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Microneedle as a Transdermal Drug Delivery System

Snehal Y. Ingole*, Pranita P. Panchal, Pradnya D. Muneshwar, Mahaveer R. Topare

Department of Pharmaceutics, SVP College of Pharmacy, Hatta. Dist., Hingoli, Maharashtra-431705, India.

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ABSTRACT: Skin, as an absorptive organ, plays a pivotal role in transdermal drug delivery systems. Among contemporary approaches, the microneedle method emerges as an innovative means to efficiently deliver compounds through the skin. Consisting of dozens to hundreds of micron-sized needles, a microneedle patch boasts various structures and advantages derived from its specialized and intelligent designs. In comparison to traditional transdermal delivery methods, microneedles offer distinct benefits such as minimal invasiveness, painlessness, convenience, and enhanced patient compliance. Over time, the field of microneedles has rapidly advanced, with researchers categorizing it into four major types: solid microneedles (SMNs), hollow microneedles (HMNs), dissolving microneedles (DMNs), and coated microneedles (CMNs). Each type presents unique advantages based on its specific properties and designs. Psoriasis, characterized as a polygenic chronic dermatological disease with no definitive cure, necessitates treatment focused on symptom management. The conventional therapeutic arsenal encompasses a diverse array of modalities including topical drugs, systemic medications, and physical therapy. However, the existing limitations in drug delivery underscore the pressing demand for novel delivery methods in psoriasis management. Consequently, this review aims to furnish a comprehensive discourse on microneedles, elucidating their progress in the treatment of psoriasis and addressing pertinent clinical challenges.

Corresponding author:
Mr. Snehal Y. Ingole
SVP College of Pharmacy,
Hatta. Dist., Hingoli,
Maharashtra-431705, India.
E. Mail ID: panchal.pranita@gmail.com

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INTRODUCTION:

Anatomy and Physiology of the Human Skin [1]:

The skin, the body's largest organ, spans approximately 20 square feet in total area. Beyond its sheer size, skin serves as a vital shield against microbes and environmental factors, aids in regulating body temperature, and enables the perception of sensations such as touch, heat, and cold.

Human skin consists of three well defined but mutually dependent tissues;

- The stratified, vascular, cellular epidermis.
- Underlying dermis of connective tissues.
- Hypodermis.

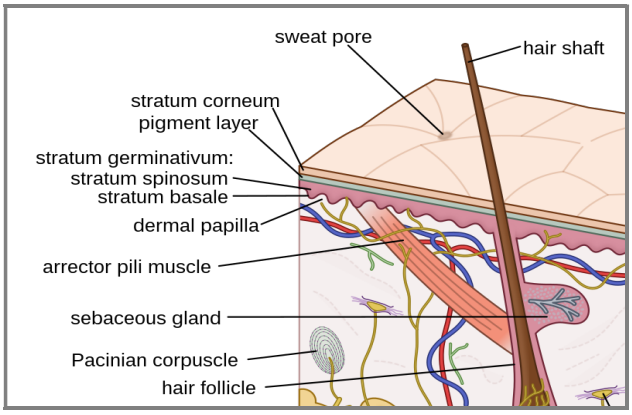

Fig 1. Anatomy of human skin.

***Epidermis*:**

The epidermis, a multi-layered structure, exhibits variation in thickness across different regions of the body, ranging from 0.06 mm on the eyelids to 0.8 mm on the palms and soles. It comprises two main layers: the outer stratum corneum and the viable epidermis.

Stratum Corneum (Horny Layer):

Also referred to as the horny layer, the stratum corneum serves as the outermost protective barrier of the skin. When dry, it measures approximately 10 µm in thickness, but expands to several times this thickness when hydrated. Composed of 10 to 30 layers of dead, keratinized cells called corneocytes, the stratum corneum can be penetrated by drug molecules through three primary routes: transcellular, intercellular, and transfollicular pathways.

***Viable Epidermis*:**

Beneath the stratum corneum lies the viable epidermis, which varies in thickness across different body regions. From the outermost layer inward, it comprises several layers including the stratum granulosum, stratum lucidum, stratum spinosum, and the stratum basale. The basal layer, where mitosis occurs, continually generates new cells to replace the shed corneocytes, thus maintaining the integrity of the epidermal barrier.

