

Microneedles: An Innovative and Increasingly Promising Method for Transdermal Drug Delivery Systems

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ABSTRACT

The most commonly used methods for transdermal drug administration include hypodermic needles, topical creams, and transdermal patches. However, the effectiveness of many therapeutic agents is often limited by the stratum corneum, the outermost skin layer, which acts as a barrier, preventing most molecules from reaching their target sites. A new drug delivery system, known as microneedles, offers a promising solution by enhancing drug penetration through this barrier and addressing the limitations of traditional formulations. The core principle behind microneedles is their ability to disrupt the skin, creating micron-sized channels that allow drugs to reach the epidermis or upper dermis, from where they can enter systemic circulation directly. This review explores the various potentials and applications of microneedles, which can be fabricated in forms such as solid, dissolving, hydrogel, coated, and hollow types. The choice of fabrication method depends on the microneedle material and type. Microneedles have found increasing applications in fields such as oligonucleotide delivery, vaccine administration, insulin delivery, and cosmetics. Although several microneedle products are already entering the market, further research is needed to address the challenges that must be overcome before microneedles can achieve widespread commercial success.

KEYWORDS: Microneedles, Transdermal Drug Delivery, Vaccine delivery.

I. INTRODUCTION

Hypodermic needles and topical creams are the most commonly used methods for delivering drugs through the skin. However, hypodermic needles are often less preferred by

patients due to the pain they cause, while topical creams tend to have lower bioavailability. The skin itself acts as a significant barrier to drug delivery via the topical route. It consists of three main layers: the outermost stratum corneum, the middle epidermis, and the thickest layer, the dermis. The stratum corneum is the primary barrier, allowing only certain molecules, such as lipophilic and low molecular weight drugs, to pass through. This limited permeability creates challenges in developing effective topical formulations. To enhance drug penetration, various transdermal delivery systems have been explored, including nanocarrier-loaded creams, transdermal patches, and microneedles.

Microneedles (MNs) have been extensively studied by researchers for their ability to deliver drugs through the transdermal route and overcome the limitations of traditional methods. The microneedle device consists of micron-sized needles arranged on a small patch. Designed to address the shortcomings of hypodermic needles and transdermal patches, the microneedle drug delivery system is considered a hybrid of both. One of the main challenges with transdermal technology is that many drugs cannot penetrate the skin at the rate needed for therapeutic effect. To tackle this issue, researchers have developed advanced microneedle technology that enables even hydrophilic, high molecular weight compounds to penetrate the stratum corneum. Using this microneedle device, drug molecules can more effectively cross the skin's outermost barrier, allowing greater drug delivery to the targeted area and efficacy [2]. In addition to improved therapeutic advantages, microneedles give highly accurate reproducible results with minimum inter-subject variability in bioavailability. Though it has many advantages it also possesses some

limitations. There is the possibility of skin irritation or allergy to sensitive skin. Since the needle size is very small and thinner as compared to the thickness of hair, breaking of microneedle tips may take place which if remained inside the skin, can cause problems. These limitations are very rare and can be overcome with advanced material selection for microneedles. The main objective of developing this technology is to create larger transport pathway of micron size which is larger than molecular dimensions and smaller than holes by hypodermic needles, to disrupt the stratum corneum to allow large molecules to pass through thus increasing the permeability [5]. Conventional methods like electric methods- iontophoresis and electroporation, chemical/ lipid enhancers create pores of nanosize which improve the permeability up to some extent but fail for large molecules [6]. A comparative discussion is compiled for various transdermal drug

delivery systems in Table 1. The drug delivery by various transdermal systems is presented in Fig. 1. The topical cream spreads only on the skin surface. It has been reported that only 10–20% of total drug loaded in cream is being permeated through the skin [3]. In case of a transdermal patch, the drug has to pass the stratum corneum barrier thus it also shows less bioavailability. Addition of permeation enhancer in the transdermal patch can improve the drug permeation but up to a very limited extent [4]. The hypodermic needle goes deep into the dermis where pain receptors are present. Thus it can deliver 90–100% of the loaded drug but it is very painful which results in poor patient compliance. Microneedle patch bypasses the stratum corneum barrier and delivers the drug directly into the epidermis or upper dermis layer which delivers 100% of the loaded drug without pain [5].

