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THE MICRONEEDLE PATCH COMPENDIUM: A CRITICAL REVIEW AND PROSPECTIVE ANALYSIS OF FABRICATION, THERAPEUTICS, AND MARKET DYNAMICS

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Abstract : Microneedles (MNs) represent a cutting-edge, minimally invasive method for transdermal medication delivery, providing a viable alternative to traditional hypodermic injections and oral medications. MNs are tiny structures, typically ranging from 150 to 1500 µm in length, designed to penetrate the stratum corneum, the skin's outermost layer, and deliver drugs directly into the epidermis or dermis. This technique offers several advantages, including improved patient compliance due to its painless application, enhanced drug bioavailability by bypassing first-pass metabolism, and the possibility of sustained drug release. Various types of MNs exist, including solid, coated, dissolving, hydrogel, and hollow MNs, each designed with specific materials and mechanisms to suit different drug types and delivery requirements. The fabrication of MNs involves advanced techniques such as laser cutting, photolithography, and 3D printing, utilizing materials like silicon, metals, polymers, and carbohydrates. MNs have shown promise in delivering a wide range of therapeutics, including insulin, vaccines, and medications for chronic conditions like arthritis and diabetes. Despite their potential, challenges such as skin irritation, limited drug capacity, and manufacturing complexities need to be addressed for widespread adoption. Nevertheless, MNs hold significant promise in revolutionizing transdermal drug delivery, offering a more patient-friendly and effective approach to treatment.

IndexTerms - Transdermal drug delivery, Microneedle patch, advanced manufacturing, polymers.

Quick look at Skin's Anatomy:

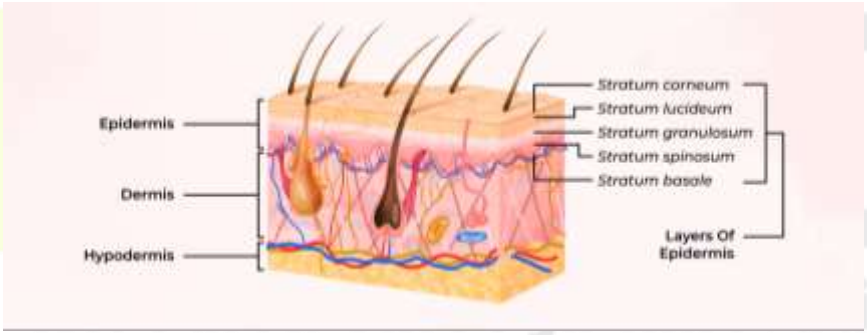

figure 1: layers of skin

The skin is a complex organ made up of three main layers: the epidermis, dermis, and hypodermis. These layers work together to protect the body and regulate temperature. The skin also contains hair shafts and glands, which contribute to its overall function. With an area of about 2m² in an average adult, the skin is the largest organ in the human body.

A large portion of the body's blood (around a third) circulates through the skin. The epidermis, the skin's outermost layer, is about 150µm thick and constantly renews itself from a base of actively dividing cells. These cells move outward, differentiating as they go. Because the epidermis lacks its own blood supply, it relies on diffusion from the dermis below for nutrients and waste removal. The epidermis is made up of five layers: the stratum germinativum (basal layer), stratum spinosum, stratum granulosum, stratum lucidum, and the stratum corneum (SC). The SC is composed of dead, keratin-filled cells and acts as the skin's main barrier against external substances. The epidermis beneath the SC is called the viable epidermis. The SC's structure, with its layers of dead cells and fatty matrix, controls how easily molecules can pass through the skin.

The stratum corneum (SC) layer of the skin is normally 10-15µm thick when dry, but it can expand to about 40µm when it's hydrated. The SC layer is made up of dead skin cells called corneocytes, which are filled with a protein called keratin. These corneocytes are arranged in a brick-and-mortar pattern, with the corneocytes being the bricks and a fatty substance called intercellular lipid matrix being the mortar. This structure helps to protect the skin from the environment and prevent water loss.

The dermis, also known as the corneum, is a strong layer of connective tissue derived from the mesoderm. It underlies and supports the epidermis. This layer is characterized by a dense network of collagen fibers interwoven with elastic tissue, particularly near the surface. The dermis is rich in various structures, including a network of small blood vessels, lymphatic vessels, nerves, hair follicles, sweat glands, and sebaceous glands.

Skin pathways for transdermal delivery systems:

There are three main ways substances can pass through the skin when using transdermal delivery systems: they can travel down hair follicles, go directly through the stratum corneum (the skin's outer layer), or pass through sweat glands.

