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Review Article

A Review On Microneedles: Scope, Strategies, Challenges And Methods

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ABSTRACT

Transdermal drug delivery (TDD) involves the delivery of drugs through the skin. This delivery system reduces side effects by avoiding vital organs like the liver, bypassing first-pass metabolism, and preventing drug degradation in the stomach. There are many types of TDD, including topical cream, hypodermic needle, transdermal patch, and microneedles. However, topical cream and transdermal patches take a long time to deliver drugs to the systemic circulation due to the stratum corneum in the skin acting as a barrier. While hypodermic needles deliver drugs into the systemic circulation, they often induce pain. Microneedles (MN) are considered the best formulation for delivering drugs to the systemic circulation with minimal pain compared to hypodermic needles. This compilation focuses on the mechanism, types, materials, manufacturing methods, delivery strategies and scope of microneedles. Additionally, evaluation, applications, and additional enhancement methods of microneedles are explored. Information regarding marketed products, patents, and research articles on microneedles is also provided.

INTRODUCTION

Transdermal drug delivery (TDD) is a painless method for systemic drug delivery by applying a drug formulation to intact and healthy skin [1, 2]. The drug initially penetrates the stratum corneum, progressing through the deeper epidermis and dermis without accumulating in the dermal layer. Upon reaching the absorption through dermal microcirculation [3, 4] aiming to deliver drug molecules to the bloodstream by controlling diffusion through the skin. Different types of transdermal drug delivery systems 5 and their relevance to microneedles (MN) are illustrated in Figure 1.

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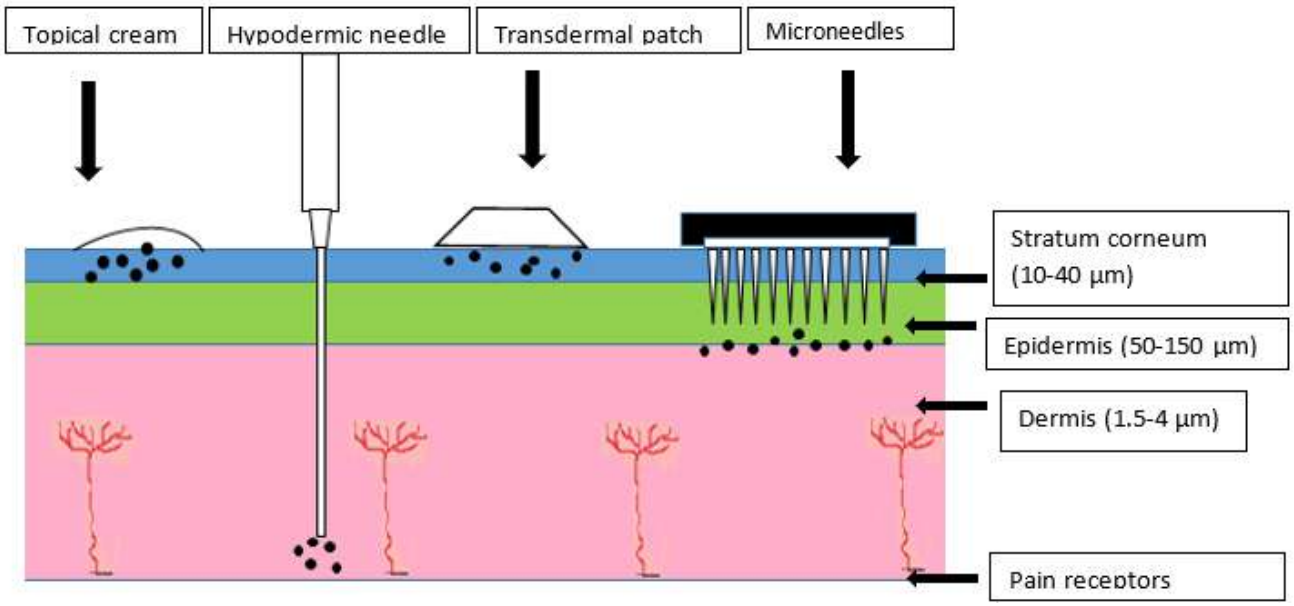

Figure 1: Different types of transdermal drug delivery in comparison to microneedles [5].

General advantages of TDD:

TDD offers several advantages over other drug delivery methods, including sustained and well-controlled drug delivery to the blood with the desired dosage [6]. It also reduces drug side effects by preventing direct exposure to critical organs such as the liver and kidneys. TDD addresses the low bioavailability of many oral drugs, particularly for macromolecules, peptides, and proteins [6]. Michal Goodman's comparison between transdermal and oral delivery concludes that transdermal delivery has a higher safety profile across various domains [6]. But the semisolid and patch forms of TDD still suffer from the drawback of low permeation. Some methods were proposed in literature to enhance transdermal permeation.

Enhancement approaches for transdermal permeation:

Significant efforts have been invested in enhancing transdermal permeation using chemical or physical enhancers [6]. Among all, microneedles serve as physical enhancers, creating disruptions in the stratum corneum to enable drug delivery through the skin. Once the stratum corneum is breached, drugs can diffuse through the skin upon contact with interstitial fluids. This method allows the delivery of drugs. Even though utilization of sweat glands and hypodermic needles as an alternate mechanism available, the microneedles approach tackle prominent issues in transdermal delivery, including the risks of vein collapse, needle phobia, and the need for sustained delivery [6].

Microneedles (MN) for Transdermal Drug Delivery:

Microneedle patches, a type of transdermal patch embedded with tiny needles, facilitate minimally invasive drug delivery [7]. These micro-sized needle arrays, ranging from 25 to 2000 µm in height, aim to penetrate the stratum corneum [8]. The ideal characteristics, advantages, disadvantages and challenges of microneedles are shown below.