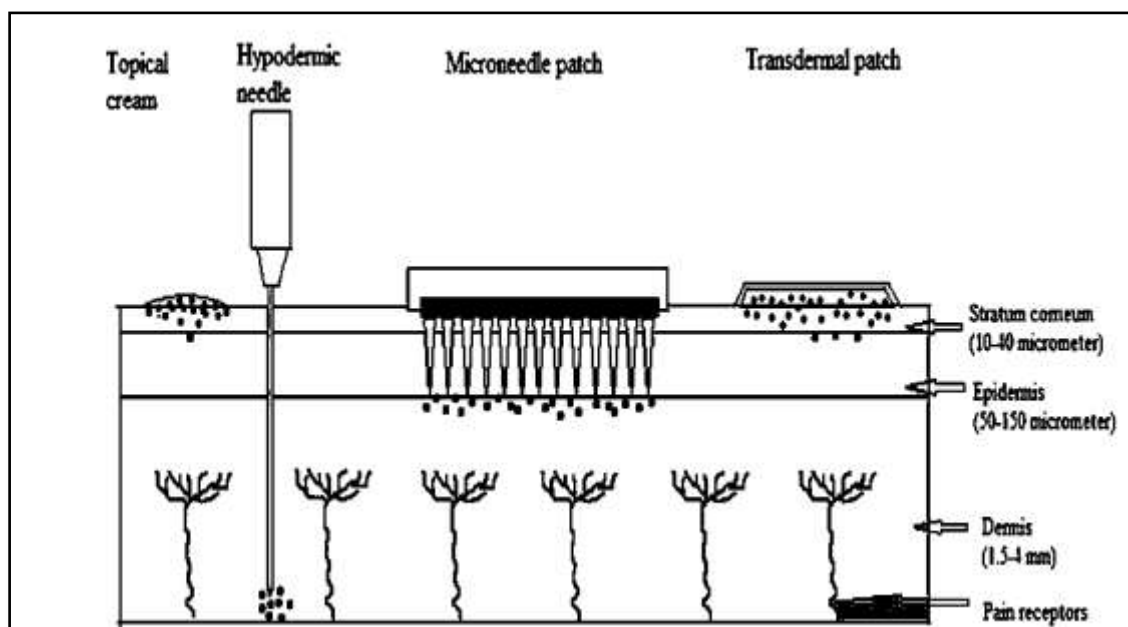


Fig. 1. A comparison between topical creams, hypodermic needles, microneedle patches, and transdermal patches

II. DRUG DELIVERY MECHANISM

Drug delivery through the topical route primarily follows a diffusion mechanism. In the case of the microneedle drug delivery system, the skin is temporarily disrupted. The microneedle device consists of hundreds of microneedles arranged in an array on a small patch, similar to a traditional transdermal patch, to deliver an adequate amount of drug for a desired therapeutic effect. The microneedles penetrate the stratum corneum, bypassing the skin's barrier layer, and deliver the

drug directly to the epidermis or upper dermis. From there, the drug enters the systemic circulation and exerts its therapeutic effect at the targeted site of action. The mechanism of drug delivery through microneedles is illustrated in Figure 2.

III. MICRONEEDLE DIMENSIONS

Microneedles can be designed in various sizes depending on the type and material used. The epidermis is typically up to 1500 μm thick, so microneedles with a length of up to 1500 μm are

sufficient to deliver the drug into the epidermis. Longer and thicker needles, however, could penetrate deeper into the dermis, potentially damaging nerves and causing pain. Typically, microneedles range from 150 to 1500 microns in length, 50 to 250 microns in width, and have tip thicknesses between 1 and 25 microns. As

previously mentioned, the primary purpose of the microneedle device is to create micron-sized transport pathways, so the needle diameters are generally kept within a few microns. Microneedle tips can be designed in various shapes, such as cylindrical, triangular, pointed, pentagonal, octagonal, and several others [7].