***Dermis*:**

The dermis, measuring 3 to 5 mm in thickness, is primarily composed of a matrix of connective tissue containing blood vessels, lymph vessels, and nerves. It plays a crucial role in regulating body temperature through its cutaneous blood supply, which provides nutrients and oxygen to the skin while removing pollutants and waste. Molecules that penetrate the skin barrier typically reach capillaries located approximately 0.2 mm from the skin's surface, highlighting the importance of the dermal blood supply in transdermal penetration.

***Hypodermis*:**

Supporting the dermis and epidermis is the hypodermis, also known as subcutaneous fat tissue. Functioning as a reservoir for fat storage, this layer provides mechanical protection, nutrient support, and assists in temperature regulation. Additionally, it facilitates the connection of major blood vessels and nerves to the skin, and may contain sensory organs for pressure detection.

Drug Delivery System:

There are many ways to deliver drugs into the human bo dy, including oral, parenteral, inhalation, transdermal an d others. The oral method is the oldest, easiest and most suitable for the patient. Long
Term use has side effects because the oral route affects v ital organs such as the liver and kidneys. Parenteral meth ods deliver hydrophobic drugs to the body through intra muscular, subcutaneous and intravenous routes. Since pa renteral administration is a rapid drug administration met hod, it is the best choice for emergency drug administrati on [2]. The inhalation method is designed to deliver medi cation directly into the lungs. This approach is painless, comfortable, and is designed for respiratory diseases or s ome drugs that have been shown to be effective across th e airblood barrier [3]. Finally, the transdermal drug delive ry method (TDD) focuses on the delivery of drugs throu gh the skin layer. TDD will also provide a better alternat ive for proteins/peptides/macromolecules that bypass the digestive system and provide better bioavailability. TD D can also deliver potent drugs without directly affectin g the body and provides a mechanism for sustained deliv ery [4].

Transdermal Drug Delivery (TDD) [5]:

Transdermal drug delivery involves the application of drugs directly to the skin, facilitating their penetration through the stratum corneum, epidermis, and dermis. Once the drug reaches the dermal layer, it becomes available for absorption into the bloodstream. This method focuses on controlling drug diffusion through the skin to achieve systemic delivery.

***Advantages of TDD*:**

Transdermal drug delivery offers several advantages over alternative methods. It enables precise delivery of drugs to the bloodstream in a sustained and controlled manner, ensuring the desired dosage is achieved. Additionally, TDD allows for the administration of

hydrophilic drugs and utilizes sweat glands as an alternative mechanism for drug delivery.

***Role of Microneedles*:**

Microneedles serve as physical enhancers, creating disruptions in the stratum corneum to facilitate drug delivery through the skin. Once the stratum corneum is breached, drugs can diffuse into the skin and reach the interstitial fluids. Microneedles address various challenges associated with transdermal delivery, including needle phobia, sustained delivery requirements, and issues with repetitive injections into collapsing veins. As a result, microneedles offer a valuable alternative method to overcome these challenges and enhance the effectiveness of transdermal drug delivery.

History of Microneedle [2]:

In the last few years, the possibility of microneedle tech niques for transdermal delivery of drugs has been widely seen. Scientists have used microneedle applications fro m scratch by creating different types of microneedles an d using them to treat various diseases. Various functions have been identified due to differences in properties suc h as structure and the relationship between the carrier an d the substrateofcourse, different types of microneedling can provide unique results. The advantages and disadva ntages are explained below respectively.

The evolution of microneedle technology spans over a century, progressing from rudimentary designs to sophisticated modern implementations. Dr. Ernst Kromayer, a German dermatologist, pioneered early microneedle concepts in 1905 by using motor-powered dental burs to treat various skin conditions. Subsequent advancements in the 1920s, highlighted by Chambers' needle injection into an egg's nucleus, laid foundational knowledge for microneedle development.

In the 1960s, interest in transdermal drug delivery surged, prompting investigations into needle-based skin penetration methods. However, it was not until the 1970s that the formal concept of microneedles emerged, with practical demonstrations not occurring until the 1990s. A significant milestone in transdermal drug delivery was reached in 1979 with the approval of the first transdermal system for motion sickness treatment.

In 1994, Orentreich introduced subcision surgery, employing hypodermic needles to release fibrous strands beneath the skin, targeting cutaneous defects responsible for scars and wrinkles. The pivotal breakthrough came in 1998 with the proposal of microfabricated silicon microneedles for enhanced drug delivery across the skin. This seminal work sparked widespread research in the field, leading to the exploration of various materials and fabrication techniques.