Introduction:

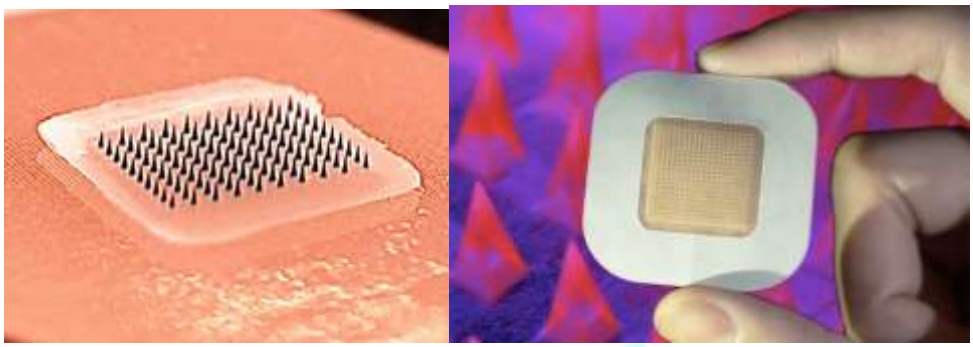

figure 2: microneedle patch

Transdermal drug delivery systems offer advantages by avoiding first-pass metabolism and providing sustained drug release.[1] Microneedles are a method of transdermal drug delivery that allows for self-administration and high drug bioavailability. Microneedle drug delivery is a painless and minimally invasive technique that allows drugs to pass directly through the stratum corneum, the skin's main barrier to drug delivery.[2] The dose, rate of delivery, and effectiveness of drugs can be controlled using microneedle drug formulations. Microneedles are typically 150-1500 µm long, 50-250 µm wide, and have a tip thickness of 1-25 µm. They are commonly made of metal, silicon, polymer, glass, or ceramic.[3]

Transdermal systems offer several benefits, including avoiding first-pass liver metabolism, improved patient adherence, consistent drug release, and reduced pill burden.[4] Microneedles are a promising technology for minimally invasive drug delivery, creating tiny pathways for drug solutions to enter the skin. Their sharp design, with submicron tips, allows for efficient skin penetration. Microneedles work by mechanically puncturing the skin, delivering drugs just below the stratum corneum where they are quickly absorbed into the bloodstream.[5-6] These microneedle punctures bypass the stratum corneum barrier, granting access to tissues rich in blood vessels for systemic delivery. This method can alter drug pharmacokinetics, often leading to faster absorption and onset of action. Furthermore, microneedle-mediated drug delivery can modulate the body's immune response, making it particularly useful for vaccinations.[7-9]

Objectives[10]:

table 1: objectives of microneedle patch and its medical impact

Design Objective	**Medical impact**
Drug is delivered across the stratum corneum.	Effective drug delivery
Correct dose can be delivered.	Effective drug delivery
No need of expertise for patch application.	Increased access to drug Cost savings
Improvement of stability.	Lower reliance on cold chain storage and transportation
Elimination of sharp waste.	Increased safety Reduced need for sharps waste disposal
Single use, single dose, fully disposable.	Increased safety Reduced drug/vaccine wastage
No need of reconstitution.	Increased safety Increased access to drug
Lack of pain.	Improved patient compliance
Delivery feedback.	Improved patient compliance
Reduced wear time of patch.	Improved patient compliance
Low manufacturing cost.	Cost saving
Targeted delivery of drug to the skin.	Faster onset of systemic delivery of drugs Improved immunogenicity of vaccines
Reduced package size	Cost saving

Advantages and Disadvantages:[11]

Advantages:

Microneedle drug delivery offers several advantages. It improves drug delivery by delivering drugs directly into the bloodstream, resulting in faster onset of action, accurate dosing, avoidance of first-pass metabolism, and high bioavailability. It's also effective for vaccine delivery due to the abundance of immune cells in the dermis. Microneedles enhance safety and patient compliance because they are painless, require minimal expertise for application, and reduce biohazardous waste. Finally, they improve manufacturing and offer cost savings as their solid-state formulation eliminates the need for cold storage, and the all-in-one patch design reduces packaging size.

Disadavantages:

Despite the advantages, microneedle drug delivery has some drawbacks. The small size of microneedles limits the drug dose that can be delivered. Temporary skin irritation or allergic reactions are possible. Manufacturing microneedle patches consistently requires advanced technology. Proper storage is needed to maintain the patches' integrity during distribution. Finally, there's a risk of microneedle fragments breaking off and remaining in the skin after application.