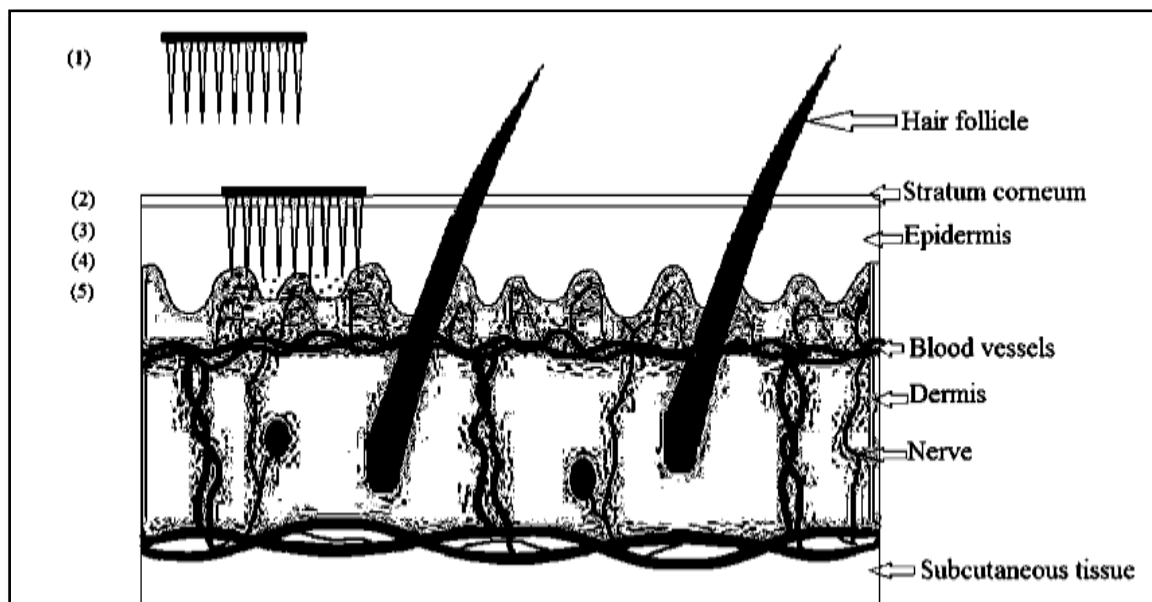


Fig. 2. Mechanism of drug delivery by microneedle device: (1) Microneedle device with drug solution; (2) Microneedle inserted into the skin; (3) Temporary mechanical disruption of the skin; (4) Releasing the drug in the epidermis; (5) Transport of drug to the site of action.

IV. MICRONEEDLE FABRICATION MATERIAL AND ITS PROPERTIES

4.1 Silicon: Silicon was used to create the first microneedles in the 1990s [6]. It is anisotropic and has a crystalline structure, with its properties varying based on the alignment of the crystal lattice, which results in elastic moduli ranging from 50 to 180 GPa [8–10]. The flexibility of silicon allows for the production of microneedles in various sizes and shapes. Its desirable physical properties make it a versatile material for microneedle fabrication, and it can be precisely manufactured in batch processes. However, the high cost of silicon and the complex, time-consuming fabrication process limit its widespread use in microneedle technology. Additionally, biocompatibility concerns arise because silicon is brittle, and fragments may break off and remain in the skin, potentially causing health issues [8].

4.2 Metal: The primary metals used for microneedle fabrication include stainless steel and titanium, with palladium, nickel, and palladium-

cobalt alloys also being utilized [11]. These metals offer excellent mechanical properties and biocompatibility. Compared to silicon, metals are more robust and less likely to break, making them a better choice for microneedle production. Stainless steel was the first metal used in microneedle fabrication [12], while titanium serves as a strong alternative to stainless steel [8,13].