By 2004, microneedle arrays were successfully utilized for transdermal drug delivery, catalyzing further advancements in fabrication methods and materials exploration. Solid, coated, hollow, dissolvable, and hydrogel-forming microneedles emerged as distinct types, each offering unique advantages. Techniques such as laser ablation, photolithography, and micro-injection molding became integral to microneedle production.

The first reported use of dissolvable microneedles for transdermal drug delivery occurred in 2005, marking a significant milestone in the field. Clinical trials utilizing microneedles began in earnest, with 43 trials completed by 2021. Recent developments in additive manufacturing have revolutionized microneedle fabrication, enabling cost-effective production through 3D printing technology. This innovation opens doors to custom-built, large-scale manufacturing of microneedles, ushering in a new era of device fabrication and therapeutic possibilities.

Microneedle Composition and Function:

Microneedles are composed of two essential components: the invasive and supporting elements. The invasive part consists of an array of hundreds of needles ranging in length from 25 to 2000 microns. These needles are designed to puncture the skin's stratum corneum (SC) to create micron-sized channels. Meanwhile, the supporting component is a base plate that provides uniform mechanical support for the sharp needle tips, enabling them to penetrate through the SC. These two parts either can be made from the same material or fabricated separately using distinct raw materials before being securely bonded together. The primary objectives of a microneedle patch (MNP) are to generate micron-sized channels in the skin and to function as a drug delivery system. The functionality of MNPs is contingent on their design and necessitates adequate hardness, mechanical strength, and toughness. Signs of MNP failure include bending, deflection, or fracture of needle tips. Hence, careful selection of suitable materials and MNP types is imperative to ensure their efficacy and reliability.

Mechanism of Drug Delivery [6-8]:

While traditional topical drug delivery relies on passive diffusion, the microneedle drug delivery system involves

temporary disruption of the skin. A microneedle device is created by arranging hundreds of microneedles in arrays on a small patch, akin to conventional transdermal patches available in the market. These microneedles penetrate the stratum corneum, effectively circumventing the barrier layer. Once the microneedles breach the skin, the drug is deposited directly into the epidermis or upper dermis layers. Subsequently, the drug enters the systemic circulation, eliciting a therapeutic response upon reaching the target site. This targeted delivery mechanism enhances drug absorption and efficacy while minimizing systemic side effects. Overall, microneedle technology presents a promising approach for efficient and controlled drug delivery through the skin.

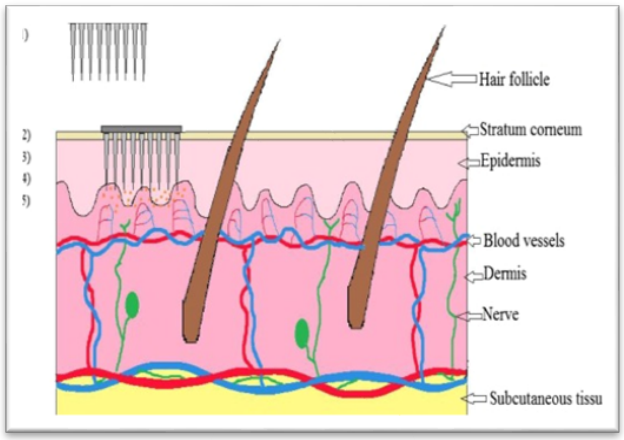

Fig 2. Drug delivery mechanism of microneedle machine: (1) Microneedle device and drug solution (2) Device placed on the skin (3) Temporary damage to the skin; 5) Delivery of medication to the workplace.

Dimensions of Microneedles [9]:

The dimensions of microneedles can be tailored based on the specific type of microneedle and the materials utilized in their fabrication. Considering that the epidermis measures up to 1500 µm in thickness, microneedles with a length of up to 1500 µm are adequate to facilitate drug delivery into the epidermis. However, needles with greater length and diameter may penetrate deeper into the dermis, potentially causing nerve damage and discomfort. Typically, microneedles range from 150 to 1500 microns in length, 50 to 250 microns in width, and have tip thicknesses of 1 to 25 microns. As previously mentioned, the primary objective of a microneedle device is to create micron-sized pathways for drug transport, necessitating the needles' diameter to be maintained within a few micrometres. Additionally, microneedle tips are available in various shapes including cylindrical, triangular, pointed, pentagonal, octagonal, and many others, offering flexibility in design to suit different applications and requirements.