Types of Microneedles:

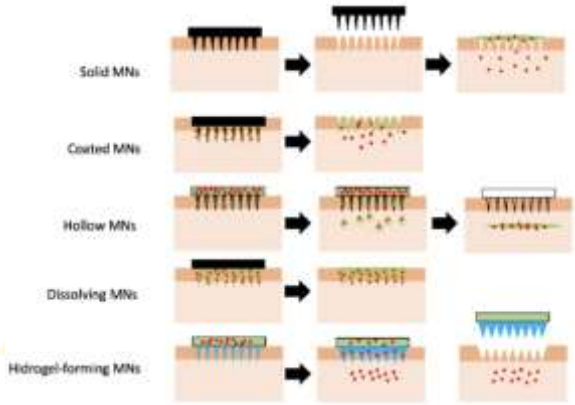

figure 3:types of microneedles

Microneedle design is tailored to the specific drug, delivery method, and mechanism of action. A typical microneedle is tapered and sharp, measuring 150–1500 μm in length, 50–250 μm in width, and 1–25 μm at the tip.[12] The drug is usually located on or within the microneedle tip, which is attached to a base substrate to form an array. This array is then fixed to a patch backing with adhesive for easy application. Microneedles are categorized into five main types: solid, coated, dissolving, hydrogel, and hollow. The ideal microneedle type is chosen based on factors like drug dose, desired onset of action, delivery duration, efficiency, packaging, waste disposal, and how long the patch will be worn.[13]

Solid Microneedles:

Solid microneedles are arrays of tiny, sharp tips made of a single material without any incorporated drugs. They work by creating microscopic holes in the skin's surface. After the microneedles are inserted and removed, the drug is applied to the treated area and passes through these pores, bypassing the skin's outer barrier (stratum corneum) and reaching the superficial dermis where it can be absorbed into the bloodstream. This increases the drug's bioavailability.[14] The pores can be kept open longer with certain reagents, allowing for extended drug delivery.[15] Essentially, solid microneedles create channels in the skin, facilitating drug permeation via passive diffusion when a drug patch is applied.[16] The drug then enters the capillaries for a systemic effect.[17]

Coated Microneedles:

Coated microneedles have a drug solution or dispersion applied to their surface.[18] Once inserted into the skin, the drug dissolves quickly and is released. These microneedles are typically solid microneedles coated with a water-soluble matrix that allows for rapid drug dissolution upon insertion.[19] The coating formulation's viscosity is crucial for ensuring it adheres to the microneedle during storage and insertion. The drug is usually concentrated at the microneedle tip for targeted delivery. Dip coating allows for precise control of the drug-coated area.[20] Coated microneedles offer a fast onset of action due to the rapid drug dissolution in skin fluids. While the coating thickness can be increased through repeated applications, this approach may not be ideal for drugs requiring larger doses due to limitations in the amount of drug that can be coated.[21]

Dissolving Microneedles:

Dissolving microneedles are made from biodegradable polymers that encapsulate the drug. Once inserted into the skin, these microneedles dissolve upon contact with skin fluids, releasing the drug. The dissolving polymer also degrades within the skin, controlling the drug release rate. Their biocompatibility and ability to dissolve make them a good option for long-term therapies and improved patient compliance.[22] A key challenge in developing dissolving microneedles is ensuring even drug distribution within the needle. Therefore, proper mixing of the polymer and drug is crucial during manufacturing.[23] While dissolving microneedles can take time to fully dissolve, and complete insertion can sometimes be difficult, they offer the advantage of not creating sharps waste as they dissolve or disintegrate quickly.[24] They are often made using a solvent-casting method with water-soluble, biodegradable polymers like carboxymethyl cellulose and methyl cellulose. Saccharides like trehalose and sucrose are often added to promote disintegration and stabilize biomolecules. The drug-containing microneedle tip formulation needs to be compatible with the drug, strong enough for skin penetration, and have a low enough viscosity to properly fill the molds without air bubbles.[25-26]

Hydrogel Microneedles:

Hydrogel microneedles contain drug throughout the entire patch, including the tip, base, and backing. The drug is released slowly after application to the skin. These patches, primarily made of hydrogel, hydrate upon contact with skin fluids but don't dissolve.[27] The drug diffuses from the hydrated hydrogel into the skin, allowing for delivery of larger doses.[28] However, this slow release means the patch needs to be worn for an extended period. These microneedles are often made with super-swelling polymers, which have a hydrophilic structure that allows them to absorb significant amounts of water. When these polymers swell in skin fluids, they create channels that connect the bloodstream to the drug patch, effectively acting as a rate-controlling membrane.

