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Review Article

An Overview on Microneedle Technology: Superior Pharmaceutical Transdermal Delivery Forms

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ABSTRACT

Microneedles, first introduced in 1976, address these limitations by creating tiny, non-invasive channels that enhance drug penetration through the skin. Transdermal Drug Delivery (TDD) is a less intrusive approach that bypasses first-pass metabolism and enables self-administration. However, the Stratum corneum, the skin's outermost layer, acts as a strong barrier, restricting drug absorption. While hypodermic needle injections are effective, they are invasive, painful, and produce hazardous waste. Moreover, they are less efficient for vaccine delivery, as they administer the drug into muscle rather than the skin. Microneedles have proven effective in enhancing the delivery of various drugs, including vaccines and protein therapeutics, and can be designed with different materials and structures to maximize performance. The success of pharmaceuticals depends not only on the drug itself but also on the delivery method. While oral administration is convenient, it presents challenges for certain drugs due to low absorption or degradation. Microneedles provide an innovative alternative, enabling the efficient delivery of both small molecules and large proteins with minimal pain and high bioavailability. As a breakthrough in drug delivery technology, they offer a promising solution to the limitations of traditional methods.

Keywords: Microneedles, Transdermal, Bioavailability, Skin, Drug delivery, Efficacy.

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INTRODUCTION

Microneedles are a revolutionary advancement in drug delivery, featuring ultra-small needles that minimally penetrate the skin while bypassing the stratum corneum-the primary barrier that restricts absorption. This innovative design enhances drug uptake and effectively eliminates the first-pass metabolism, significantly improving delivery efficiency (Tibbitt *et al*., 2016). There is improvement in the efficacy of the medication and possibly the loss of pain and what is commonly referred to as the invasiveness of injections (Engelke *et al*., 2015). Material selection is crucial in microneedle design, as it directly impacts performance. Polymer-based systems have gained significant attention for microneedle fabrication due to their biocompatibility and biodegradability within the body. This versatility allows microneedles to be tailored to specific drug types and delivery requirements, enhancing their effectiveness (Prausnitz and Langer, 2008; Choy and Prausnitz, 2011).

Microneedles (MN) have emerged as a highly promising drug delivery system, capable of efficiently administering a wide range of substances, including vaccines, insulin, growth hormones, and oligonucleotides (Kim *et al*., 2012). Their ability to penetrate tissue with minimal damage makes microneedles ideal for delicate applications such as ocular drug delivery and gene transfer. However, despite their promise, further research and development are necessary to fully optimize their potential (Boehm *et al*., 2012). The delivery of large molecules, such as proteins, remains a challenge due to their size, hydrophilicity, and potential instability. However, continuous research and technological advancements are making significant progress in overcoming these obstacles (Bhatnagar *et al*., 2017). Microneedles represent a groundbreaking innovation in drug delivery technology. With their ability to administer drugs painlessly, efficiently, and minimally invasively, they offer a compelling alternative to traditional methods. As advancements in material

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science continue, their role in drug therapy is expected to expand significantly (Amorij *et al.*, 2010).

Needs of microneedles aspects from other dosages form

Significantly less painful than traditional injections, microneedles offer a nearly pain-free alternative. Research also suggests that children are more willing to have their blood drawn using microneedles, as they cause considerably less discomfort than conventional needles (Traverso *et al.*, 2015). The likelihood of greater compliance with medical therapies and improved patient experience are also probable advantages with lesser pain from this invention. They are also smaller; thus, less chance of tissue damage, making them safer for certain uses (Lhernould *et al.*, 2015). Microneedles also benefit physicians by generating less hazardous waste and offering greater ease of handling, making them a safer and more efficient alternative to traditional needles (Kochhar *et al.*, 2019). Microneedles are more cost-effective than traditional needles, requiring less material and being manufactured from more affordable substances (Ma and Wu, 2017). Microneedles are less painful, cause less waste, and provide a safer, more convenient at-home administration alternative to conventional needles. A potential disadvantage is the risk of unintentional needle-stick injury (Figure 1) (Donnelly and Douroumis, 2015). Microneedles significantly reduce the risk of infection at the puncture site following vaccine or drug administration (Lee *et al.*, 2010). Unlike traditional needles, which create larger wounds that can become infected over time, allowing bacteria to enter the bloodstream, microneedles cause much smaller, shallower punctures that heal significantly faster, reducing the risk of infection. However, further research is needed to determine whether certain bacteria can still penetrate these relatively shallow wounds (Xiang *et al.*, 2014).

