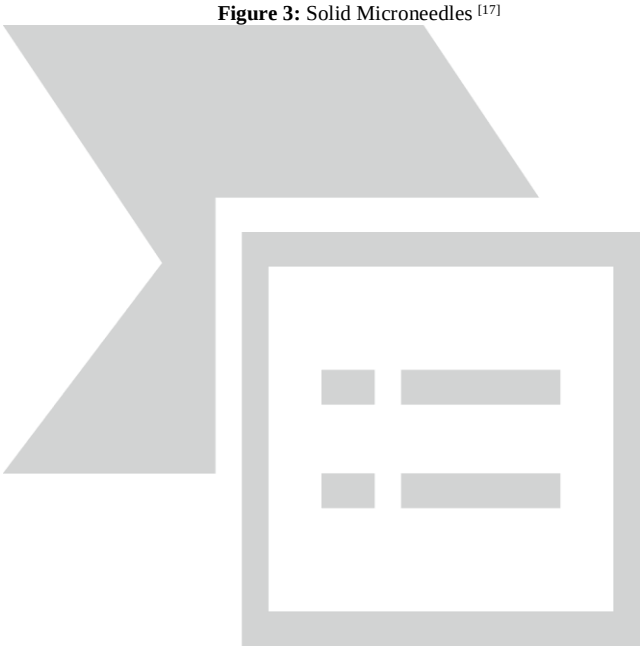


Solid Microneedles

Solid MNs are made of substances that can penetrate through the epidermis, including titanium, silicon, ceramic, or stainless steel, to create microchannels that can be used to administer drugs. The purpose of these microneedles is to pre-treat epidermis. As the needles are driven into the skin, the stratum corneum temporarily develops tiny holes. The medication has a systemic effect after being absorbed by the capillaries. It can also have a localized impact. Drug delivery via passive diffusion to skin layers is facilitated by solid microneedles. The main focus of fabricating solid microneedles is to guarantee sufficient mechanical strength by selecting microneedle materials and geometric configurations with attention. By making the points of the microneedles as sharp as possible, the insertion force needed to pierce tissue is reduced. Typically, silicon, metals, ceramics, even polymeric materials are used to create solid MNs. They mostly serve as the skin's pre-treatment before a medication is administered. Molds can be used to create solid MNs using injection molding, hot embossing, micro-molding, and soft lithography, among other processes. Wet etching, laser cutting, three-dimensional laser ablation, as well as metal electroplating are some of the methods used to create metal microneedles. Although two-dimensional data structures of microneedles are made by slicing microneedles into layers of titanium along with stainless steel and then folding them at a ninety-degree angle, rows of solid metal microneedles are made directly from the source [14]. Photolithography is used to create polymer microneedles using optically sensitive polymers. For this purpose, the UV-curable polymer SU-8 is extensively employed. Polymer microneedles are frequently used as master components in molding replication. Ceramic micro-molding along with sintering are the processes used to create ceramic microneedles [15].

Some microneedles are made on a cylinder and then rolled onto the skin with roller tools. These commercially available microneedle rollers are used in cosmetic treatments to enhance skin permeability for drug delivery and to promote skin renewal and collagen introduction. Depending on the components and configuration of the microneedles, different manufacturing techniques are utilised to fabricate solid microneedles. These microneedles have been significant in enhancing the transdermal administration of medications [16].

Figure 3: Solid Microneedles [17]