Ideal Characteristics of Microneedles:

- The dimensions of microneedles typically range from 150 to 1500 micrometers in length, 50 to 250 micrometers in width, and 1 to 25 micrometers in diameter [9, 10].
- Microneedles aim to provide a quick onset of action, efficient drug delivery, and enhance

- self-medication and personalized medication at different dose levels [5].
- They must withstand deep insertion into the skin without breaking, possess optimum size and mechanical stability, and enable controlled drug delivery at a predetermined rate [5].
- The durability of these products is crucial, ensuring they are leak-proof and adhere well, similar to regular transdermal patches [11].

Advantages of microneedles [12]:

1**. Improve drug delivery**

- Improved drug delivery through the stratum corneum.
- Rapid onset of drug action due to capillary beds and lymphatic vessels in the superficial dermis.
- Accurate drug dose delivered by controlling microneedle formulations.
- Avoidance of first-pass metabolism.
- High drug bioavailability.
- Effectiveness for vaccine delivery due to the abundance of immune cells in the dermis.

2. Safety and Compliance Advantages:

- Painless and safe application due to small length and size.
- Reduced need for expertise in patch application.
- Reduction or elimination of biohazardous waste.

3**. Manufacturing Process and Cost-Saving:**

- Optimized solid-state formulation eliminates the need for a cold-chain system.
- Microneedle patches reduce the overall size of the drug package, encompassing drug, needle, and syringe functionalities.
- Cost savings in terms of dose sparing, manufacturing, and logistics.
- Disadvantages of microneedles [12]:
- Limited drug dose loaded, due to the small size of microneedles.
- Temporary inflammation and allergy may occur.
- Sophisticated technologies needed for manufacturing with reproducibility.
- Storage containers required to hold microneedle patches hygienically during distribution.
- Risk of broken or leftover microneedles when solid microneedles are applied.

Challenges of microneedle delivery system:

The primary concerns and challenges [13] associated with the development of a microneedle-based delivery system are depicted in Figure 2. These challenges were tackled by using different materials, microneedle types which were further elaborated in the subsequent sections about the each parameters along with factors.

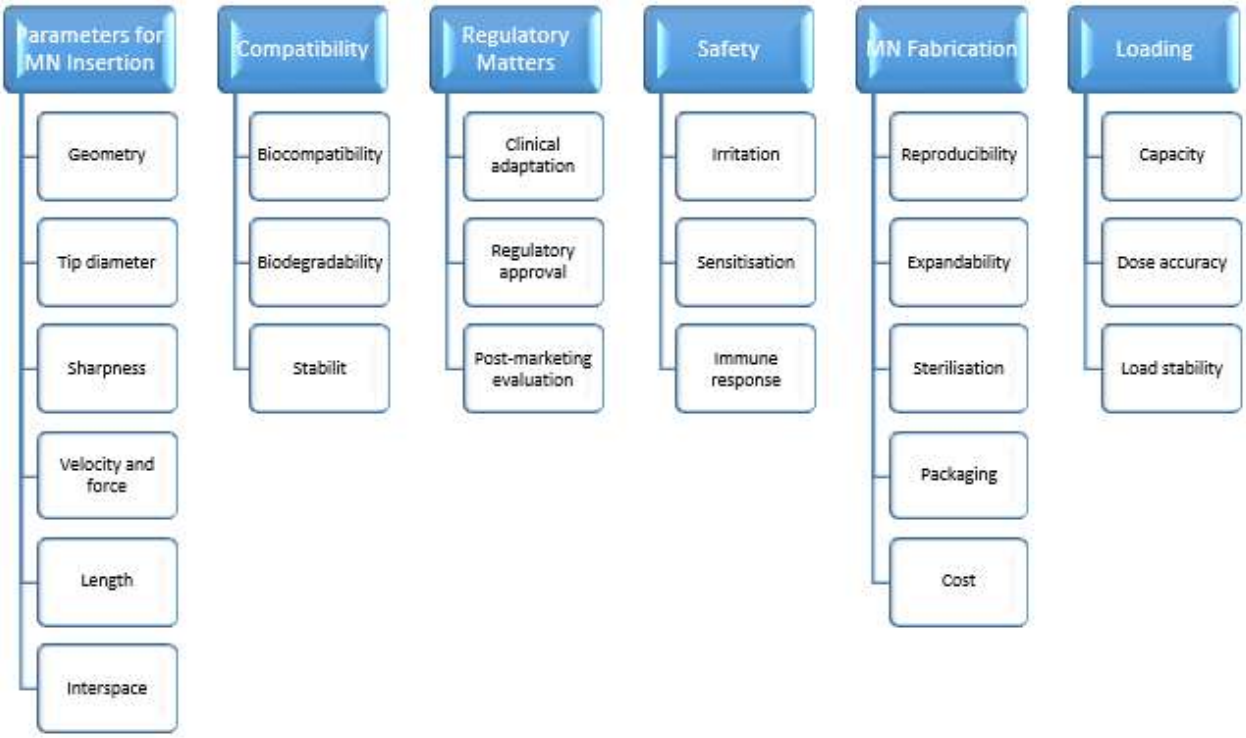

Figure 2: Challenges associated with microneedles at various levels [13]

Microneedle History:

Even though the journey of microneedle research was started in 1900, but in recent times after 2020, it was associated with other technologies like nano delivery and 3D printing for its better acceptability and adaptability. The timelines of microneedle history [6] was depicted in figure 3.