Hollow Microneedles:

Hollow microneedles contain a space within them that is filled with a drug solution or dispersion. They have openings at their tips, allowing the drug to be delivered directly into the epidermis or upper dermis upon insertion. This type of microneedle is often used for delivering large molecules like proteins, vaccines, and oligonucleotides.[29] The drug's flow rate and release pressure can be controlled. Because of the internal space, hollow microneedles can deliver larger drug doses. Maintaining a consistent flow rate is a critical factor for effective delivery with this method.[30]

Approaches for Microneedles:

Microneedle patches (MNPs) can be used in several ways for drug delivery. The "poke-and-patch" method involves first creating tiny holes in the skin with drug-free microneedles. Then, a drug-loaded patch is applied to the treated area, allowing the drug to slowly permeate through the microneedle-created pores.[31-34] This patch can be similar to regular transdermal patches and may contain agents to keep the pores open longer, extending drug delivery.[35] Alternatively, the drug can be placed directly on or within the microneedle tip and delivered upon insertion. In the "coat and poke" method, the drug is coated onto the microneedle surface in a rapidly dissolving matrix. The "poke and dissolve" approach uses microneedles made of a dissolving material that encapsulates the drug, releasing it as the microneedles dissolve in the skin.[36-39] Finally, the "poke and release" method involves encapsulating the drug within the patch backing, and sometimes the microneedles themselves, for sustained release. These patches often use hydrogels that swell upon contact with skin fluids, facilitating drug diffusion from the backing, through the microneedles, and into the skin. While other MNP methods exist, these four are the most prevalent.[40-46]

Materials used for Microneedles:

Microneedles are made from various materials, ranging from metals to polymers, and the specific material chosen depends on the microneedle design and patch components. A key requirement for any microneedle material is sufficient mechanical strength to effectively penetrate the skin.[47]

Silicon:

Silicon was the first material used for microneedles in the 1990s. Its anisotropic nature and crystalline structure make it versatile for creating various microneedle sizes and shapes. Silicon's mechanical strength is sufficient for skin penetration, making it suitable for solid and coated microneedles.[48] Fabrication techniques like deep reactive ion etching and photolithography allow for precise manufacturing of silicon microneedles with sharp tips as small as 100 µm.[49] However, these manufacturing processes are expensive, slow, and require specialized equipment.[50] A key safety concern with silicon microneedles is the risk of breakage and fragments remaining in the skin.[50] Currently, silicon is more commonly used in creating reverse master molds rather than for the microneedles themselves.[51-52]

Metals:

Metals are strong and can easily penetrate the skin, making them suitable for solid, coated, and hollow microneedles. Common metals used include stainless steel[53] and titanium[54], with others like palladium, nickel, and palladium-cobalt alloys also being employed. Stainless steel is the most frequently used due to its relative ease of use, but it corrodes faster than titanium alloys. While titanium alloys are stronger, they are also more expensive.[55]

Ceramic:

Ceramic materials, including alumina, calcium phosphate, and calcium sulfate, are biocompatible and mechanically strong, making them suitable for microneedle fabrication.[56] Alumina is particularly popular due to its chemical resistance. Other ceramics used in microneedles include gypsum and brushite.[57] More recently, an organically modified ceramic known as Ormocer® has also been explored for this application.

Glass:

Silica glass is biologically inert but fragile. Borosilicate glass, a combination of silica and boron trioxide, is more resilient.[58] Glass microneedles are usually hollow and made using wet etching or a micropipette puller.[59] Glass offers adequate strength for skin penetration and is easily shaped into tapered needles. It can also be easily sterilized due to its stability at high temperatures and pressures, and it's biocompatible. However, a significant drawback is its brittleness; if the tip breaks off and remains in the skin, it can lead to inflammation or granulomas.