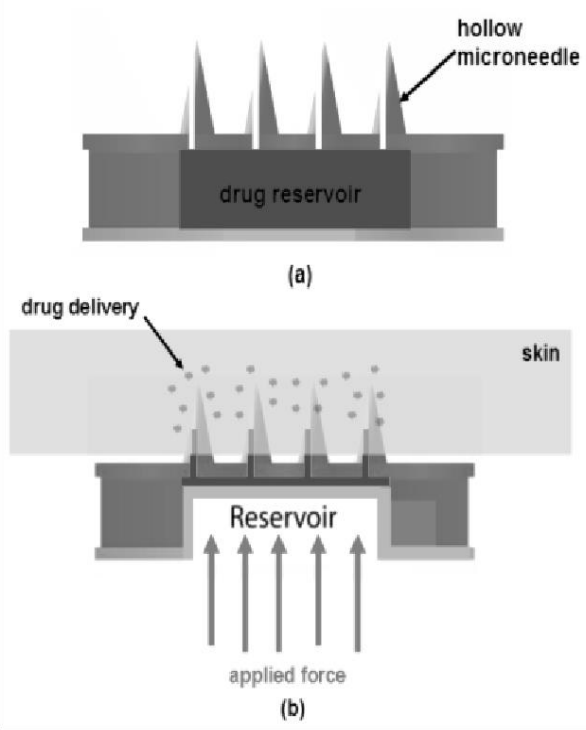
Hollow Microneedles

Miniaturized needles for hypodermic injections, or hollow MNs, gather fluid through their internal channels. They are used for identifying bio-analytes and have been produced from a range of component, incorporating metals (like titanium, nickel, and stainless steel), polymers (like polydimethylsiloxane and poly (methyl methacrylate)), silicon, along with ceramics (silicon carbide with alumina) [18].

They can be filled with a therapeutic approach or distribution, or they can be unfilled and fastened to a drug repository. After being interject into the skin, these microneedles open a channel that allows the medication to enter the epidermis or the top layer of

the dermis. If the medicine is to be distributed via a fast bolus administration, pressure release and rate of flow can be changed. Since there is more room for the drug in the empty area inside the needle, these microneedles can deliver a higher dosage of the medication. Aligned on the silicon substrate, hollow microneedles measuring 500–600 μm in length and 100 μm in outer diameter. These techniques include deep X-ray photolithography, integrated lithographic moulding, deep reactive ion etching on silicon, laser micromachining, and wet chemical etching for the creation of hollow microneedles. With its precise and adaptable ways for administering medications and drawing bodily fluids out of the body, hollow microneedles constitute a significant advancement in medical as well as medications delivery advances [19].

Figure 4: Hollow Microneedles [20]

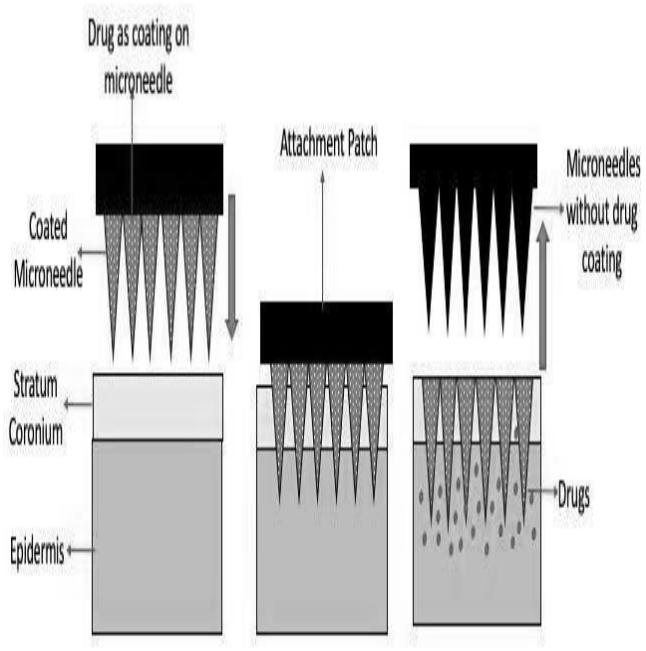


Coated Microneedles

MNs coated with an active ingredient can carry a wide variety of active components, including as proteins, peptides, small molecules, DNA, and viruses. Since the active substance is only applied to the MNs' surface and not their core, this sort of MN has a lesser concentration of it. However, the active ingredients reach the skin extremely quickly. For instance, ligand-modified gold nanorods encased on polydimethylsiloxane (PDMS) MNs have been utilised to sample ISF for the identification of illegal substances. While polyimide MNs coated with glucose-detecting enzymes have been utilized to directly monitor glucose levels in biosensing applications. The three most prevalent methods for coating microneedles are electrodeposition, spin coating, and dip coating [21].

Typically, water-soluble inactive excipients and active chemicals make up the solid film that is utilised as a coating. The interstitial fluid dissolves these excipients, which causes the coating to separate from the microneedle surfaces. The amount of medication loaded depends on the microneedle magnitude, layer of coating thickness, and protecting technique; the maximum drug loading capacity is 1 mg. Medication delivery for arthritis by MNs still has various obstacles.