Limitation of microneedles

Actually, correct use of microneedles helps in the proper delivery of a full dose of medication or vaccine (Jiang *et al.*, 2009). If applied incorrectly or damaged, microneedles may cause the drug to leak onto the skin rather than penetrate the body effectively. Therefore, proper training for healthcare providers is essential to ensure correct application and maximize the drug's efficacy (Dharadhar *et al.*, 2019). Microneedles are typically much softer than conventional needles. However, there is a risk of tiny fragments breaking off and remaining in the skin, potentially causing irritation or other complications. Therefore, they should be used with caution (Prausnitz *et al.*, 2017). The available literature on drug delivery through microneedles is limited, as current research primarily focuses on developing practical microneedles and optimizing their design and application (Ye *et al.*, 2018).

Classifications of Microneedles

Categorized by material

The MNs can be fabricated using a host of materials: silicon, glass, ceramics, metals, hydrogels, polymers, and sugar (McAllister *et al.*, 2000; Bediz *et al.*, 2014). Silicon was the preferred material for early generations of microneedles due to its rigidity and ease of penetration. However, its high cost and susceptibility to breakage rendered it impractical for widespread use (McConville *et al.*, 2018). Metals like stainless steel, titanium, nickel, and palladium have good mechanical properties and can be produced cost-effectively by methods such as electroplating, photochemical etching, micro-milling, and laser cutting. But because of safety issues, stainless steel and titanium are the only metals that are viable for use in medicine. Metal microneedles also produce biohazardous waste, which has to be disposed of in a responsible manner (Jeong *et al.*, 2017).

The selection of microneedle materials varies based on the optimal balance of cost, performance, and safety for specific applications. While silicon offers advantages such as rigidity and ease of penetration, its drawbacks often outweigh these benefits in certain implementations (Coulman *et al.*, 2006). Metals offer superior mechanical properties and cost-effectiveness; however, their safety and environmental impact must be carefully considered (Cormier *et al.*, 2004). Material selection significantly influences the biocompatibility of microneedles with the skin, as certain materials may trigger immune responses or cause irritation. Additionally, penetration efficiency depends on surface properties such as roughness and coating, which further impact the release of active substances (Rzhevskiy *et al.*, 2018; Daddona *et al.*, 2011).

Categorized by structures of Microneedles

From a structural perspective, microneedles can be categorized as either in-plane or out-of-plane. In in-plane microneedles, the needle length runs parallel to the substrate surface, whereas in out-of-plane microneedles, the longitudinal axis is perpendicular to the substrate (Thakur *et al.*, 2016). From a fabrication perspective, array densities of out-of-plane MNs are generally relatively high and this could increase drug delivery efficiency. Long out-of-plane MNs, for instance, through etching or molding, are theoretically possible, but such configurations raise some issues (Martanto *et al.*, 2006).

In the initial stage, in-plane microneedles were fabricated using inclined ultraviolet lithography and electroforming. Subsequently, these in-plane microneedles were assembled layer by layer into an out-of-plane microneedle array (Badran *et al.*, 2009). A polycarbonate out-of-plane microneedle array was generated by hot embossing in a machine with the negative Mold after a duplication process produced a negative Mold of the microneedle array (Banga, 2009).

Categorized by drug transportation method

While the design of microneedles varies based on the route of administration, type, and mechanism of action, most patches share common fundamental characteristics (Yan *et al.*, 2010). A typical microneedle measures between 150 and 1500 μm in length, 50 to 250 μm in width, and has a tapered, sharp-pointed tip with a thickness ranging from 1 to 25 μm (Oh *et al.*, 2008). The drug is typically either coated onto or encapsulated within the microneedle tip, which is then mounted on a base substrate to form an array (Waghule *et al.*, 2019). This array is then placed onto a patch backing for convenience, and the backing will typically feature a skin adhesive to ensure good contact with the skin (Haj-Ahmad *et al.*, 2015). Microneedles are typically categorized into five types:

a. Solid

b. Hollow

c. Coated

d. Dissolvable

e. Hydrogel-forming

Solid Microneedles

These needles, made from a single material such as silicon or stainless steel, are designed to puncture the skin and create microchannels for drug delivery (Jiang *et al.*, 2007). This approach significantly enhances drug absorption by bypassing the stratum corneum, the outermost skin layer, and directly accessing the underlying capillaries (Gill and Prausnitz, 2007).

Hollow microneedles

Hollow-core microneedles can be filled with a liquid drug solution, with the hollow opening serving as a channel for drug release into the skin. While this technique enables direct drug delivery, it may encounter challenges such as clogging or buckling, which can disrupt the administration process (Shakya *et al.*, 2019).