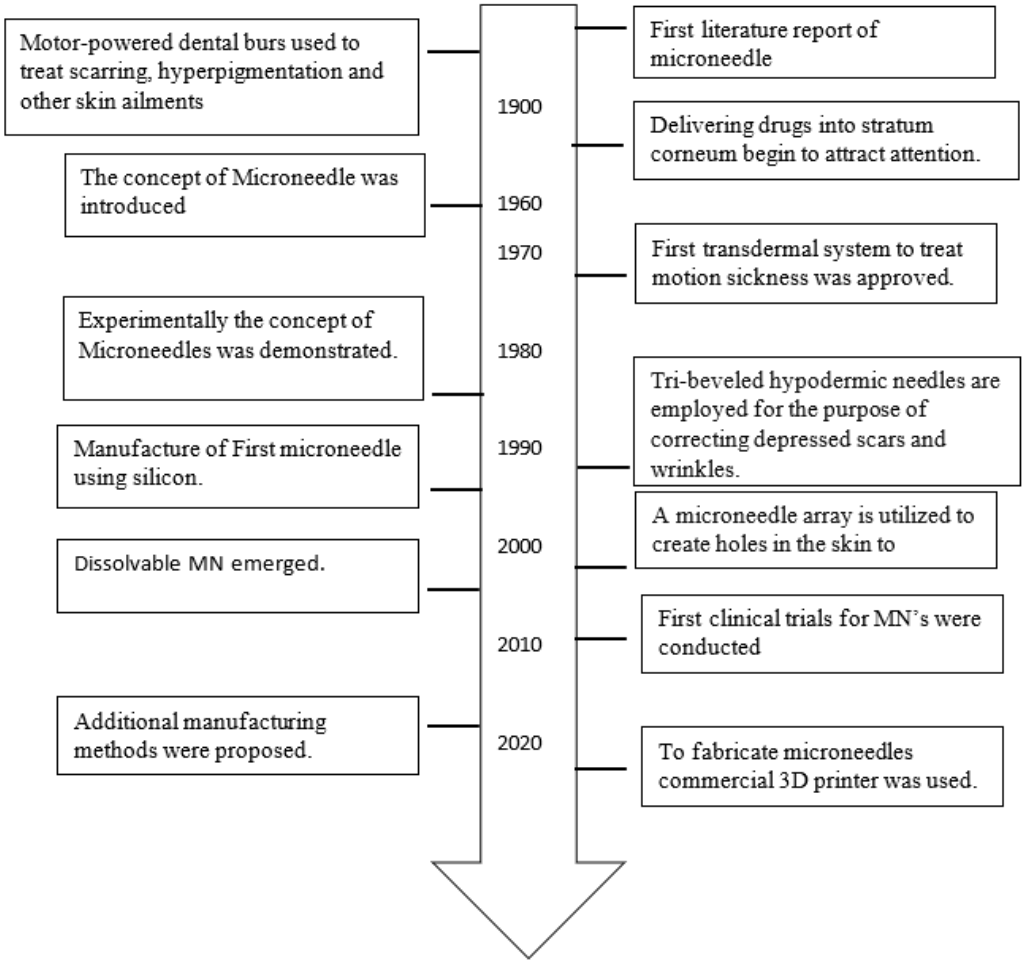

Figure 3: Timelines of microneedles research and development6

Mechanism of drug delivery:

In the microneedle drug delivery system, the skin is temporarily disrupted by arranging one to hundreds of microneedles in arrays on a tiny patch, similar to a standard transdermal patch. This patch, when applied, pierces the stratum corneum, bypassing the skin's barrier layer. The microneedle device facilitates the direct placement of the drug into the epidermis or upper dermis layers. Subsequently, the drug enters the systemic circulation, eliciting a therapeutic response upon reaching the site of action [5].

Types of microneedles:

To cater the needs drug delivery microneedles were made into different types like solid, hollow, coated and dissolving type as shown in the figure 4.

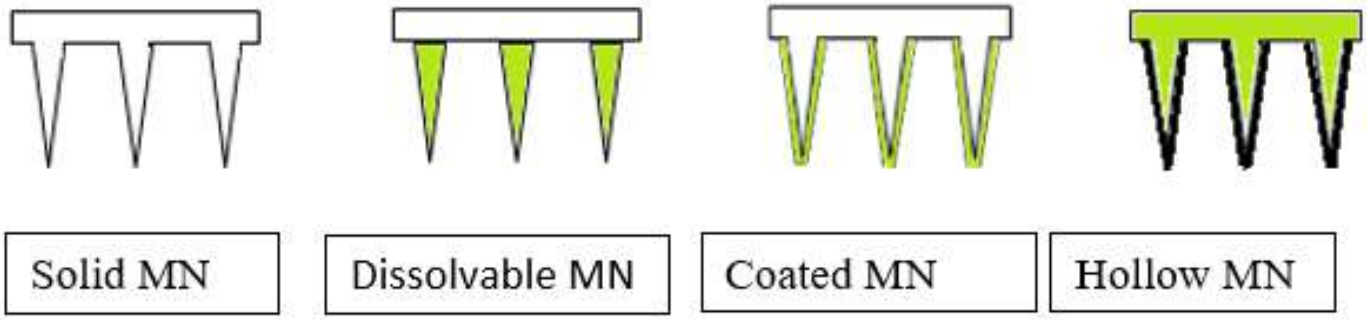

Figure 4: Types of Microneedles

Solid Microneedles [14]:

Solid microneedles are designed to penetrate the stratum corneum, enhancing drug delivery to the dermis and facilitating kinetic transport across the skin [14].

Coated Microneedles [6]:

Coated microneedles, a subtype of solid microneedles, act as carriers to transport and deposit drugs within the skin or other tissues. This involves coating the microneedles with a drug in a formulation suitable for subsequent dissolution, ensuring rapid delivery of the desired drug dose upon insertion [6]. Different techniques were employed for coating microneedles which include: (a) dip coating, (b) gas-jet drying, (c) spray drying, (d) Electro hydro dynamic atomization (EHDA) processes, and (e) ink-jet printing.

Hollow Microneedle [14]:

Hollow microneedles feature an empty core or chamber into which drug fluid is injected or stored. They can accommodate a larger dose or amount of drug solution compared to solid microneedles. Hollow microneedles are suitable for delivering drugs into the viable epidermis or dermis, making them ideal for high molecular weight compounds. By containing a hollow bore, these microneedles create a direct channel through the stratum corneum into the lower layers of the epidermis upon skin insertion [14].

Dissolving Microneedle [14]:

Dissolving microneedles offer a promising technique characterized by the rapid release of macromolecules and a one-step drug application, simplifying drug administration. The dissolvable microneedle tip, quickly releases the drug upon insertion. Water-soluble materials are the preferred choice for producing dissolvable microneedles [14].