Figure 5: Coated Microneedles [22]

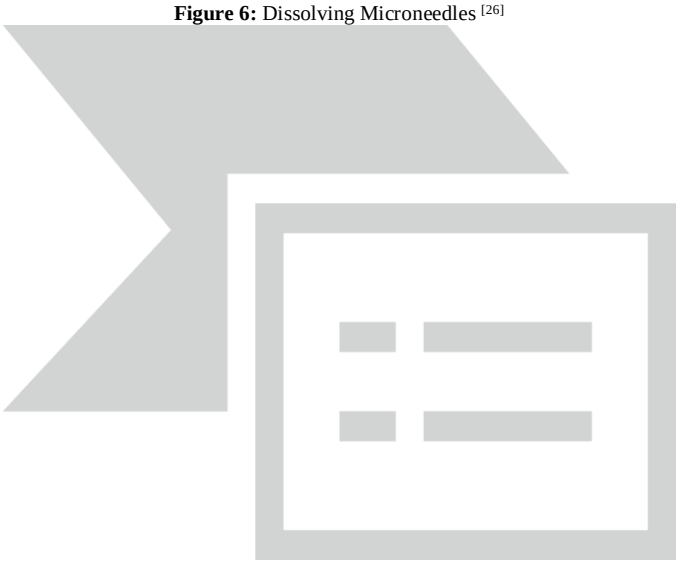


Dissolving Microneedles

Based on its features, the dissolvable MN method, first debuted in 2005, shows promise. These features include the ability to release macromolecules more quickly and the ability to apply drugs in a single step, making drug administration simpler. Dissolvable MN distribution subsequent "poke-and-release" has become better, elevating this tactic above others. The dissolvable MN tip can be deposited rapidly employing a two-stage casting process. When the dissolvable MN is introduced into the layer of skin, the needle tip breaks down, allowing the medication load to come out and disseminate more easily. The best materials to use for making the soluble MN are those that dissolve in water [23].

By encasing the medication within the polymer, biodegradable polymers are used to create them. After the microneedle is introduced into the skin, the drug is delivered through disintegration. Many dermatological disorders, such as psoriasis, atopic dermatitis, excessive pigmentation, hair growth, acne, keloids, skin tumours, infections, and other illnesses of inflammatory skin conditions, have been treated using dissolving MNs. For those having arthritic conditions require regular medication, it also improves the standard of life. Drugs can be injected into the entire needle body of dissolving MNs, which enhances MN drug loading and offers a fresh approach to improving arthritis therapy outcomes [24-25].

Figure 6: Dissolving Microneedles [26]



Application of microneedles for Rheumatoid Arthritis

Minimally Invasive and Pain

Patients along with rheumatoid arthritis (RA) endure prolonged inflammation of joint, and conventional drug delivery methods like injections add further discomfort and exacerbate their suffering. Microneedles (MNs) suggest a novel outlook to transdermal medication transport directly to patients' joints [27]. Typically, smaller than 800 μm, MNs are painless and the microchannels they create in the skin heal quickly after removal. This significantly reduces the likelihood of microorganisms entering the body, minimizes bleeding risk, and lowers infection rates. MNs also diminish the reliance on traditional needles, thereby decreasing occupational exposure risks for healthcare workers. For RA patients who are apprehensive about long metal needles, MNs provide a fear-free alternative, enhancing patient compliance [28].

Maintain Drug Activity

Microneedles (MNs) serve as an effective delivery system for rheumatoid arthritis (RA) treatments, yet ensuring the stability and efficacy of the drug within the MNs is crucial. Previous studies have demonstrated that MNs packed among other macromolecules, such as insulin as well as vaccines, retain the original activity of these substances [29-30]. The immune response of vaccines and the blood sugar-lowering result of insulin delivered via MNs are contrast to those of subcutaneous injections. For instance, Cao et al. successfully incorporated the cryopreserved biological agent etanercept into hyaluronic acid MNs (HA-MNs) plus cross-linked them using ultraviolet light [31-32]. Circular dichroism analysis confirmed that the secondary structure of etanercept remained intact. Consequently, MNs have a great deal of potential for RA transdermal medication administration in the future [33].