Coated microneedles

The surface of such needles is drug-coated and usually made of some water-soluble polymer or other biodegradable material (Sullivan *et al.*, 2010). As the microneedle dissolves or degrades upon contact with the skin, the drug is gradually released, enabling controlled and sustained drug delivery while minimizing systemic side effects (Edens *et al.*, 2015).

Dissolvable microneedles

Dissolvable microneedles are made from biodegradable or water-soluble materials that break down upon contact with the skin, eliminating the need for special sharps disposal (Hirobe *et al.*, 2015). This approach is highly beneficial as it minimizes the risk of accidental needle-stick injuries and associated infections. Common materials used for dissolvable microneedles include carboxymethyl cellulose, methyl cellulose, and various saccharides (Quinn *et al.*, 2015).

Hydrogel microneedles

The hydrogel matrix contains the drug embedded in the needles. In that way, the hydrogel expands upon contacting the skin and slowly delivers the drug afterwards (Mistilis *et al.*, 2015). This method is particularly suitable for drugs intended for prolonged retention in the skin, such as growth factors and hormone injections. Hydrogel microneedles can be engineered to enable controlled drug release, ensuring optimal therapeutic outcomes (Raphael *et al.*, 2016).

Material for microneedles

A key advantage of microneedles is their resistance to bending or breaking upon skin penetration. Overcoming manufacturing challenges requires careful selection of materials, production techniques, and design. A wide range of materials, including silicon, metals, ceramics, and polymers, has been utilized to develop various types of microneedles (Al Sulaiman *et al.*, 2019).

Silicon

Silicon was first used to create microneedles in the 1990s, offering two key advantages, its flexibility enables the fabrication of a wide range of shapes and sizes, and it is suitable for manufacturing solid, hollow, and coated microneedles. However, silicon also has notable drawbacks, including a lengthy fabrication process, high production costs, and the risk of breakage within the skin during application (He *et al.*, 2020).

Metal

Metals have been widely utilized in microneedle production due to their biocompatibility and outstanding mechanical properties, including high fracture toughness and superior yield strength. These attributes make metal-based microneedles more durable and less prone to breakage compared to their silicon counterparts (Yu *et al.*, 2015). Stainless steel and titanium are the two primary metals evaluated for microneedle fabrication. While metal microneedles effectively penetrate the skin, they may occasionally trigger allergic reactions (Zhao *et al.*, 2018).

Ceramic

Ceramic materials such as alumina are employed during MN preparation because of their high chemical stability and compressive resistance. Tensile strength in the case of alumina is considerably less compared to other materials (Desai *et al.*, 2021). Other ceramics, such as calcium sulfate dihydrate and calcium phosphate dihydrate, have been utilized in microneedle fabrication. The micro-molding technique plays a crucial role in the large-scale production of ceramic microneedles, offering a cost-effective manufacturing solution (Yang *et al.*, 2013).

Polymer

Polymer-based microneedle arrays show great potential for drug delivery applications due to their biocompatibility, low toxicity, and cost-effectiveness. However, they are generally less durable than those made from silicon or metals (Martanto *et al.*, 2004). Polymers are the most commonly used materials for manufacturing dissolvable, hydrogel-forming, solid, coated, and hollow microneedle arrays (Harvey *et al.*, 2011). Various drugs have been successfully delivered using microneedle arrays made from biodegradable polymers. Some of the most commonly used polymers for microneedle fabrication include poly (methyl methacrylate) (PMMA), Polylactic Acid (PLA), polycarbonate, polystyrene, and SU-8 photoresist (Marquetti and Desai, 2019).

Manufacturing methods for microneedles

Lithography

The lithography process used in microneedle fabrication is known as lithography. In this technique, a photoresist, a light-sensitive material is utilized to capture intricate patterns on surfaces. These patterns are then transferred onto the substrate through subsequent chemical etching (McAllister *et al.*, 2003). Although lithography offers superior resolution and flexibility, it has certain limitations. The process demands a highly controlled cleanroom environment to prevent sample contamination and ensure the precise replication of patterns (Kendall *et al.*, 2007). Furthermore, it is a slow process involving several sequential operations, including photolithographic application of the resist, exposure, development, and etching. All these elements bring out the comparatively high price it has in producing products in large quantities (Cormier *et al.*, 2004). Despite these limitations, lithography remains one of the most important techniques for manufacturing complex geometrical and high-precision microneedles (Sharma, 2018). Indeed, lithography enables the fabrication of microneedles using a wide range of materials, including glass, metal, ceramics, and plastics. By meticulously controlling the lithography process, researchers can achieve microneedles with precisely tailored dimensions, shapes, and surface characteristics (Larrañeta *et al.*, 2016).