Hydrogel-forming Microneedles [16]:

The latest advancement in microneedle technology, hydrogel-forming microneedles, consists of arrays made from a swelling material with an attached drug reservoir at the baseplate. After insertion into the skin, the array absorbs interstitial fluid, swells, and forms continuous conduits between the dermal microcirculation and the attached patch-type drug reservoir, facilitating drug diffusion into the skin [16]. The characteristics, advantage, disadvantage, application and materials used for making of these types were shown in table 1. These types were also represented in pictorial form in figure 4, for better understanding and visualization.

Table 1: Various types of microneedles along with their parameters [6]

MN Type	Characteristics	Advantages	Disadvantages	Application	Material
Solid	Creates channels in the skin; adequate mechanical strength; sharper tip	Allows more drugs to pass into the skin; easy to manufacture	Damage to the skin and micro incisions need closure to avoid infections	Drug delivery, Cosmetic	Silicon, Metal, Polymer
Hollow	Empty shape to be filled with the drug; ability to control drug release over time	Handles a large dose/amount of drug solution	Weak needles; requires intensive care in needle design and insertion method; may cause leakage and clogging	Disease diagnosis	Silicon
Coated	Carries less amount of the drug; ability to	Delivers the drug quickly to the skin	Prone to infection	Drug delivery,	Silicon

	deliver proteins and DNA.			Vaccine delivery	
Dissolving	Facilitates rapid release of macromolecules	Ease of administration with one-step application	Requires technical expertise to manufacture, takes time to dissolve	Drug delivery, Cosmetic, Vaccine delivery	Polymer

Materials used for Microneedles manufacture:

Various types of materials are being used in manufacture of microneedles. The selection of suitable materials is based on the type of characteristics desired, type of needle fit for patient need and after taking due consideration of their advantages and disadvantages. The factors affecting the selection of material is tabulated in table 2.

Table 2: Overview of Materials and factors to be considered for their selection in microneedle manufacture [6]

Material Type	Advantages	Disadvantages	Manufacturing Method	MN Fit design
Silicon	Flexible enough to manufacture desirable shapes and sizes.	Time-consuming fabrication. High cost. Possibility of skin fracture.	Etching	Solid, Hollow, Coated
Metal	Good biocompatibility and mechanical properties. High fracture toughness. Strong and hard to break.	High startup cost. Required post-fabrication process. May cause an allergic reaction.	Laser ablation, Etching, Injection mold	Solid, Hollow
Ceramic	Possesses chemical and compression resistance.	Low tension strength.	Micro molding, Lithography	Solid, Hollow
Polymer	Excellent biocompatibility. Low toxicity. Low cost.	Low strength.	Lithography, Injection molding, Casting, Laser ablation	Solid, Hollow, Coated, Dissolving

Methods of manufacturing microneedles [6]:

Wide varieties of technologies were adopted for manufacture of microneedles to meet the requirements of manufacturers and patients. Each technology employs different principle of making which are categorized as below.

1. **Laser Ablation**

This method utilizes a focused optical light beam to create an MN array on a substrate.

2. **Lithography**

Lithography involves transferring the master pattern of geometric shapes onto the substrate's surface.

3. **Micro-molding**

It is a process of replicating a master mold and casting it with a solution.

4. **Injection Molding**

This entails injecting molten plastic materials into a mold.

5. **Additive Manufacturing**

This is the one of the recent techniques which uses 3D Printing where the microneedles are made layer by layer. The above mentioned technologies have their own advantages and disadvantages which were tabulated in table 3. This information helps to select suitable material and type of microneedle to meet the challenges associated with it.

Table 3: Manufacturing methods of microneedles with their advantage and disadvantages [6]

Manufacturing Method	Advantages	Disadvantages
Laser Ablation	Offers quicker fabrication.	May lead to substrate (MN array) cracks or fatigue resistance. It is costly and not suitable for large-scale production.
Lithography	Enables MN production from various materials with precise geometries and smooth vertical sidewalls	It is time-consuming.
Micro-molding	Suitable for mass production, cost-effective, and allows control over the depth of penetration, drug load capacity, and mechanical behavior.	Chance of breakage during removal from mold.
Injection Molding	Ideal for mass production	Comes with a high initial cost for machine equipment and involves complex processes.
Additive Manufacturing	Customizable design.	Requires a high-quality 3D printer.

Strategies for delivery of drug with microneedles [15, 16]:

The microneedles can be made without drug meant for only disruption of the stratum corneum. The drug loading can be done in form of matrix, coating. Sometimes the drug in solution or gel form presented in hollow needles. The prominent delivery strategies employed for microneedle drug delivery are:

1. Pierce and patch
2. Coat and pierce
3. Pierce and release
4. Pierce and flow

Each of the above strategies can handle the challenges of microneedle delivery. The concept associated with the each strategy is elaborated below.

1. **Pierce and Patch**:

This method involves piercing an array of solid microneedles into the skin and then applying a drug patch at the pierced site. Drug transport across the skin can happen through diffusion or potentially through iontophoresis with the application of an electric field. Interestingly, this technique has been explored for non-invasive measurement of glucose levels by extracting interstitial fluid [16].

2. **Coat and Pierce:**

In this approach, needles are initially coated with the drug and then inserted into the skin for drug release through dissolution. The entire drug payload is coated onto the needle itself. A variation of this method, known as the dip and scrape approach, entails dipping microneedles into a drug solution and then scraping them across the skin surface to deposit the drug within micro abrasions created by the needles. However, this approach typically allows for a limited amount of drug coating (approximately 1 mg), necessitating extensive optimization for uniform coating [16].

3. **Pierce and Release:**

This strategy involves the release of encapsulated drug into the skin from microneedles made of polymers and polysaccharides that either slowly

dissolve or can be modulated using various available materials [16].

4. **Pierce and Flow**:

Here, the skin is first pierced under external pressure, allowing the drug to flow through hollow microneedles from the reservoir in the patch. This method enables the administration of a significant amount of drug. Moreover, pressure-driven delivery provides the opportunity to precisely control the flow rate for a more targeted delivery [16].