Microneedles Therapy in Rheumatoid Arthritis

The primary hallmark of rheumatoid arthritis (RA), an autoimmune illness, is persistent polyarticular pain. Historically, RA treatment relied on oral medications or intra-articular injections. Nevertheless, oral administration suffers from low bioavailability and significant side effects, limiting its clinical use. Additionally, joint cavity injections can be painful and carry a possibility of infection, adding to patients' psychological burden [34-35]. As an innovative transdermal drug delivery method, microneedles (MNs) enable direct delivery of drugs to the joint cavity through the skin, permitting for a higher concentration of the medication at the site of the lesion [36]. This method mitigates systemic side effects and enhances drug bioavailability. Furthermore, MNs are minimally invasive and gentle on skin tissue, boosting patient compliance [37-38].

Solid and Coated MNs Therapy in Rheumatoid Arthritis

Solid microneedles (MNs) typically avoid carrying medication directly but instead facilitate drug release through a "poke and patch" method. Their robust mechanical properties allow them to sneak out the stratum corneum (SC) plus create microchannels. In the context of rheumatoid arthritis, solid MNs enhance skin penetration to improve the transdermal absorption and bioavailability of insoluble drug [39].

SiRNA drugs exhibit excellent targeting and specificity, achieving significant efficacy in treating rheumatoid arthritis (RA). However, the development of these drugs has been hindered by the lack of suitable carriers. The advent of microneedles (MNs) has brought new hope to researchers. For instance, Rosalind et al. applied the siRNA onto coated MNs, enabling up to 40 μg of siRNA to be loaded, and used MNs to distribute the siRNA. To improve the MNs' loading capacity, the medication solution can be applied to them more than once. This advancement enables MNs to deliver sufficient siRNA for effective RA treatment [40].

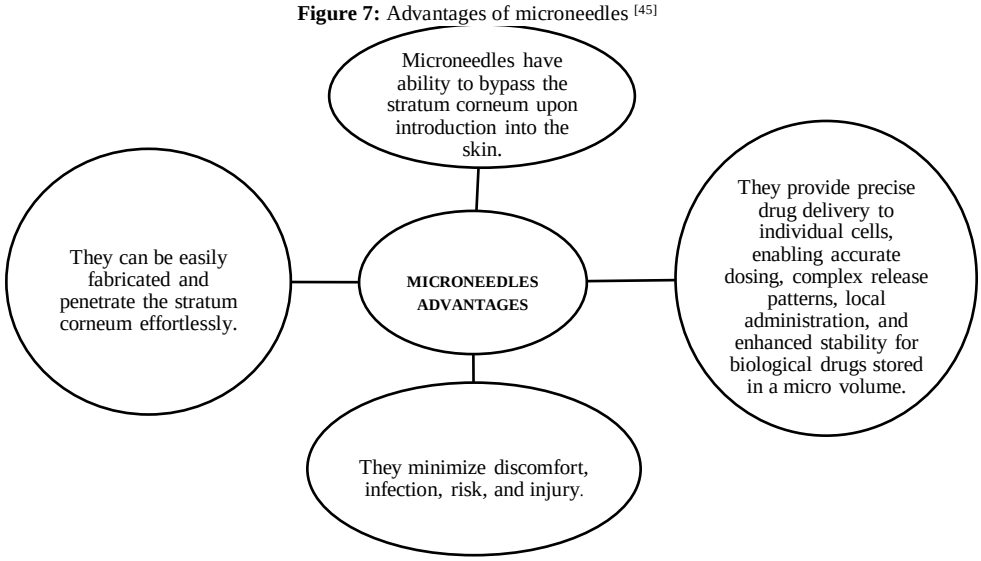
Hydrogel-Forming MN Therapy in RA

The initial regimen for rheumatoid arthritis (RA) is methotrexate (MTX), a drug that suppresses immunity that comes with a weekly dosage recommendation of 7.5–25 mg. Traditionally MTX is administered orally or through subcutaneous (SC) injections. While oral MTX is effective, it often causes gastrointestinal side effects like nausea along with vomiting. SC injections, on the other hand, can be painful and result in high blood concentrations. Microneedles (MNs) offer a novel drug delivery method. Initially, solid MNs were used to create microchannels to enhance MTX penetration. However, this approach proved difficult in controlling dosage, and the microchannels tended to close, reducing drug penetration. Hydrogel-forming MNs, made of cross linked polymers, address these issues. These MNs expand as well as absorb interstitial fluid when introduced into the skin, establishing a continuous conduit connecting the dermal microcirculation in addition to the medication reservoir. This allows for the sustained delivery of large quantities of the drug through the reservoir [41].