Laser Ablation

Laser ablation is a highly promising technique for precise material removal and has also emerged as an advanced method for fabricating microneedle arrays. This process relies on a focused laser beam to ablate material from a substrate, creating intricate patterns and well-defined structures (Ma *et al.*, 2014). Different laser types, including carbon di oxide, ultra violet excimer, and femtosecond lasers, have been used to create microneedles (O'Mahony, 2014). The use of a high-energy laser beam enables exceptional removal speed and precision within nanoseconds, completely ablating the material. This rapid and precise process is ideal for fabricating microneedles with intricate geometries and precisely controlled dimensions (Niinomi and Nakai, 2011). Although laser ablation has numerous advantages, the ablation point is still attached to thermal effects. Thus, such thermal effects might influence the microneedle structure and therefore the mechanical properties, leading to undesirable effects like cracking or reduced fatigue strength. Optimal adjustment of the laser parameters utilized as well as proper material choice is thus necessary (Monteiro-Riviere, 2010).

Despite the drawbacks of thermal effects, laser ablation remains a highly viable technique for microneedle fabrication. Its versatility, speed, and precision make it invaluable for various applications, including drug delivery, diagnostic testing, and cosmetic procedures. However, the process often requires significant initial investment in laser equipment and may pose challenges for large-scale manufacturing (Ita, 2015; Verbaan *et al.*, 2007).

Micro-Molding

One highly precise and cost-effective manufacturing technique for mass-producing microneedles is both scalable and efficient. This method typically involves creating a master mold, followed by casting with a suitable polymer material containing active pharmaceutical ingredients. As a result, it enables the fabrication of an exceptionally high volume of microneedles with outstanding precision and uniformity (Aldawood *et al.*, 2021). The work material, Polydimethylsiloxane (PDMS), is characterized by having excellent features of low price, easy hand ability, low surface energy, and high thermal stability. The unique features favour the use of PDMS as an excellent option to create elaborate microneedle structures of definite geometries with well-distinguishable surface properties (Indermun *et al.*, 2014). As with any process, however, advantages may go hand-in-hand with other challenges that must be overcome before it could successfully realize the desired output (Bystrova and Luttge, 2011). For instance, the penetration depth and drug load capacity of microneedles significantly impact the overall safety and effectiveness of drug delivery. By leveraging micro-molding, researchers can produce high-quality microneedles for medical applications, ensuring precise control over these critical factors through well-implemented regulatory measures (Mikszta *et al.*, 2006).

Injection Molding

Injection molding is a highly versatile technique for manufacturing microneedles. When combined with hot embossing, it enables the production of hollow polycarbonate-based microneedles that offer exceptional puncture resistance while maintaining sharpness, even after multiple insertions and withdrawals (Arbós *et al.*, 2002). Micro-injection molding can also be utilized to produce solid microneedles that can effectively transport high-molecular-weight molecules (Donnelly *et al.*, 2014). Polymer-based microneedles fabricated through this method have proven capable of penetrating human skin tissue and effectively extracting fluids.

Moreover, this technique offers a cost-efficient solution for the large-scale production of microneedles (Larrañeta *et al.*, 2016).

Laser Cutting

The fabrication of metal microneedles is typically achieved through advanced techniques such as 3D laser cutting, laser ablation, and electroplating. The process often begins with infrared-laser-cut stainless steel or titanium sheets, utilizing designs generated from Computer-Aided Design (CAD) software to ensure precision and consistency in manufacturing (Hong *et al.*, 2013). These post-processed mass-produced microneedle arrays are cleaned, bent, and polished to make their shape finer so that they can function in the best possible way. This provides the possibility of single-row or multi-row arrays of microneedles of practically any geometry (Chu *et al.*, 2010).

Atomized Spraying Method

This atomized spray technique holds the potential to revolutionize the production of dissolvable microneedles with customizable shapes and properties. Freed from the limitations of surface tension and viscosity, this method enables the fabrication of microneedles from a wide range of materials, including sugars and polymers (Donnelly *et al.*, 2010). The atomized spray is sprayed into PDMS molds and dries to form the desired microneedle structure. This process enables the fabrication of a layer-by-layer microneedle with various properties, and thus has more control over active substance release (Gaikwad and Desai, 2018).