All of these approaches can be employed to administer drugs either systemically or at a localized site for targeted action. But each has the advantages and disadvantages. Each strategy with the mechanical strength, method of preparation, capacity of drug payload, the target tissue with their advantages and disadvantages are shown in the table 4 to handle the challenges associated with making of microneedle and their subsequent usage.

Table 4: The strategies of microneedles and the associated distinctive features [15]

MN types	Solid MN	Coated MN	Hollow MN	Dissolvable MN	Hydrogel-forming MN
Strategy	Pierce and patch	Coat and pierce	Pierce and flow	Pierce and dissolve	Pierce and release
Preparation Method	Featuring pointed tips for efficient skin penetration with 3D printing, dry or wet etching, laser ablation, electroplating, micro molding, etc.	Spray coating, dip coating, rolling coating based on solid Microneedles	Laser micromachining, deep reactive ion etching, lithographic molding, deep X-ray photolithography, wet chemical etching, micro fabrication	Solvent casting, droplet-born air blowing, laser machining, hot embossing, microinjection molding, ultrasonic welding, lithography, drawing lithography, 3D printing	Micro molding, lithography, etc.
Drug Loading Capacity	No drug loading	Limited loading capacity, typically less than 1 mg	Ample loading capacity, ideal for high molecular weight substances	versatile loading capability, accommodating both small and large amounts of drugs	versatile loading capability, accommodating both small and large amounts of drugs
Mechanical Property	Higher mechanical properties	High mechanical strength	moderately low mechanical strength	Low mechanical strength	Low mechanical strength
Ideal Targeted Tissue	Penetrate the deep epidermis or the	Able to reach the deep epidermis or	Able to reach the deep epidermis or	Able to reach the deep epidermis	Able to reach the deep epidermis

	superficial dermis; joint cavity, bone surface, and muscles	the superficial dermis.	the superficial dermis.		
Advantages	These microneedles offer the potential to synergize with external forces such as iontophoresis and sonophoresis	They share the benefits of solid microneedles, providing convenience and improved drug stability, thereby mitigating exposure risks.	These microneedles aim to decrease insertion frequency while offering a heightened drug loading capacity. They enable TDD with a quantitative, precise dosage in a speed-controlled manner, holding promise for delivering bio-macromolecules.	They exhibit excellent biocompatibility, are easy to fabricate and utilize, boast low production costs, generate no waste post-use, and are generally well-accepted by patients.	With a relatively high drug-loading capacity and the ability to modulate drug release rates, these microneedles maintain high biocompatibility, leaving no residual substances in the skin after use.
Disadvantages	Need two steps to accomplishment, fragile and prone to breakage, low biocompatibility	Low capacity; insertion affected by the coating; drug retention caused by friction	The preparation process is intricate and costly, and the resulting product is fragile, susceptible to breakage and clogging. External forces, such as syringe plunger force, pressure differences, and spring elasticity, are necessary.	The material demands are high, with both sufficient mechanical strength and solubility.	Lower mechanical strength, posing a relatively higher risk of infection.

The microneedle molds are made of different materials and designs. These molds should be made of inert, non-leachable materials for reproducibility and accuracy of microneedle

making. The microneedles made by using different materials and strategies are need to tested at in-process and finished product stages.

Evaluation of Microneedles:

Various physicochemical characteristics such as particle size, polydispersity index, viscosity, and zeta potential are assessed during loading of drugs at pre-formulation stage, depending on the microneedle formulation. Tests include drug release, adhesion, and permeation, along with stability studies under different conditions are necessary for finished products. Additional tests like solubility studies, drug content analysis, in-vitro release tests, and biocompatibility studies are also conducted but not restricted to above for evaluation of designed microneedles [5]. Some critical parameters evaluated are mention below.

Dimensional Evaluation [5]:

Needle geometry, including tip radius, length, and height, is evaluated using methods such as optical or electrical microscopy. Advanced techniques like Scanning Electron Microscopy (SEM) and confocal laser microscopy provide high-resolution images for quality control and better understanding of needle geometry [5].

Mechanical Characterizations [6]:

This evaluation helps to detect mechanical strength of prepared microneedles to withstand different forces during making, transportation, storage and usage.

i. **Axial Force:**

The axial force test is a widely employed method, involving the application of force to the needle tips vertically and to the base of the MN array. This mechanical test holds significance as it aims to ascertain the failure force of the needles. Understanding the measurement of the needles' failure force provides crucial information, often referred to as the safety point, offering an approximate range of the needle insertion force [6]

ii. **Transverse Force:**

In the transverse force test, a force is applied parallel to the MN base plate along the y-axis. The skin's uneven surface may cause transverse bending of the MN, underscoring the significance of measuring the transverse fracture force. Additionally, when considered alongside the axial force, the transverse force provides a comprehensive understanding of the microneedles mechanical properties and aids in predicting its bending behavior during insertion. A constraint of this test is the need for manually aligning the metal probe with a specified length of the microneedle [6].

iii. Insertion Test:

The insertion test holds greater importance and distinction from the axial force test, as the latter does not provide as accurate a measurement as the former. Moreover, this test specifically targets various skin subjects, including pigs, rats, and humans. One notable advantage of employing microneedles lies in their capacity to load drugs and effectively deliver them to the skin [6].

While numerous mechanical tests aim to simulate the fracture force of the needle, it remains crucial to validate these results through real skin experimentation6. The description, significance and limitation of each test is places in table 5 for the selection suitable measurement method for different types of microneedle.

Table 5: Microneedles Mechanical Characterization [6].

Mechanical Characterizations	Description	Importance	Limitation
Axial Force	Apply force into the tip of the needle in the x-axis	Assess the failure force of the tip needle	Simulation (not accurate)
Transvers Force	Apply force into the MN base in the y-axis	Assess the failure force of the needle base	Simulation (not accurate)

Insertion Test	Insert the needles into rat, pig, or human skin.	Assess the actual force applied to the skin, and evaluate the drug release capability..	This necessitates access to skin resources.