Materials Utilized in Microneedle Fabrication:

The fabrication of microneedles is driven by the necessity to achieve skin penetration without breakage or deformation. To address this challenge, several factors including material selection, manufacturing methods, and design considerations are taken into account. Various materials have been explored and employed in the fabrication of diverse types of microneedles. These materials include:

***Silicon* [10]:**

Silicon possesses an anisotropic nature with a crystalline structure, exhibiting different elastic moduli (ranging from 50 to 180 GPa) depending on the alignment within the crystal lattice. Its flexibility enables the production of needles in various sizes and shapes, making it a versatile material choice. Silicon substrates can be precisely manufactured and enable batch production. However, the cost of silicon and its complex fabrication process limit its widespread use in microneedle production. Moreover, concerns about biocompatibility arise due to silicon's brittleness, which may lead to fragment retention in the skin, potentially causing health issues.

***Metal* [11].**

Common metals utilized include stainless steel, titanium, palladium, nickel, and palladium-cobalt alloys. These metals exhibit excellent mechanical properties and biocompatibility. Unlike silicon, metals are less prone to breakage, making them more suitable for microneedle production. Stainless steel was among the first metals employed in microneedle fabrication, while titanium serves as a viable alternative due to its desirable properties.

***Ceramic*:**

Ceramic materials, such as alumina, offer superior chemical properties and compression resistance [13]. However, alumina possesses lower tensile strength compared to other materials. Other ceramics like calcium sulfate dihydrate and calcium phosphate dehydrate have also been utilized. Fabrication techniques involving micro-molding enable cost-effective production of ceramic microneedles, although

studies have shown instances of fracture upon manual application to the skin [12-15].

***Polymer*:**

Polymers present a promising alternative for microneedle fabrication, offering excellent biocompatibility, low toxicity, and cost-effectiveness. However, polymers generally exhibit lower mechanical strength compared to silicon and metals. They are commonly employed in the production of dissolvable and hydrogel-forming microneedle arrays, with various types including poly (methyl methacrylate) (PMMA), polylactic acid (PLA), poly (carbonate), polystyrene, and SU-8 photoresist being utilized [2].

***Silica Glass*:**

Silica glass allows for the production of varying geometries on a small scale. While physiologically inert, silica glass is brittle, posing challenges in fabrication.[16] Borosilicate glass, composed of silica and boron trioxide, offers increased elasticity. However, glass microneedles are primarily used for experimental purposes due to limitations in commercial viability and efficiency in fabrication processes [16, 17].

Types of Microneedle:

***Solid Microneedles*:**

Solid microneedles are designed to penetrate the stratum corneum, enhancing drug delivery to the dermis to improve bioavailability and kinetic transport across the skin. They are particularly suitable for vaccine delivery, offering longer-lasting effects and robust antibody responses compared to intramuscular delivery. Solid microneedles boast ease of manufacture, superior mechanical properties, and sharper tips compared to hollow microneedles. They can be fabricated from various materials including silicon, metals, and polymers [2].

***Hollow Microneedles*:**

Hollow microneedles feature an empty internal space filled with drug dispersion or solution and have holes at the tips. Upon insertion into the skin, the drug is deposited directly into the epidermis or upper dermis layer. They are commonly used for administering high molecular weight compounds such as proteins, vaccines, and oligonucleotides. Adjustments to the drug flow rate and release pressure are possible, making them versatile for different administration requirements. Hollow microneedles can accommodate larger drug doses and offer options for maintaining a constant flow rate, although increasing the bore size may compromise strength and sharpness. Various fabrication techniques have been employed to develop hollow microneedles, with examples including silicon-based substrates and fused silica microneedles [10].

***Coated Microneedles*:**

Coated microneedles consist of solid microneedles coated with a drug solution, carrying a smaller amount of drug depending on the thickness of the coating layer [18]. Successful drug delivery using coated microneedles relies on the ability to reliably coat a controlled drug layer onto the microneedles. While coated microneedles offer rapid drug delivery to the skin, there is a concern regarding remnant drug at the needle tip potentially causing infection. However, they have demonstrated similar vaccine delivery efficacy compared to intradermal and intramuscular routes [2, 18].

***Dissolving Microneedles*:**

Dissolving microneedles, introduced in 2005 [20], offer promising characteristics such as rapid release of macromolecules and ease of drug administration through a one-step application process. Upon insertion into the skin, the dissolvable microneedles release their drug load, which then diffuses easily through dissolution of the needle tip [20]. Water-soluble materials are commonly used for dissolvable microneedle fabrication, typically produced using the micro-mold method. Despite their advantages, dissolving microneedles may encounter challenges such as incomplete insertion and delayed dissolution, requiring technical expertise in design and production [19, 20].