Carbohydrate:

Carbohydrates, such as maltose (a common choice), mannitol, trehalose, sucrose, xylitol, galactose, and polysaccharides, can be used to create microneedles.[60] These carbohydrate materials are typically molded using silicon or metal templates. A drug-loaded carbohydrate mixture is poured into the molds to form the microneedles. The controlled dissolution of the carbohydrate regulates drug release within the skin. While carbohydrates are inexpensive and safe, their susceptibility to degradation at high temperatures can make the manufacturing process challenging.[61]

Polymers:

Polymers used for microneedles need to be water-soluble, biocompatible, and strong enough to penetrate the skin. Solvent casting is the most common manufacturing method, involving creating a mold, pouring a polymer solution onto it, drying, and then removing the formed microneedles. Dissolving and hydrogel microneedles are often made this way using polymers like hydroxypropyl methylcellulose[62], hyaluronic acid[63], carboxymethyl cellulose (CMC)[64], polyvinyl pyrrolidone[65], and poly(lactic-co-glycolic acid) (PLGA)[66]. Many other polymers are also used, including poly(methyl methacrylate) (PMMA), polylactic acid (PLA), PLGA, polyglycolic acid (PGA), poly(carbonate), cyclic-olefin copolymer, poly(vinylpyrrolidone) (PVP), poly(vinyl alcohol) (PVA), polystyrene (PS), poly(methyl vinyl ether-co-maleic anhydride), and SU-8 photoresist.[67]

Microneedle fabrication techniques:

Microneedle design begins with careful consideration of the drug (type and dose), desired pharmacokinetic and pharmacodynamic properties, and the intended application. Once these factors are established, the optimal microneedle design and materials are selected. The manufacturing process then depends on the chosen design and materials.

Laser- mediated fabrication techniques:

Laser cutting:

Laser cutting is a common method for creating metal or polymer microneedles, especially those made of stainless steel.[68] A laser cuts a flat metal sheet according to a 2D design generated by CAD software. This 2D shape is then bent to form the 3D microneedle. Electropolishing can be used to refine the needle tips or smooth out any rough surfaces.[69]

Laser ablation:

Laser ablation is another technique used to create metal or polymer microneedles.[70] While laser cutting cuts a sheet into a 2D shape, laser ablation engraves the material to create a 3D structure. This process involves directing a laser beam (like a CO2 laser) onto a substrate. The substrate absorbs the laser's energy and heats up, causing it to evaporate or sublimate. This controlled removal of material can be used to create an inverse mold with the desired microneedle pattern.

Photolithography:

Photolithography is a precise technique used to create solid or hollow microneedles, particularly those made of silicon or dissolving/hydrogel materials. It involves creating an inverse mold based on the desired microneedle structure. For silicon microneedles, the process begins with depositing a thin film sacrificial layer on a cleaned silicon wafer. A photosensitive polymer (photoresist) is then applied. A photomask with the desired microneedle pattern is aligned on the substrate and exposed to UV light. This exposure creates the pattern in the photoresist. After development, the exposed (or unexposed, depending on the photoresist type) silicon that isn't covered by the photoresist is etched away. This transfers the pattern from the photomask, through the photoresist, and onto the silicon, creating the microneedle structure.[70]

Etching:

Etching is a crucial step in microneedle fabrication, especially when using photolithography, as it defines the tapered shape of the needle tip. The size of the microneedle base and the spacing between needles are determined before etching. The etching process itself then determines the length and shape of the needles.[71] Etching is broadly categorized into dry and wet etching, each producing either isotropic (uniform in all directions) or anisotropic (directional) etching.

Dry etching:

Dry etching is commonly used for creating solid or hollow microneedles and can be divided into physical and chemical methods. Physical dry etching methods, like ion milling and sputtering[72], use ionized inert gases (e.g., argon or sulfur hexafluoride) propelled by high-energy electrodes. The directed impact of these ions on the silicon substrate results in anisotropic etching, where only the unprotected areas are etched, while areas covered by an oxide film or photoresist remain largely untouched. Chemical dry etching, such as high-pressure plasma etching, uses highly energetic plasma gas that reacts with the substrate surface, creating volatile byproducts that are removed, leading to isotropic etching. Reactive ion etching combines both physical and chemical methods, leveraging both plasma and sputter etching to control the etching process and achieve either isotropic or anisotropic results.[73] By carefully optimizing reactive ion etching, very sharp microneedle tips can be precisely fabricated.

Wet etching:

Wet etching is another method used to create metal or silicon microneedles.[74] It involves using a chemical etchant to create the desired pattern on the substrate. For silicon wafers, a potassium hydroxide solution is often used, and the varying etch rates depending on the crystal orientation of the silicon can be used to create sharp tips.[75] Wet etching is generally an isotropic process driven by chemical reactions, and it's considerably faster than dry etching. While wet etching is a low-cost method, it lacks the precision of dry etching, making it less suitable for creating very fine patterns.