In-vitro Skin Permeation Studies:

Permeation of drugs through the skin is assessed using a diffusion cell apparatus. Experiments are often conducted on pig ear skin mounted between the receptor and donor compartments, comparing cumulative permeation profiles of microneedle-treated and untreated skin [17].

In-vivo Animal Model Studies:

Hairless rats, under suitable anesthesia, are commonly used for in-vivo studies. Parameters such as trans-epidermal water loss (TEWL) are measured before and after microneedling using devices like the Delfin Vapometer [17].

The microneedles prepared and evaluated are applied at different diseased states. This may for local or systemic treatments for normal patients or to treat the unconscious/agitated patients with behavioral abnormalities. Various applications of microneedle delivery systems are given below.

Applications of Microneedles:

1. Drug Delivery:

Microneedles have been applied for drug delivery since the introduction of solid silicon microneedles in 1998. Various types, including dissolvable patches and coated microneedles, have been used to deliver drugs such as human growth hormone, caffeine for weight control, salmon calcitonin, protein antigens, and a range of other pharmaceuticals. These delivery methods have been demonstrated in various skin types, including mice, pigs, and humans [16].

2. Oligonucleotide Delivery:

Microneedles offer a promising approach for delivering oligonucleotides, challenging molecules due to their short DNA or RNA nature. Solid microneedles made of stainless steel or titanium, along with techniques like poke with patch and iontophoresis, have shown increased drug delivery efficiency compared to intact skin [18, 19].

3. Vaccine Therapy:

Vaccine therapy involves the use of microneedles for effective delivery, providing active acquired immunity against specific diseases. A vaccine typically consists of a killed or weakened form of disease-causing microorganisms, their toxins, or surface proteins. This approach stimulates the body's immune system, offering protection against future encounters with the targeted microorganisms [20, 21]. The dissolvable microneedle (MN) emerges as a versatile tool for vaccine delivery, replacing traditional hypodermic injection needles. In contrast to other types of microneedles, dissolvable microneedles exhibit biocompatibility, durability, scalability, and generate no bio-hazardous waste [22].These Microneedles have successfully delivered vaccines for various diseases, including malaria, diphtheria [23], influenza [24], Hepatitis B [25], HIV [26], and polio [27]. In a separate study, a microneedle coated with a DNA vaccine encoding the hepatitis C virus protein demonstrated effective priming for specific cytotoxic T lymphocytes (CTLs) in mice [28]. Additionally, a coated microneedle carried the influenza virus antigen, showcasing its potential in vaccination applications for mice [29]. Hollow Microneedles have been employed to deliver the anthrax recombinant protective antigen vaccine to a rabbit, offering an alternative to regular injection [30]. Evaluation of a hollow microneedle for vaccination against plague in a mouse model yielded promising results [31]. A clinical trial involving humans utilized hollow microneedles for influenza vaccination, showing comparable

immune system responses to intramuscular injection [32].

4. **Hormone Delivery:**

Insulin, a vital peptide hormone for lowering blood sugar levels, has shown improved efficacy when delivered through microneedles [34]. Li et al fabricated solid microneedles and investigated their impact on blood glucose levels in diabetic mice upon insulin delivery [35]. The results revealed a 29% reduction in blood glucose levels after 5 hours, confirming the improved permeability of insulin through the skin using microneedles.

5. **Cosmetics:**

The cosmetic industry is increasingly exploring microneedle applications for skin enhancement, blemish, and scar treatment. Microneedles have been utilized to deliver cosmetic active ingredients like ascorbic acid, eflornithine, and retinyl retinoate [36]. Incorporating melanin into phosphatidylcholine liposomes (nanoliposomes) demonstrated increased solubility in lipids, with more pigment reaching deep near hair structures upon application using an e-roller [37].

6. **Pain Therapy:**

Polymeric microneedles loaded with meloxicam were prepared, showing approximately 100% drug release in 60 minutes. In-vitro permeation studies indicated a 63.37% drug deposition and an improved transdermal flux of 1.60 µg/cm2/hr, resulting in a 2.58 times increase compared to the free drug solution [38].

7. **Ocular Delivery:**

For treating posterior segment indications, iontophoresis was employed to deliver nanoparticles through the suprachoroidal space. When combined with microneedles, over 30% of nanoparticles were successfully delivered to the eye's posterior segment [39]. The patient compliance and irritation concerns are to be considered with due care for ocular administration.

8. **Cancer Therapy:**

Microneedles have been explored for delivering various anticancer drugs. Self-degradable microneedles investigated for melanoma treatment delivered anti-PD-1 (aPD1) in a sustained manner. A topical cream containing 5-fluorouracil, used to treat basal cell carcinoma, demonstrated enhanced permeability (up to 4.5 times) when applied on the skin treated with solid microneedles. This approach significantly inhibited tumor growth, affirming improved efficacy using microneedles [40, 41].

Combination approaches with microneedle delivery:

Microneedles can be combined with additional enhancement methods to enhance transdermal drug delivery.

1. **Microneedles in combination with Iontophoresis:**

The transdermal iontophoresis technique involves applying a physiologically acceptable low electric current (typically less than 0.5 mA/cm²) to the skin, functioning on the principle of "like repels like." This process promotes the transfer of charged and polar substances across the stratum corneum of the skin [42]. By incorporating iontophoresis with microneedles, the resulting barrier disruption expands the potential for administering a variety of drugs transdermally. Moreover, this approach enables controlled drug delivery by managing the applied electric current [43].

2. **Microneedles in combination with Sonophoresis:**

Sonophoresis encompasses the application of ultrasound, with a frequency ranging from 20 kHz to 10 MHz and intensity up to 3 W/cm². This induces perturbation of the lipid bilayer, causing a change in the lipid arrangement of the stratum corneum and forming cavitation, ultimately enhancing drug transportation across the skin. The frequency of ultrasound can be controlled to manage drug permeation, with an increase in

sound frequency resulting in a substantial increase in skin perturbation. Combining sonophoresis with microneedles achieves a synergistic effect on molecule permeation through the skin [44, 16].