Drug delivery by microneedles

Vaccines formation

Traditional vaccines are primarily administered through subcutaneous injection. However, recent research highlights microneedles as a promising vaccine delivery platform, as they can directly present antigens to dendritic cells in the skin, eliciting a stronger immune response. Unlike traditional vaccines, microneedle-based vaccines also offer the advantage of being less reliant on refrigeration for storage (Gaikwad *et al.*, 2020). Monoclonal antibodies are powerful agents with significant diagnostic and therapeutic applications, including delivery through microneedles. They enable precise targeting of specific cells for immune system modulation, minimizing the over-activation of autoreactive T cells and reducing adverse side effects. However, challenges such as protein inactivation and diminished efficacy remain key concerns in their application in Table 1 (Odujole and Desai, 2020).

This study reveals that the merging of trehalose and the parent formulation in microneedles significantly improves stability in comparison to that produced with sucrose (Odujole and Desai, 2020). Trehalose treatment helps preserve antibody integrity even under harsh conditions, such as prolonged exposure to high temperatures. Additionally, delivering GM-CSF through microneedles can significantly enhance immunogenicity and extend the duration of the antibody response (Saurer *et al.*, 2010). Microneedles made of various materials consisting of trehalose,

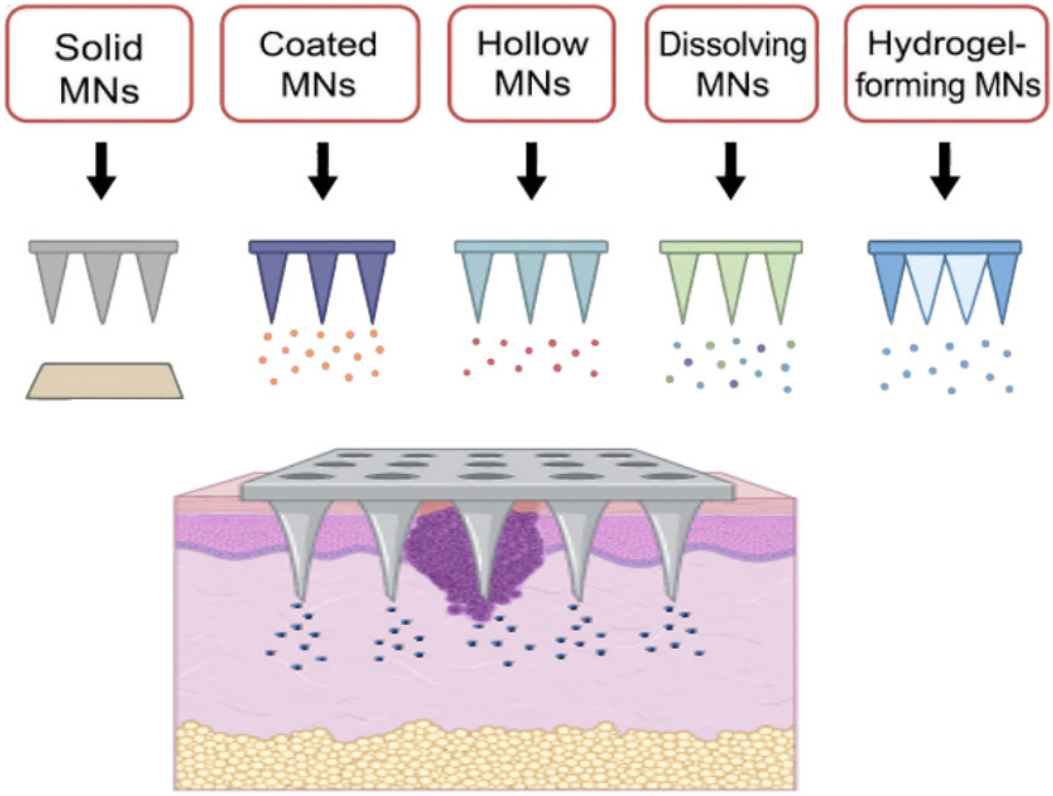

Figure 1: Micro needle under skin superior drug delivery technology.

Table 1: Comparison of microneedles over parenteral dosages forms.