4.3 Ceramic: Alumina (Al₂O₃) is primarily used in microneedle fabrication due to its excellent chemical resistance. It forms a stable oxide layer due to the strong ionic and covalent bonds between aluminum and oxygen atoms [14]. Other ceramics employed include calcium sulfatedihydrate (Gypsum, CaSO₄·0.2H₂O) and calcium phosphate dihydrate (Brushite, CaHPO₄·2H₂O) [5]. More recently, an organically modified ceramic called Ormocer® has been utilized. This material is a three-dimensionally cross-linked copolymer [15], which can be tailored to exhibit different properties by incorporating various organic units during polymerization. Ceramic microneedles are primarily fabricated using a micromolding

technique, where ceramic slurry is poured into a micro-mold to form the desired shape. Micromolding techniques are cost-effective and have the potential for easy scalability [8].

4.4. Silica Glass: Silica glass can be used to produce a variety of geometries on a small scale. While silica glass is physiologically inert, it is also brittle in nature [16]. Borosilicate glass, which is composed of silica and boron trioxide, offers greater elasticity. However, glass microneedles are primarily fabricated manually, making the process less time-efficient [17]. Currently, glass microneedles are not commercially available and are mainly used for experimental purposes [8].

4.5. Carbohydrates: Maltose is one of the most commonly used sugars for microneedle fabrication [18]. Other sugars such as mannitol, trehalose, sucrose, xylitol, and galactose, as well as polysaccharides, can also be utilized [19]. Carbohydrate slurries are molded using silicon or metal templates, with a drug-loaded carbohydrate mixture cast into the molds to form the microneedles [20]. The rate of dissolution of carbohydrates over time regulates drug release within the skin. Carbohydrates are inexpensive and safe for human health, but their degradation at high temperatures can make the fabrication process challenging [8].

4.6. Polymers: A wide range of polymers have been explored for microneedle production, including poly (methyl methacrylate) (PMMA) [21], polylactic acid (PLA) [22], poly (lactic-co-glycolic acid) (PLGA) [23], polyglycolic acid (PGA) [17], poly (carbonate) [24], cyclic-olefin copolymer, poly (vinylpyrrolidone) (PVP) [25], poly (vinyl alcohol) (PVA) [25], polystyrene (PS) [26], poly (methyl vinyl ether-co-maleic anhydride) [27], and SU-8 photoresist [28]. These polymers are often used to create dissolving, biodegradable, or hydrogel-forming microneedle arrays. While microneedles made from these polymers tend to have lower strength compared to other materials, they are still tougher than those made from glass or ceramics [8,9].

V. TYPES OF MICRONEEDLES:

Several types of microneedles have been developed and studied for their application in drug delivery, including solid, coated, dissolving, hollow, and hydrogel microneedles. Each type has distinct properties, as shown in Figure 3. These microneedles deliver drugs to the epidermis in different ways: some are designed to create pores in the stratum corneum, others are coated with a drug solution on their surface, some are dissolvable, and others are prefilled with the drug solution [29–32].