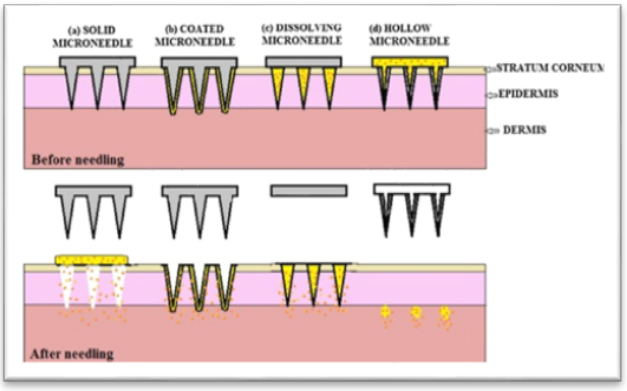

Fig 3. Different types of microneedles.

- Solid microneedles are used in skin treatment by pat ch poking method.
  Coated microneedles use the coating and poking met hod to coat the solution on the surface of the needle.

- Dissolving microneedles are made of biodegradable polymers.
- Hollow microneedles are filled with solution and the drug is inserted into the dermis [16].

Advantages of MN [21,22,1]:

- Bypasses hepatic first-pass metabolism, ensuring optimal drug efficacy.
- Sustains steady blood levels over extended durations, enhancing therapeutic effectiveness.
- Enhances bioavailability, maximizing the proportion of administered drugs reaching systemic circulation.
- Mitigates adverse effects and unwanted reactions, promoting safer medication usage.
- Enhances patient adherence and compliance due to simplified dosing regimens.
- Allows for reduced dosing frequency, easing treatment burden and improving convenience.
- Guards against gastrointestinal absorption issues, such as pH variability and enzymatic activity, ensuring drug effectiveness and reducing digestive disturbances.
- Lowers plasma drug concentrations, minimizing systemic side effects while maintaining therapeutic efficacy.
- Eliminates the need for invasive parenteral therapies, offering a non-intrusive drug delivery method.
- Reduces the risk of systemic drug interactions, enhancing medication safety and effectiveness.
- Prolongs drug action duration, offering sustained therapeutic effects for prolonged relief.

Disadvantages [21,22,1]:

- Associated with higher costs, potentially limiting accessibility for some patients.
- Unable to deliver ionic drugs, restricting applicability for certain medication types.
- Challenges in achieving high drug concentrations in blood/plasma, affecting potency in some cases.
- Infeasible for drugs with large molecular sizes, limiting formulation options.
- Incapable of delivering drugs in a pulsatile manner, potentially impacting treatment efficacy in certain conditions.
- Unsuitable for drugs or formulations causing skin irritation, hindering applicability for some patients.
- Possibility of skin irritation at the application site, affecting patient tolerance and compliance.
- Economically unsustainable in some contexts, affecting widespread adoption.
- Primarily suitable for chronic conditions, limiting its utility in acute therapeutic settings.
- Vulnerable to cutaneous metabolism, potentially affecting drug effectiveness.
- Most effective for drugs with lower molecular weights (<500 Daltons), restricting applicability for larger molecules.

Microneedle Applications:

Micro-needles (MNs) have garnered considerable attention from researchers, scientists, and industry stakeholders alike, owing to their versatility and promising capabilities across various domains. Numerous investigations have showcased the versatility and efficacy of MNs in diverse applications. These encompass drug delivery, vaccination, disease diagnostics, and cosmetic enhancements.

***Drug Delivery*:**

The inception of micro-needles (MNs) for drug delivery dates back to 1998 when solid silicon MNs were first employed [23]. Since then, various innovative approaches have emerged, showcasing the efficacy of MNs in transdermal drug delivery. Dissolvable MN patches have been utilized to administer diverse substances, ranging from human growth hormone for transdermal delivery to hairless rat skin [24], to caffeine for weight management in obese mice, serving as an anti-obesity treatment [25]. Coated MN patches have facilitated the delivery of salmon calcitonin [26], while solid microneedles have effectively transported protein antigens like ovalbumin into hairless guinea pig skin [27]. Solid silicon and metal MNs have been employed for the delivery of various compounds, including calcein [28], bovine serum albumin (BSA), and insulin. Additionally, MNs have facilitated transdermal permeation of drugs such as ibuprofen, ketoprofen, and paracetamol [29], along with substances like L-ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine hydrochloride, ketoprofen, and glycerol [30]. While most studies have utilized MN arrays for drug delivery into mice, pig, and human skin, notable demonstrations include successful microneedle injections into chicken thigh [31] and brain tissue [32].