Sl. No.	Parameter	Microneedle	Parenteral	References
1	Invasiveness and Pain	These microneedles are actually very fine and should penetrate only up to the top layers of the skin, excluding deeper tissues and blood vessels. It thus causes little to almost negligible pain and can significantly reduce the fear and discomfort a patient endures, especially for needle-phobic patients.	These methods, namely the subcutaneous, intramuscular and intravenous injections, require deeper penetration into muscle, fat, or veins and, hence, generally painful or uncomfortable. Intramuscular injections may even result in tenderness, while intravenous injections might cause distress from the access in a vein.	(Prausnitz, 2004).
2	Drug Delivery Efficiency and Bioavailability	Microneedles bypass the stratum corneum, directly depositing drugs into the epidermis or dermis where it could be absorbed into systemic circulation. Thus, higher bioavailability as compared with most oral routes can be expected, though delivery will not be faster than intravenous administration. Penetration depth and drug release are controllable, and microneedles can deliver a wide variety of molecules, including vaccines, peptides, and small molecules.	Parenteral injections are for the most part intravenous, hence they give a 100% bioavailability. Though Subcutaneous and Intramuscular injections also give high bioavailability, the rate of absorption is slower as compared to IVs. With parenteral methods, a broad range of drugs could be administered, such as biologics, chemotherapeutics, and vaccines, therefore parenteral are useful to provide systemic and rapid drug effects.	(Prasad and Koul, 2012).
3	Safety and Risk of Complications	Microneedles are less likely to cause infection as compared to parenteral injections because they do not prick deeper into the skin or blood. Moreover, the shallow non-penetrating nature of the instrument also helps it avoid blood vessels, which further reduces the risk of contamination and infection. Dissolvable microneedles also avoid sharp objects risk factors; hence, they reduce the risks of needle-stick injuries and consequently the biohazard waste.	The risk of infection, phlebitis, or extravasation is greater with parenteral methods, particularly intravenous injections. Localized reactions to subcutaneous and intramuscular injections can include pain, bruising, or abscess formation. Perhaps one of the most serious risks to health care workers is needle-stick injury.	(Mistilis *et al.*, 2015).
	Speed of Drug Action	The slow and controlled release of drugs through microneedles is quite effective for vaccines and long-term therapies. However, their activity onset usually is not as quick as intravenous administration because their effect is based on the absorption through the various layers of the skin and local circulation.	The drug is administered directly into the bloodstream, thus intravenous injection provides the fastest onset of drug action. This is very important for emergencies or when immediate systemic effects are needed (for example, anesthesia, antibiotics in critical care). In comparison, intramuscular and subcutaneous injections offer slower absorption but still faster than transdermal routes.	(Jung and Jin, 2021).

	Drug Stability and Cold Chain Requirements	Dissolvable polymers-based microneedle patches offer the advantage of improved drug stability, thereby eliminating or minimizing refrigeration requirements-the major logistics headache of vaccine transportation. This is a critical requirement for vaccines. It makes them ideal for use in resource-poor settings or mass immunization campaigns.	Most biologics, vaccines, and insulin rely on strict cold chain management to ensure stability. This involves high logistical complexity and cost, particularly in remote or underdeveloped areas. Some parenteral formulations are not very stable in non-sterile conditions.	(Heneweer *et al.*, 2012).
	Application and Cost	Microneedles are mass-producible at relatively low expense, especially dissolvable microneedles made from inexpensive polymers. The scalability and ease of use for mass drug delivery-even in low-resource public health settings-are the cost-effectiveness reasons associated with the cost to deliver drugs at scale. At the same time, microneedle use is associated with reduced healthcare costs related to the clinical administration process.	Parenteral injections generally require more resources, such as sterilized equipment, healthcare professionals and more complex manufacturing processes. It is also much more costly, especially with intravenous therapy and the possibility of hospitalization or medical observation.	(Li *et al.*, 2018).

Carboxymethyl Cellulose (CMC), and gelatin have been proven to be suitable for stable GM-CSF delivery (Griss *et al.*, 2001). The third-generation hepatitis vaccine was also demonstrated to be administered through microneedles consisting of 15% trehalose. In comparison to a liquid vaccine, it was found in this study that it remained viable at higher temperatures and multiple freeze-thaw cycles (Gaikwad and Desai, 2021).

This highlights the potential of vaccines and antibody delivery via microneedles to achieve optimal healthcare outcomes through superior efficacy, convenience, and stability in drug administration (Madou, 2018).

Proteins Regulation

Protein drugs serve as essential therapeutic agents for treating various cancers, genetic disorders, and related diseases. However, challenges such as stability, absorption, and large molecular size have hindered their overall therapeutic effectiveness (Plummer, 2009). The microneedles hold great promise for protein delivery and overcome some of the limitations associated with traditional delivery systems. The microneedles have the ability to avoid the digestive tract by delivering the protein drugs into the body via the skin directly, thus enhancing absorption and reducing degradation (Tran and Nguyen, 2017). This method has been successfully utilized to deliver a diverse range of protein pharmaceuticals, including insulin, desmopressin, erythropoietin, lysozyme, glucagon, glucagon-like peptide-1, parathyroid hormone, and growth hormone, with remarkable effectiveness. Ensuring protein stability throughout production, storage, and delivery is crucial for maintaining therapeutic efficacy (Lycke, 2012). Temperature, humidity, and the inclusion of stabilizers can significantly impact protein integrity. However, recent advancements in microneedle stability have been remarkable. For example, glucose-sensitive microneedles loaded with phenylboronic acid, which exhibit enhanced thermal stability, have successfully delivered insulin to diabetic patients with precision and effectiveness (Adarkwa and Desai, 2016).