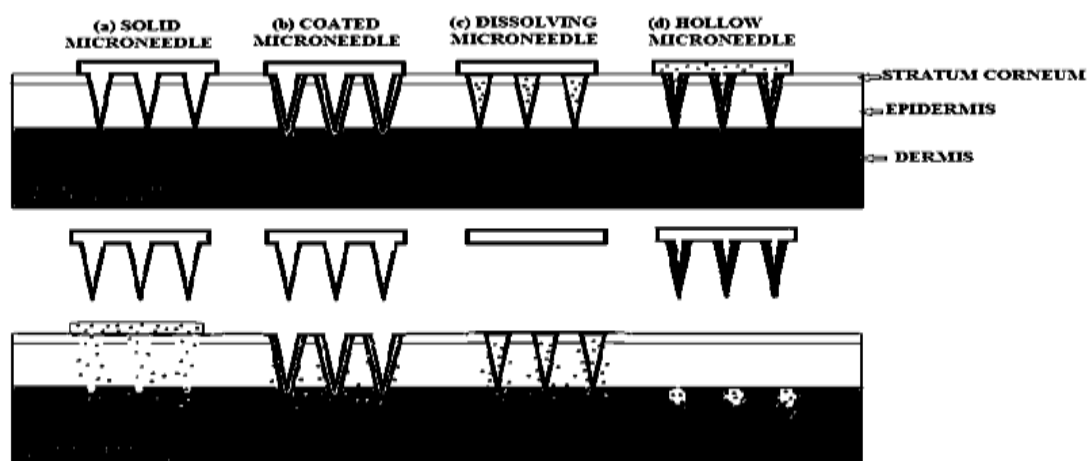


Fig. 3. Different types of microneedles (a) Solid microneedles use poke with patch approach, are used for pre-treatment of the skin; (b) Coated microneedles use coat and poke approach, an coating of drug solution is applied on the needle surface; (c) Dissolving microneedles are made of biodegradable polymers; (d) Hollow microneedles are filled with the drug solution and deposit the drug in the dermis.

5.1. Solid Microneedles : Solid microneedles are primarily used to pre-treat the skin by creating small pores. The pointed tips of the microneedles penetrate the skin and form micron-sized channels, allowing the drug to enter the skin layers upon the

application of a drug patch, thus enhancing permeation. The drug is then absorbed by capillaries, producing a systemic effect, although it can also be used for local effects [29]. Solid microneedles deliver the drug to the skin through

passive diffusion [1,30]. Narayanan et al. fabricated long, tapered solid silicon microneedles using a tetramethylammonium hydroxide etching process. These microneedles had an average height of 158 μm and a base width of 110.5 μm [33]. He later developed gold-coated solid silicon microneedles with a height of 250 μm , base width of 52.8 μm , aspect ratio of 4.73, and tip angle and diameter of 24.5° and 45 μm , respectively. These microneedles showed improved bioavailability and mechanical strength [34]. Li et al. studied polylactic acid (PLA) microneedles and found that biodegradable polymer solid microneedles possess sufficient mechanical strength to pierce the stratum corneum and enhance drug absorption. Microneedles with a depth of 800 μm and a density of 256 microneedles per cm^2 were shown to significantly improve drug permeation [35]. Stainless steel microneedles have also been researched, with studies demonstrating enhanced delivery of captopril and metoprolol tartrate after applying stainless steel microneedle arrays [1].

5.2. Coated Microneedles

Coated microneedles are encased in a layer of drug solution or drug dispersion [1]. When applied, the drug is quickly released as the coating dissolves, delivering the medication efficiently. The amount of drug that can be loaded depends on the thickness of the coating layer and the size of the needle, although it is typically limited [29]. Baek et al. loaded lidocaine onto poly L-lactide (PLLA) microneedle arrays, which released the drug rapidly in phosphate-buffered saline and remained stable for up to 3 weeks [36]. Coated microneedles have also been explored for the simultaneous delivery of multiple agents. Li et al. coated each microneedle with different formulations and drugs, enabling the co-delivery of water-soluble and water-insoluble dyes [37]. In another study, Chen and colleagues coated PLA microneedles with sulforhodamine B, achieving a drug delivery efficiency of about 90%. In vivo studies in mice confirmed the sustained release of the drug [38].

5.3. Dissolving Microneedles

Dissolving microneedles are made from biodegradable polymers that encapsulate the drug within the polymer matrix. Upon insertion into the skin, the microneedles dissolve, releasing the drug. This approach requires only a single-step application since the microneedles are not removed after insertion, unlike other types. The polymer degrades within the skin, controlling the drug

release over time. Due to their bio-acceptability and dissolution properties, dissolving microneedles are ideal for long-term therapies, offering improved patient compliance [1]. However, achieving effective drug distribution can be challenging, as polymer-drug mixing plays a crucial role in the fabrication process [30]. Chen and his team developed tip-dissolving microneedles, which demonstrated rapid and efficient drug delivery without causing skin irritation [39]. While dissolving microneedles require time to fully dissolve, completing the insertion process can be difficult. To address this, Zhu et al. developed rapidly separating microneedles mounted on solid microneedles, providing sufficient mechanical strength, with about 90% drug delivery efficiency within 30 seconds [40]. Wang et al. introduced the concept of incorporating bubbles into dissolving microneedles, which helped prevent drug diffusion throughout the entire needle. This modification resulted in approximately 80% drug delivery efficiency within 20 seconds [41]. Additionally, Chu et al. developed separable arrowhead microneedles, where sharp polymer tips containing the drug were mounted on blunt metal shafts. These microneedles either separated or dissolved upon insertion into the skin within a few seconds, showing potential for rapid drug delivery with controlled release kinetics [42].