3. **Microneedles in combination with Electroporation:**

Electroporation involves the application of a high-voltage, short-duration current (typically 50-1000 V/cm) to induce transient, localized perturbation of the lipid bilayer. This process leads to structural rearrangements of the cell membrane due to the electric fields produced during current application. The resulting aqueous pores act as pathways, providing a local driving force for facilitating the transport of molecules across the stratum corneum. In-vitro electroporation of the stratum corneum utilizes a trans-membrane potential of up to 1 kV for durations ranging from 10 ms to 500 ms [44].

4. **Microneedles in combination with Vibratory Actuation:**

Achieving precise control of the insertion force during microneedle penetration into the skin is crucial, ensuring it does not exceed the fracture force of the microneedle. Consideration of both structure rigidity and miniaturization of microneedles is essential, and a satisfactory balance between these factors must be maintained. Vibration actuation, causing tissue damage through fluid cavitation and thermal damage due to frictional interaction, can be combined with microneedles to reduce the insertion force [16].

5. **Microneedles in combination with Vesicles:**

Numerous studies have explored the use of lipid vesicles for transdermal drug delivery. However, controversies surround their delivery mechanism, often associated with the accumulation of vesicles and encapsulated drugs in the stratum corneum due to their limited ability to penetrate the skin deeply. This renders them less valuable as carriers for transdermal drug delivery [16].

6. **Microneedles in combination with Microparticles and Nanoparticles [46]:**

The versatility of microparticles and nanoparticles for the effective and targeted release of various therapeutic agents to diverse anatomical regions positions them as promising candidates for drug carriers or vehicles in topical and transdermal drug delivery. Microparticles and nanoparticles, distinguished by their size (micrometric and nanometric, respectively), biopharmaceutical properties, and therapeutic applications, can be composed of biodegradable polymers or lipid materials. The penetration of nanoparticles through human skin relies on factors such as nanoparticle size, shape, and material properties. Nanospheres or nanocapsules of varying sizes can be obtained by altering the materials used and the preparation method. Reducing the size of nanoparticles dramatically increases cellular uptake, enhancing transdermal drug delivery. The combination of microneedles with these nanoparticulate systems may create microchannels sufficient to deliver drug-loaded nanostructures into the skin, addressing the challenge of delivering microparticles into the skin. Even relatively large microparticles can be delivered into the skin by utilizing appropriate microneedle design and insertion methods. However, a potential limitation of controlled-release microneedles is that they may administer a limited dose due to the small size of both the microneedles and the encapsulated drug, likely to be less than 1 mg [46].

7. **Microneedles in combination with Micro Pumps:**

The conjunction of microneedles with micro pumps offers precise drug delivery control by regulating flow rate and pressure. This integration ensures the controlled delivery of concentrated drug solutions as required. Such combinations, incorporating micro valves and micro-pumps, have been employed to develop integrated systems

capable of controlling fluid withdrawal for medical analysis and delivering drugs in response to metabolite levels [47].

8. Pocketed and Grooved Microneedles:

Modifying the surface of microneedles can be implemented to enable targeted drug delivery to specific depths in the skin and facilitate the loading of a greater amount of drug onto the microneedle. This can be achieved by applying a protective coat or a second drug coat on the same microneedles after filling the first part in the pockets. Pocketed microneedles, identified as such due to their design, can be achieved by creating microneedles with one or more holes cut through the center. Moreover, grooved microneedles, designed to accommodate a larger drug load, offer potential for improving drug delivery [48, 49]. The advancement in the technological front, some drugs are loaded in microneedles and available in market.

Marketed products of Microneedles:

The table 6 briefs the availability of microneedles in market with their brand names, manufacturer, loaded drug and the disease states for which they are meant for.

Table 6: Transdermal products featuring microneedle technology available in the market [11, 80].

Brand name	Manufacturer	Drug	Application
Microhyala®	CosMED Pharmaceutical Ltd. Japan	Hyaluronic acid, Collagen	Treat wrinkles
Corplex™	Corium International Inc. USA	Donepezil & Corplex memantine	Alzheimer's disease
Dermaroller®	Derma spark, Canada	Minoxidil, Hyaluronic acid etc.,	Treat stretch marks, acne, spots, hair loss.
V-Go	Valeritas Inc. USA	Basal bolus insulin	Type-2 diabetes
Adhesive dermally applied Microarray	Zosano pharma	Zolmitriptan	Migrane
JewelPUMP™	Debiotech, Switzerland	Insulin	Type-1, Type-2 Diabetes

So many patents were also published with innovations in microneedle delivery. The table 7 shows the published invention, name of applicant along with patent number for further exploration and continual reaserch.

Table 7: Innovations within micro-needling technology that are protected by patents.

Sr No	Invention	Patent No	Applicant	Ref
1	Microneedle patches and methods	US 11,590,330B2	Georgia Tech Research Coorporation, Atlanta	(D McAllister et al.,2023) [50]
2	Microneedle for promoting wound healing	CN114668778A	Southwest National University	(Yu Yunlong et al., 2022) [51]
3	Microneedle array with an interlocking feature	WO2022197452A2	University Washington State [US]	(Chen Kuen Ren, et al., 2022) [52]
4	Microneedles and methods for treating the skin	WO2022183126A1	Brigham and Women's Hospital Inc [US], Massachusetts Inst Technology [US]	(Artzi Natalie et al., 2022) [53]
5	Microneedle patch system for transdermal drug delivery	WO2022177205A1	Nat University Gyeongsang Iacf [KR]	(Rhee Yun Seok et al.,2022) [54]