3D printing (Additive manufacturing):

3D printing, an additive manufacturing technology, enables rapid prototyping with low cost and high throughput.[76] This technology has recently been applied to create microstructures, including microneedles.[77] Traditional microneedle manufacturing methods often struggle to produce complex shapes, but 3D printing overcomes this limitation. High-precision stereolithography (SLA), digital light processing (DLP), and fused deposition modeling (FDM) are some of the 3D printing techniques used to fabricate microneedles.[78]

Microstereolithography:

Microstereolithography (μSL) is a common technique in biomedical and tissue engineering,[79] used to create structures like tissue scaffolds, nerve guides, and cardiovascular stents. μSL builds 3D objects by photopolymerizing a liquid resin with a light source, typically UV radiation, in a controlled manner. A computer precisely controls the building platform and the light source (laser or projector), directing the light onto the resin surface to create the object layer by layer.[80] For example, μSL has been used to create microneedles from poly(propylene fumarate) mixed with diethyl fumarate (to enhance strength) for skin cancer treatment.[81] This system allowed for controlled release of the anti-cancer drug dacarbazine over five weeks by adjusting the drug dose and the molecular weight of the polymer.

Continuous Liquid Interface Production (CLIP):

Continuous Liquid Interface Production (CLIP) is a faster additive manufacturing technique compared to traditional layer-by-layer methods. CLIP uses light reflected from a DLP chip to photopolymerize a resin, similar to DLP.[82] However, CLIP avoids the slow peeling and repositioning steps required in traditional methods. This allows for much faster production of microneedles, reducing fabrication time significantly—from potentially hours to just 2-10 minutes.

Two-photon polymerization (TPP):

Two-photon polymerization (TPP) is a highly precise additive manufacturing technique with a resolution down to about 100 nanometers.[83] It works by using multiphoton absorption to trigger polymerization of a resin, specifically through the excitation of a photoinitiator. Unlike standard stereolithography (SLA) which uses UV light, TPP uses a near-infrared laser, such as a titanium-sapphire laser. A key difference is that with TPP, the curing reaction happens only at the laser's focal point,[84] not along the entire beam's path. This allows for the creation of very intricate and complex 3D structures.

Drug delivery by Microneedles:

Proteins:

Protein drugs hold great promise for treating various conditions like cancer, genetic diseases, and for vaccinations. However, their delivery is often hampered by issues such as instability and poor absorption. Factors like protein denaturation during storage and administration, as well as limited absorption and cell permeability due to molecular size, can reduce their effectiveness. Microneedle technology is being explored to improve protein drug delivery. Microneedles have shown promise for delivering various proteins, including insulin, desmopressin, erythropoietin, lysozyme, glucagon, glucagon-like peptide-1, parathyroid hormone, and growth hormone. A continuing challenge is selecting appropriate materials and formulations that maintain protein stability, particularly when scaling up production and storage for clinical use.[85]

Vaccines/Antibodies:

Current vaccines are typically administered through subcutaneous injection. Microneedle-based vaccines are a newer area of research, showing promise for inducing antibody immune responses. A key benefit of microneedle vaccines is their ability to stimulate stronger local immunity compared to injections. This is because they deliver the antigen to dendritic cells in the skin, which play a crucial role in immune responses. Current vaccine availability is often limited by the need for cold storage and transport. Microneedle vaccine patches offer the potential for long-term preservation of the vaccine's ability to trigger an immune response and more flexible storage conditions. Monoclonal antibodies, used in various diagnostic and therapeutic applications, can target specific cells and modulate the immune system. Microneedle delivery of monoclonal antibodies has been explored to reduce overstimulation of certain immune cells and minimize side effects. However, antibody delivery faces challenges like reduced effectiveness and the risk of triggering an immune response against the antibodies themselves due to protein inactivation. Maintaining antibody stability within the microneedle is therefore essential.[86]

Applications of Microneedle patches:

The treatment of Osteoarthritis:

Microneedle patches show promise for treating osteoarthritis (OA), a prevalent degenerative joint disease.[87] MNs offer several advantages for OA treatment, including bypassing liver metabolism, minimizing gastrointestinal side effects associated with oral medications, enabling sustained drug release, and allowing easy discontinuation if toxicity occurs.

Multifunctional, bio-inspired MNs can deliver drugs to specific areas of the body flexibly and over extended periods. Studies in rats have shown that MNs loaded with glucocorticoids can effectively reduce swelling and inflammation in knee joints affected by OA.[88] MN patches have also been developed for meloxicam, a poorly water-soluble NSAID that often causes gastrointestinal issues. These patches demonstrated rapid drug release, effective skin penetration, minimal irritation, good bioavailability, and strong anti-inflammatory and analgesic effects. While MNs offer a potential solution to challenges like poor oral bioavailability and patient compliance in OA treatment, their use in this specific area remains under-explored.