Careful optimization of microneedle manufacturing parameters is essential to preserve protein activity and efficacy. Research has shown that factors such as temperature control, drying conditions, polymer concentration, and the incorporation of protein stabilizers play a crucial role in enhancing protein stability (Desai *et al.*, 2012). Under optimized conditions, lysozyme activity was remarkably retained at 99.8±3.8%. These findings highlight the groundbreaking potential of microneedles in the efficient delivery of protein-based drug (Huang and Fu, 2007). New discoveries in this field address challenges associated with conventional delivery methods, paving the way for enhanced therapeutic outcomes and improved patient care. These advancements hold immense potential for revolutionizing drug delivery and treatment efficacy (Suzuki *et al.*, 2018).

Applications of Microneedles

Vaccine Delivery

Dissolvable microneedles represent a groundbreaking vaccine delivery platform, offering a superior alternative to conventional

hypodermic needles. They are biocompatible, durable, and highly scalable, with key advantages such as the elimination of biohazardous waste. To date, dissolvable microneedles have been successfully employed for vaccine delivery against numerous diseases, including malaria, diphtheria, influenza, hepatitis B, HIV, and polio (McKenzie and Desai, 2018). While dissolvable microneedles have gained significant popularity, coated microneedles have also demonstrated remarkable potential. Studies have reported enhanced immunogenicity in pigs following immunization with the BCG vaccine using coated microneedles (Prausnitz, 2017). DNA vaccines coated onto microneedles and administered intradermally have been shown to effectively prime cytotoxic lymphocytes in mice. Additionally, coated microneedles have been successfully utilized for influenza vaccination, further demonstrating their potential in immunization strategies in Table 2 (Desai *et al.*, 2015).

Hollow microneedles are another promising vaccine delivery platform, successfully used in animal studies to administer anthrax and plague vaccines, effectively inducing protective immunity (Desai *et al.*, 2013). In a clinical human setting, a microneedle for the purpose of influenza vaccination elicited immune responses that were similar to those elicited by intramuscular injection; in this sense, microneedles hold promise as a substitute for the conventional mode of needle-delivery of vaccines (Ahmed *et al.*, 2020). Their biocompatibility, durability, and scalability make them highly suitable for a wide range of vaccines. Ongoing research and development in this field will continue to unveil innovative applications of microneedles, advancing vaccine delivery and strengthening public health efforts (Ismail *et al.*, 2020).

Drug Delivery

Since their introduction in 1998, microneedles have rapidly evolved into a groundbreaking platform for transdermal drug delivery. Over time, various types of microneedles have emerged, including dissolvable, coated, and solid microneedles, each capable of delivering drugs for a wide range of medical applications. Dissolvable microneedle patches have been successfully used for the delivery of human growth hormone and caffeine, offering potential treatments for conditions such as obesity and growth disorders. Coated microneedles have facilitated the delivery of salmon calcitonin, while solid microneedles have been employed for the administration of protein antigens, with ovalbumin serving as a notable example (Menazea *et al.*, 2021; Mostafa *et al.*, 2020). Solid silicon and metal microneedles have demonstrated exceptional efficacy in delivering various compounds through

Table 2: Comparison of microneedles over transdermal patch.

Sl. No.	Parameter	Microneedle	Transdermal Patch	References
1	Drug delivery mechanism	These are tiny, needle-like projections known as microneedles that penetrate either the epidermis or dermis to inject drugs directly into the outermost layer of the skin. These produce minute channels bypassing the skin barrier and thus allow the delivery of a much greater range of drugs, thereby including large molecules such as proteins, peptides, and vaccines.	Small, lipophilic molecules utilize passive diffusion through the skin in delivering activity from transdermal patches. However, there is an important barrier in the stratum corneum that restricts the size and the type of drugs delivered via patches. Hydrophilic or larger molecules cannot permeate the skin by traditional patch delivery systems.	(Prasad and Koul, 2012).
2	Range of Drugs Delivered	These can release a wide variety of drugs ranging from small molecules to large proteins, DNA, vaccines, and peptides. Since they may deliver drugs deeper into the skin, they are of special interest for applying biologics, hydrophilic drugs, and even gene therapies.	Only small, lipophilic drugs can cross the skin from patches. Since these can diffuse past the permeability barrier, a strong limitation exists in this respect on the drug variety that can be delivered via patches.	(Vandervoort and Ludwig, 2008).
3	Drug absorption and efficiency	They are valid for vaccines, insulin, and other biologics that require accurate dosing since they bypass the skin's natural barrier to deliver drugs straight into the dermis or epidermis, leading to fast and efficient drug absorption.	With passive diffusion through the skin, the absorption of drug from patches is slow and variable. It is usually lower than that in other routs of administration, and efficiency will depend upon the drug's permeability in the skin.	(Prausnitz, 2004).