Table 1: Summarizing impact of microneedles on rheumatoid arthritis with treatment

Category	Drug	Drug Delivery Carrier	Materials	References
Solid Microneedles	Alkaloids extracted from Aconitum Sinomontanum	Nanostructured Lipid carriers	Metals	[42]
Dissolving Microneedles	Miloxicam	Liposomes	PVA/PVP	[43]
	Etanercept	Liposomes	HA	[43]
Hydrogel Microneedles	Methotrexate	PEGylated star shaped PLGA	Novel PVA/PVP	[44]
Coated Microneedles	SiRNA	Nanostructured Lipid carriers	Methacrylate modified HA metal	[44]

Figure 7: Advantages of microneedles [45]



Applications of Microneedles

Oligonucleotide Delivery

Delivering oligonucleotides to their intracellular site of action is indeed a challenging task due to the biological barriers that impede their efficient uptake and intracellular delivery. To overcome these barriers, several innovative techniques have been developed, one of which is the use of microneedles. Microneedles are a minimally invasive delivery system designed to enter the outermost film of the skin (stratum corneum) as well as deliver therapeutic agents directly into the epidermis and dermis [46].

They come in several forms, including as solid, coated, dissolvable, and hollow microneedles, each designed to enhance the delivery of different types of drugs and biomolecules.

Titanium or stainless steel are frequent materials used to make solid microneedles. These microneedles are utilized in a method called the "poke with patch" approach. Here's how it works:

Microneedle Insertion

To generate microchannels in the skin, solid microneedles are inserted.

Patch Application

A patch containing the oligonucleotide is then applied over the microchannels, permit the medication to release through the channels into the innermost layers of the skin.

This technique has been shown to deliver a higher amount of oligonucleotide to the target site contrast to the application on intact skin, thereby enhancing its therapeutic efficacy [47].

Iontophoresis along with Microneedles

Iontophoresis utilizes a little electrical impulse to facilitate the transport of charged molecules into tissues. When used in conjunction with microneedles, this method can significantly improve the delivery efficiency of oligonucleotides. The process includes the following steps.

Application of Electric Current

A low electric current is then applied to drive the negatively charged phosphonothioate oligonucleotides deeper into the skin through these microchannels. Research indicates that the combination of iontophoresis with microneedles enhances oligonucleotide delivery more effectively than iontophoresis alone [48].

Vaccine Therapy

A biological preparation known as a vaccination works to create an active developed immunity against a particular illness. It usually includes one of the pathogen's membrane proteins, contaminants or an infectious agent that has been attenuated or destroyed.

DNA vaccines administered via microneedles elicited stronger immune responses compared to traditional injections. The creation of a microneedle patch regarding influenza immunization has also been explored. Using hollow microneedles for drug delivery requires a lower dose compared to intramuscular injections. Studies have looked into the use of hollow microneedles for rabies as well as anthrax vaccines. Polyglycolic acid hollow microneedles were developed by Ogai et al. to improve the effectiveness of intradermal immunization. Precise drug delivery to the upper dermis significantly boosted immunity, with antibody titres notably higher 15 days post-vaccination compared to subcutaneous

injections. Furthermore, the potential of dissolving microneedles for intradermal immunisation has been studied [49].

Peptide Delivery

Peptides are often degraded by enzymes when administered orally, which limits their effectiveness. Transdermal delivery avoids enzymatic degradation but faces challenges with skin penetration. Using microneedles for peptide delivery can overcome these limitations. Desmopressin, a synthetic form of the peptide hormone vasopressin, is employed to manage conditions like diabetes insipidus, micturition in children, as well as haemophilia A. Studies have shown that delivering desmopressin via microneedles is both safe and more efficient than other routes. Many skin conditions are managed with cyclosporin A, which is insoluble in water, cyclic peptide with a large molecular weight. Researchers developed dissolving microneedles containing cyclosporin A, measuring 600 μm in length as well as 250 μm in width, through a molding process. When these microneedles, loaded with 10% cyclosporin A, were applied to porcine skin for 60 minutes, approximately 65% of the microneedle dissolved, delivering 34 ± 6.5 μg of the drug. In another study, Liu et al. fabricated polyethylene glycol diacrylate-based microneedles loaded with GAP-26, a gap junction blocker, to deliver peptides undergo a swelling effect. The microneedles exhibited enhanced peptide permeation, as evidenced by the suppression of keloid fibroblast differentiation and decreased production of collagen I [50].