The treatment of Rheumatoid Arthritis:

Beyond meloxicam for osteoarthritis, microneedle (MN) technology has been explored for delivering other drugs to treat rheumatoid arthritis, including methotrexate[89-91], artemether[92-93], alkaloids[94-95], capsaicin[96], neurotoxin[97], triptolide[98], paeoniflorin[99], sinomenine[100], and Etanercept[101]. MN transdermal delivery offers a promising approach for arthritis treatment by controlling drug release, reducing dosage, and minimizing side effects through minimally invasive delivery. Nanocarriers, like nanostructured lipid carriers (NLCs), have been used to encapsulate drugs and overcome solubility limitations, improving delivery via dissolving MNs.[95] NLCs also help avoid first-pass liver metabolism and toxicity, while MNs enhance drug delivery and create skin reservoirs for sustained release.[95] One study used an "in situ" phase transition strategy to convert a poorly soluble, crystalline drug (capsaicin) into a nano-sized, amorphous form suitable for transdermal delivery using dissolving MNs. This approach proved effective in treating inflammation associated with rheumatoid arthritis.

The treatment of Dermatology Dermatosis:

Skin diseases are a major area of microneedle (MN) research. While traditional skin patches, with their simple structure and slow drug delivery, have limitations in wound healing, MNs offer advantages. MNs possess porous microstructures and can incorporate antibacterial polymers, like chitosan, to deliver growth factors or drugs in a sustained or controlled manner, promoting tissue remodeling and preventing infection. Chitosan, a naturally occurring alkaline polysaccharide, is particularly useful due to its biodegradability, non-toxicity, biocompatibility, and natural antibacterial and blood-clotting properties. MN-based drug delivery offers improvements over topical application, which can have low transdermal efficiency, and subcutaneous injection, which involves short drug residence times and frequent administration. For example, chitosan-based MN patches have been developed for enhanced wound healing.[102] MNs can also improve the delivery of drugs like UK5099 and exosomes, overcoming their respective limitations.

The delivery of Vaccines:

Microneedles (MNs) have been extensively researched for vaccine delivery, making it a relatively mature field. MN vaccines offer advantages like room temperature storage and transport in a solid form, and can be used to deliver various vaccine types, including DNA, subunit antigen, inactivated, or live virus vaccines.[103] They provide a painless, non-invasive, and convenient administration method, eliminating the need for cold chain storage and transport, and reducing sharps waste. This is particularly beneficial in developing countries or rural areas with limited healthcare resources,[104] as it can also minimize the spread of blood-borne diseases. Given the recent threat of coronaviruses, the need for safe and effective vaccines is urgent.[105] Studies in mice have shown that MN delivery of MERS-CoV and SARS-CoV-2 vaccines can induce a stronger immune response compared to traditional injections, with long-lasting antibody production. Importantly, these MN vaccines remain effective even after gamma ray sterilization, a crucial step for human use. MN vaccine delivery has the potential to accelerate vaccine production and lower costs by reducing the required dose. Further advances in MN technology are expected to improve our preparedness for future pandemics.[106]

The treatment of Cancer:

Microneedles (MNs) are being used to deliver anticancer drugs (chemotherapy), photodynamic therapy (PDT), and photothermal therapy (PTT) agents directly to skin tumors, improving effectiveness while minimizing invasiveness. In mouse studies, delivering ovalbumin-pulsed dendritic cells via cryomicroneedles resulted in stronger immune responses and slower tumor growth compared to traditional injection methods. These cryomicroneedles also preserved cell viability and proliferation, suggesting their potential for minimally invasive cell therapies.[107] Combining MN delivery with cancer immunotherapy is a promising approach.[108] Studies have shown that MN delivery of vaccines and adjuvants can induce stronger and longer-lasting immune responses compared to traditional injections. Combining photothermal therapy with chemotherapy also holds great potential for improving cancer treatment outcomes and preventing recurrence.[109] For example, layered MNs have been developed to deliver both chemotherapy drugs (like adriamycin) and photothermal agents (like gold nanorods) directly to cancer cells. These patches have shown improved therapeutic effects when combining chemotherapy and photothermal therapy. This type of localized MN delivery avoids the systemic side effects often associated with traditional anticancer drug administration.