***Vaccine Delivery*:**

Dissolvable microneedles (MNs) stand out as a prominent tool for vaccine delivery, offering a viable alternative to traditional hypodermic needles. Their

biocompatibility, robustness, scalability, and minimal generation of biohazardous waste make them particularly advantageous [33]. Dissolvable MNs have been instrumental in administering vaccines against various diseases, including malaria, diphtheria [34], influenza [35], Hepatitis B [36], HIV [37], and polio [38].

While dissolvable MNs are commonly employed for vaccine delivery, coated MN arrays have also demonstrated efficacy in this realm. Studies have showcased the successful administration of vaccines using coated MNs, offering simple, safe, and compliant vaccination methods. For instance, a study enhanced the immune response in pigs by administering the bacillus Calmette–Guérin (BCG) vaccine with a coated MN [39]. Another study effectively encoded hepatitis C virus protein in a DNA vaccine coated on microneedle, priming specific cytotoxic T lymphocytes (CTLs) in mice [40]. Additionally, coated microneedles have carried influenza virus antigens for vaccination applications in mice [41].

Hollow MNs have emerged as another modality for vaccine delivery, demonstrating efficacy in preclinical and clinical settings. Hollow MNs have been utilized to deliver the anthrax recombinant protective antigen vaccine to rabbits, offering an alternative to traditional injections [42]. In a mouse model, hollow microneedles were evaluated for vaccination against plaque, showcasing their potential in disease prevention [43]. Furthermore, clinical trials in humans utilizing hollow microneedles for influenza vaccination have yielded comparable immune responses to intramuscular injections [44].

***Disease Diagnosis*:**

Disease diagnosis and therapeutic efficacy can be monitored via several established bioassays that sample body fluids to assess and monitor health conditions. The current methods induce pain; require specialized techniques, tailored equipment, and professional medical personnel. However, microneedle technology offers bioassay solutions with painless experience and simple implementation [45].

A hollow MN has the ability to diagnose several diseases such as cancer, diabetes [46], and Alzheimer's [47] disease. Patient health monitoring is another application of the MNs. For example, a hollow glass MN may be used to investigate the glucose level [48]. Furthermore, O'Mahony et al. proposed the MNs system for electrocardiography signal optimization [49]. A microneedle-based enzyme was functionalized to monitor alcohol in artificial interstitial fluid [50]. Microneedles with nanoparticles were able to identify the biomarkers in the early stage of osteoarthritis [51]. Microneedles were used as sensors for hydrogen peroxide, lactate, dissolved oxygen, and glutamate.

***Cosmetic Application*:**

MNs have widely been used in cosmetic applications such as skin treatment and hair growth. Kim, *et al*. developed a hyaluronic acid-based dissolvable MN patch for the intradermal delivery of ascorbic acid and retinyl retinoate [52]. Kumar, *et al*. showed an enhancement of local delivery of eflornithine (used to reduce facial hirsutism) *in vitro* and *in vivo* using a solid MN [53]. Further, MN technology was able to treat two patients suffering from alopecia areata disease [54]. These patients experienced hair growth after treatment. Effective clinical trials have been conducted in atrophic facial scarring [55], atrophic acne scars [56], and hypertrophic burn scars [57] using a MN. Microneedles are considered as an effective treatment for cosmetic applications related to aging, skin lesions, vulgaris, and wrinkles. With an increasing demand for cosmetic products, microneedles (patches and rollers) have a high potential in the future.

FUTURE DIRECTIONS AND CHALLENGES:

Looking ahead, the paper identifies key research directions and challenges in the field of MN technology. From enhancing drug-loading capacity to optimizing MN insertion and retention, several avenues for innovation are delineated. Additionally, regulatory considerations and commercialization barriers are addressed, underscoring the need for multidisciplinary collaboration to accelerate the translation of MNs from bench to bedside.

CONCLUSION:

In summary, this paper provides a comprehensive overview of MN technology in the context of transdermal drug delivery. From all these findings, the present work concluded that transdermal drug delivery systems are useful for topical and local action of the drug. The drugs which show hepatic first pass effect and unstable in GI conditions are the suitable candidate for TDDS. Through continued research and innovation, MNs are poised to drive paradigm shifts in drug delivery, offering safer, more efficient, and patient-friendly therapeutic solutions.

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