6	Microneedle for treating psoriasis through percutaneous delivery of lipidosome and preparation method of microneedle	CN114432230A	Zhejiang Industrial University	(Yan Qinying et al., 2022) [55]
7	Preparation method of a hollow microneedle patch, hollow microneedle patch and injection device	CN114344699A	University Sichuan	(Gou Maling et al., 2022) [56]
8	A method for manufacturing a microneedle	KR102427901B1	Daewoong Therapeutics [KR]	(Kang Yoonsik et al., 2022) [57]
9	Dissoluble microneedle containing active microalgae, microneedle patch, preparation method and application	CN114557954A	Australia University	(Wang Ruibing et al., 2022) [58]
10	Microneedles to deliver therapeutic agent across membranes	US2022176096A1	University Columbia [US	Aksit Aykut et al., 2022) [59]
11	Drug delivery using microneedle arrays	US2022273926A1	University Nebraska [US]	(Tamayol Ali et al., 2022) [60]
12	Microneedle arrays and methods for making and using	US2022111189A1	Johnson and Johnson Consumer Inc [US]	(Alary Marc et al.,2022) [61]
13	Methods and devices for drug delivery to ocular tissue using microneedle	US10905586B2	Emory University, Georgia Tech Research Corp	(Mark Prausnitz et al., 2021) [62]
14	Devices and methods for enhanced microneedle penetration of biological barriers	US 6,743,211 B1	Georgia Tech Research Corporation (University System of Georgia)	(Henry et al., 2004) [63]
15	Microneedle drug Delivery Device	US-6611707-B1	Georgia Tech Research Corporation	(Prausnitz et al., 2003) [64]

Wide research has been reported in journals which already explored various excipients suitable for the active pharmaceutical ingredients loaded in different types of microneedles. The data was segregated and compiled in table 8, as ready reference to meet the challenges encountered during the microneedle making and usage.

Table 8: Typical drugs and excipients used for different types of microneedles published in research Articles

Sr No	Title of research work	Drug used	Excipients used	Types of MN
1	Design and Evaluation of Dissolving Microneedles for Enhanced Dermal Delivery of Propranolol Hydrochloride	propranolol hydrochloride	hyaluronic acid and polyvinyl pyrrolidone	Dissolving microneedles

2	Formulation and evaluation of heparin Microneedle transdermal patch	Heparin	PVA and PVP	Dissolving microneedle
3	Anastrozole Nanoparticles for Transdermal Delivery through Microneedles: Preparation and Evaluation	Anastrozole	Kollicoat MAE100-55, PVA	Dissolving microneedles
4	Preparation and Evaluation of Microneedles-mediated Transdermal Delivery of Montelukast Sodium Nanoparticles	Montelukast Sodium	Eudragit L100, PVA, PVP-K 30, Gantrez S97, Sodium hyaluronate	Dissolving microneedles
5	Formulation and Evaluation of Iornoxicam as Dissolving Microneedle Patch	Iornoxicam	PVA, PVP, PEG 400	Dissolving Microneedle
6	Formulation and Evaluation Coated Microneedles for the Treatment of Hairless	Minoxidil	Eudragit E 100, Propylene glycol	Coated Microneedles
7	Formulation of hydrophobic peptides for skin delivery via coated microneedles	Hydrophobic peptides	PVA2000	Coated microneedles
8	Formulation of Microneedles Coated with Influenza Virus-like Particle Vaccine	Influenza VLP Vaccine	CMC	Coated Microneedles
9	Effective humoral immune response from a H1N1 DNA vaccine delivered to the skin by microneedles coated with PLGA-based cationic nanoparticles.	H1N1 DNA vaccine	poly lactic-co-glycolic acid/polyethyleneimine (PLGA/PEI), Stainless steel	Coated Microneedles
10	Evaluation of fabricated Solid microneedles as smart approach for transdermal drug delivery system of Astaxanthin.	Astaxanthin	HPMC, Eudragit e 100, PEG	Solid microneedles
11	Solid Microneedles for Transdermal Delivery of Amantadine Hydrochloride and Pramipexole Dihydrochloride.	Amantadine Hydrochloride and Pramipexole Dihydrochloride	0.1 M isotonic phosphate buffered saline (PBS), Stainless steel microneedle rollers	Solid microneedles
12	Hollow microneedle-mediated intradermal delivery of model vaccine antigen-loaded PLGA nanoparticles elicits	ovalbumin (OVA)	PLGA	Hollow microneedle

	protective T cell-mediated immunity to an intracellular bacterium,			
13	Intradermal delivery of vaccine nanoparticles using hollow microneedle array generates enhanced and balanced immune response,	ovalbumin (OVA) and TLR agonists imiquimod and monophosphoryl Lipid A	PLGA	Hollow microneedle
14	Smart Microneedle Fabricated with Silk Fibroin Combined Semi-interpenetrating Network Hydrogel for Glucose-Responsive Insulin Delivery	Insulin	Silk fibroin (SF) and phenylboronic acid/acrylamide	Hydrogel forming Microneedles
15	Microarray needles comprised of arginine-modified chitosan/PVA hydrogel for enhanced antibacterial and wound healing potential of curcumin	Curcumin	chitosan/PVA	Hydrogel forming Microneedles

CONCLUSIONS:

Microneedles are a new emerging technique for delivering drugs to the systemic circulation, bypassing the stratum corneum, which acts as a barrier to drug delivery through the skin. Microneedles and microneedle molds can be fabricated using different materials such as metals, silicon, ceramics, and polymers. Different types of microneedle types are used to cater different release mechanisms. The evaluation of microneedles includes dimensional evaluation, mechanical characterizations, in-vitro skin permeation studies, and in-vivo animal model studies. Microneedles can be applied to delivery of wide categories of drugs belonging to oligonucleotides, vaccines, hormones, cosmetics, common pain management to specific cancer therapy. Microneedles can also be combined with additional enhancement methods like iontophoresis, sonophoresis, vibratory actuation, vesicles, microparticles, nanoparticles, micro-pumps, and pocketed and grooved microneedles to enhance transdermal delivery, patient compliance and specific needs with good mechanical strength to permeate the skin and release the drug. Vast number of patents, research articles and different marketed products showcased the effectiveness of microneedles. With the advent of nanotechnology and 3D printing, the challenges can be met with ease for making of the microneedles as a promising delivery system in recent times.

CONFLICT OF INTEREST

No conflict of interest.

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