Usage in the Contraception field:

Microneedle (MN) patch technology, after showing promise in various biomedical applications, is now being explored for contraception.[110] Researchers have developed long-acting contraceptive MN patches that are easy to use and avoid generating hazardous waste. These patches use biodegradable polymers, like PLGA, loaded with contraceptive hormones (e.g., levonorgestrel) to

provide sustained release over approximately one month. Studies have also indicated that effervescent microneedle patches may further enhance long-acting contraception.[111]

The treatment of Diabetes:

Insulin, a hormone crucial for blood sugar regulation, is often administered through long-term injections for both type 1 and type 2 diabetes. However, insulin dosing can be challenging, and incorrect doses can lead to hypoglycemia, a potentially dangerous condition. Therefore, continuous blood sugar monitoring is essential for diabetics. Microneedle (MN) delivery of insulin is a promising area of research.[112] The "Smart Insulin Patch," developed by Zhen Gu's research group, combines a glucose-responsive insulin release mechanism with a hyaluronic acid (HA) MN array. These small MNs offer a less painful alternative to injections, improving patients' quality of life.[113-117] This technology continues to be refined for better glucose response. Beyond glucose-responsive systems, researchers have also developed pH-responsive MN patches that release insulin and other therapeutic agents based on the body's pH levels. Light-responsive MNs have also been created, which release drugs like metformin when triggered by near-infrared (NIR) light.[118]

Other Applications:

figure 4: applications of microneedle patch

While initially used to improve transdermal drug delivery, microneedle (MN) applications have expanded significantly. Beyond treating skin and other diseases, MNs are now used in areas like eye treatment, cell delivery, and blood vessel applications.[119] Hollow and porous MNs are particularly useful in biosensor research, showing promising results.[120] For example, porous MNs have been integrated with microfluidic chips for continuous interstitial fluid (ISF) sampling, enabling minimally invasive and long-term health monitoring. As different fields of study converge, MNs are expected to take on even more roles. Researchers are also exploring combining MNs with other drug delivery enhancement methods, like chemical enhancers, to deliver macromolecules. These combined systems could potentially create targeted drug delivery systems within the gastrointestinal tract.[121]

Market survey:

S.R	PRODUCT	MANUFACTURER	TYPE	APPLICATION
1	Derma roller	Derma spark, Canada	Solid Metal	Scar Treatment
2	MicroHyala	CosMeD, Japan	Dissolvable	Intradermal Delivery of hyaluronic acid to combat skin aging
3	Macroflux	Zosano Pharma , USA	Coated metal	Hormonal treatment for post-menopausal osteoporosis
4	Qtrypa	Zosano Pharma , USA	Coated metal	Delivery of zolmitriptan for the treatment of acute migraine.
5	Micronjet600	NanoPass, Israel	Hollow Silicon	Vaccination: pandemic Influenza(H1N1)
6	MicroCore	Corium, USA	Dissolvable	Hormonal treatment for post-menopausal osteoporosis
7	Micro structured transdermal Patch	3M Crop, USA	Hollow polymeric	Hormonal treatment for post-menopausal osteoporosis
8	Nano patch	Vaxxas, Australia	Coated polymeric	Influenza vaccine delivery
9	Dissolvable	Micron Biomedical, USA	Dissolvable	Influenza and contraceptive drug delivery

10	IDflu*Intanza	Sanofi,Pastcur	Intradermal Micro needle	Prefilled with influenza
11	Soluvia	Becton Dickinson, USA	Hollow micro needle array	Intradermal delivery of drug and vaccines.
11	Drugmat	TheraJeet Inc, USA	Dissolvable micro needle Patch	It delivery hundreds of micrograms of drug rapidly
10	Dermapen		Micro needle array-based device	Used for treating stretch mark and hair loss
10	VaMat	Theraject inc,USA		It dissolvable in micro needles
11	Micro-Trans	Valeritas inc, USA		The patients Skin Characteristics
12	Nanoject	Debiotech , Switzerland		Useful for Intradermal
13	Janisys	Janisys, Ireland		Actively delivery drug from transdermal patches
14	BD Soluvia	Becton Dickinson, USA		It is prefill able microinjection system
15	Onvax	Becton Dickinson, USA		It is skin micro abrader having plastic
16	MicronJet	NanoPass Inc, Israel		It can be used with any slandered syringe for painless delivery
17	Macroflux	Zosano Pharma Inc, USA		Metallic micro needles
18	Micro saturated transdermal system technology (MTS)	3 M Crop, USA		This technology is used to administered drugs

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