Hormone Delivery

Insulin, a peptide hormone used to lower high blood sugar levels, has been found to be more efficiently delivered using microneedles. Li et al. fabricated solid microneedles and investigated their effect on blood glucose levels in diabetic mice, finding that insulin delivery via microneedles reduced blood glucose levels to 29% of the initial level within 5 hours, demonstrating improved skin permeability for insulin. Ye et al. experimented with microneedles in conjunction with insulin-secreting pancreatic β-cell pills that sense blood glucose, although the patch didn't work. As a result, a microneedle array was created that included artificial glucose signal amplifiers (GSAs). A clinical study on parathyroid hormone (I-34) coated microneedles showed a Tmax three times shorter and an apparent T1/2 two times shorter than conventional injection therapy. Additionally, combining iontophoresis with microneedles offers further potential for hormone delivery [51].

Lidocaine Delivery

Using a microneedle to administer lidocaine, a local anaesthetic agent results in less discomfort than a hypodermic administration, which improves patient adherence. Lidocaine was applied to the microneedle tips by Baek et al. In two minutes, these microneedles improved the distribution of drugs along with consistent in vitro adhesion to skin. Therefore, quick and painless local anesthesia can be achieved with microneedles. In one trial, PEG-lidocaine dispersion-coated microneedles delivered medication more effectively within three minutes than the cutaneous version [52].

Pain Therapy

Molds made of polydimethylsiloxane were employed to create polymeric microneedles filled with meloxicam. Studies on drug penetration in vitro showed that within 60 minutes, around 100% of the medication was released. Drug deposition was 63.37%, with an improved transdermal flux of 1.60 μg/cm²/hr, showing a 2.58-fold increase in permeation compared to the free drug solution. Neuropathic pain, which is often challenging to treat, typically does not respond well to existing therapies and can cause side effects. Strong receptor sensitivity has been established by the selective delivery of calcitonin gene related peptide (CGRP) antagonist peptide via dissolvable microneedles. About 75% of the analgesic microneedle patch dissolved after 20 minutes of application, with no discomfort to the skin or adverse effects reported [53].

Ocular Delivery

Numerous posterior segment conditions can be managed via targeted medication distribution. Nanoparticles have been introduced through the suprachoroidal space using iontophoresis. The nanoparticles stayed concentrated at the site of injection position in the absence of iontophoresis. Nevertheless, more than 30% of the nanoparticles accessed the backside of the eye when paired with microneedles [54].

Cancer Therapy

Each year, millions of individuals globally are impacted by cancer, which poses many treatment-related difficulties. Many anticancer medications have been explored for administration via microneedles. Self-degradable microneedles were employed to provide anti-PD-1 (aPD1) over an extended period for the management of melanoma. These microneedles dispensed pH-sensitive dextran nanoparticles laden with glucose oxidase as well as anti-PD-1. For basal cell carcinoma, applying a 5-fluorouracil topical cream on skin pre-treated with solid microneedles increased the drug's permeability by up to 4.5 times, significantly inhibiting tumor growth and confirming the enhanced efficacy of microneedles [55]. Tamoxifen as well as gemcitabine, two chemotherapy medications used to treat breast cancer, were delivered via microneedles in a study by Bhatnagar et al., showing that localized distribution could minimize undesirable effects. To treat carcinoma of the skin, polymeric microneedles have also been studied for localized administration of anticancer medications [56].

CONCLUSION

Two key mechanical events are crucial in microneedle distribution: (1) the force of friction that counters the skin's

resistance, allowing microneedles to insert before piercing the skin, and (2) the force of friction that must surpass the skin's resistance to effectively rupture the skin plus function as intended. An analysis evaluated the relation among microneedle geometries plus their insertion force. The tip radii of microneedles typically range from 30 to 80 mm, with lengths around 500 mm. Various microneedles exhibit different friction forces, insertion forces, and interfacial forces. They have advanced significantly in every application field, including immunology, dermatology, cancer treatment, immune-biological diagnosis, and treatment of diseases. Furthermore, there are still uncharted areas in the creation of smart, wearable sensor-based equipment for wireless data modification, individualized diagnostics, and ongoing treatment.

Conflict of Interest

None

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