4	Dosing Precision and Control	Such microneedles can offer precise dosing control by governing the depth of penetration and size of needle array. In particular, some microneedles are designed to degrade in the skin, thereby enabling controlled drug delivery over time.	Patches can deliver drugs continuously over an extended period and are appropriate for drugs that must be maintained in plasma at a steady level (e.g., nicotine, hormones). Poorer control of drug delivery sometimes results because skin permeability varies between patients.	(Sullivan *et al.*, 2010)
5	Application and Self-Administration	They are often designed to be self-administered, particularly true for the case of microneedle patches. That makes them outstanding for vaccines and chronic conditions in which frequent dosing is required. In some formulations, such as dissolvable microneedles, sharps disposal is not required.	Patches are designed for simple self-application, allowing patients to use them with minimal training. They are widely used in long-term drug therapies, such as hormone replacement and nicotine cessation.	(Jung and Jin, 2021).
6	Patient experience	The use of microneedles provides a painless minimally invasive approach without causing any pain. Insertion of these microneedles is painless because, unlike the normal hypodermic needle, they do not pierce the pain receptors located deeper within the skin layers. Patient tolerance is therefore ideal, which leads to more compliance.	Patches are non-invasive and painless, but the range of drugs they can deliver is limited. Their passive nature makes them highly acceptable to patients, though some users may experience irritation or allergic reactions to the adhesives.	(Yanes and Tamanoi, 2012).

the skin, including calcein, BSA, and insulin. Microneedles have significantly enhanced the transdermal permeation of numerous medications, such as ibuprofen, ketoprofen, and paracetamol. Additionally, they have been successfully utilized for the delivery of ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine hydrochloride, and glycerol, further showcasing their versatility in drug administration (Nejad *et al.*, 2020; Aoyagi *et al.*, 2007). While significant focus has been placed on skin penetration in both animals and humans, microneedles have also demonstrated their capability for drug delivery into deeper tissues, including chicken thighs and brain tissue. This underscores their versatility and immense potential for diverse drug delivery applications (Prausnitz and Langer, 2008).

Cosmetic Application

Microneedles have emerged as an important delivery platform in cosmetic medicine. One of the applications where new innovation has been created is the delivery of hyaluronic acid, which actually is an essential component of skin hydration, for improved health and appearance of skin (Kim *et al.*, 2018). Dissolvable microneedle patches have been developed which deliver hyaluronic acid, other beneficial compounds, like ascorbic acid, and retinyl retinoate directly into the skin. Treatment with facial hair growth has also shown promise in some studies (Park *et al.*, 2005). A study aimed at demonstrating the enhancement of delivery of eflornithine, a drug used in treating facial hirsutism, has proven the effectiveness of solid microneedles in *in vitro* as well as *in vivo* analysis. Apart from skin rejuvenation and hair growth, microneedles have been studied for their treatment of alopecia areata, an autoimmune condition causing hair loss (Lhernould *et al.*, 2015). In clinic studies, there have been benefits observed; hair growth has been seen in patients who received this form of treatment. Another application of microneedles has been in the treatment of skin conditions other than keloid scars, such as atrophic facial scarring, atrophic acne scars, and hypertrophic burn scars (Sammoura *et al.*, 2007). Since direct access to target sites is made possible through penetration and delivery of active ingredients in the skin via microneedles, they are useful for treatment applications for such cosmetic conditions as well (Gill and Prausnitz, 2007).

CONCLUSION

One of the most promising transdermal drug delivery systems that have recently gained much popularity with regards to its ability to improve access to medications for patients through providing an alternative for more traditional methods of administration is the MNs. There are several types of MNs, including those that are solid and coated, dissolvable, and hydro gel-based formulations;

they can also be produced from silicon, metals, polymers, glass, and ceramics. A broad variety of manufacturing methods has been employed to fabricate the microneedles in wide ranges of geometrical dimensions and specifically tailored properties to meet the varied requirements for medical purposes. As the technology develops, it has become the mainstay of many clinical trials and studies for drug delivery purposes. Most of the research outcomes have been reported to be successful, especially in regard to promising a great potential of delivering therapeutic agents across a range of applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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