5.4. Hollow Microneedles

Hollow microneedles contain an internal space that is filled with drug dispersion or solution and feature holes at their tips. Upon insertion into the skin, the drug is directly delivered into the epidermis or upper dermis. These microneedles are typically used for delivering high molecular weight compounds such as proteins, vaccines, and oligonucleotides [1]. The drug flow rate and release pressure can be adjusted, allowing for rapid bolus injections when necessary. Hollow microneedles can accommodate larger drug doses due to the space inside the needle. Ensuring a constant flow rate is crucial in these systems [32]. While increasing the microneedle bore size can enhance the flow rate, it may also compromise the needle's strength and sharpness. To address this, a metal coating is sometimes applied to reinforce the microneedles, although this can affect sharpness [1]. Mishra et al. developed hollow microneedles aligned on a silicon substrate, with a length of 500–600 μm and an outer diameter of 100 μm . These microneedles achieved a flow rate of 0.93 $\mu\text{l/s}$ at a pressure difference of 2 kPa [43]. Maaden and

colleagues fabricated fused silica hollow microneedles using hydrofluoric acid etching, which allowed for automated vaccine injection in small amounts, overcoming the limitations of hypodermic needles [44]. In an interesting development, Suzuki and team created hollow microneedles that mimicked the action of mosquito bites, enhancing skin penetration for drug delivery [31].

5.5. Hydrogel-Forming Microneedles

Hydrogel-forming microneedles are a recent innovation, crafted from super-swelling polymers. These hydrophilic polymers have a three-dimensional structure that enables them to absorb large amounts of water. When inserted into the skin, they swell due to interstitial fluid, creating channels that connect the capillary circulation with the drug patch. Initially, these microneedles are used to disrupt the skin barrier, but upon swelling, they act as rate-controlling membranes for drug release. These microneedles offer flexibility in terms of size and shape, easy sterilization, and straightforward removal from the skin, making them highly practical for use [45]. Migdadi et al. explored hydrogel-forming microneedles for the transdermal delivery of metformin, which helped reduce the gastrointestinal side effects associated with oral administration. The study showed improved drug permeation and bioavailability with the use of these microneedles [46]. Cross-linked polymers are also being utilized to create swellable microneedles for efficient drug delivery.

VI. METHODS OF DRUG DELIVERY

There are several methods for delivering drugs into the epidermis using microneedles. One method involves puncturing the skin with the microneedles to create small holes, then removing the microneedles and applying a drug-containing patch over the area. This allows a direct pathway for the drug to enter the skin. The effectiveness of this approach can be enhanced by applying an electric field. Another method involves coating the surface of the microneedles with a drug-containing layer. When the microneedles are inserted into the skin, the drug dissolves from the coating and is delivered. A third approach is to dip the microneedles into a drug solution and scrape them across the skin, allowing the drug to be deposited into the created abrasions. Additionally, microneedles can be fabricated from a biodegradable polymer that contains the drug, or a

hollow microneedle can be designed and filled with the drug solution for delivery [8,34].

VII. FABRICATION TECHNIQUES

The choice of fabrication or manufacturing method for microneedles depends on factors such as the microneedle type, geometry, and material used [29]. Different fabrication techniques for various types of microneedles are listed in Table 2 [47–49].

VIII. EVALUATION OF MICRONEEDLES

8.1. Characterization Methods

The drug can be loaded into or onto microneedles either in suspension/dispersion form or encapsulated in carriers such as liposomes, nanoparticles, or nanoliposomes [37]. It can be coated onto the microneedles using a polymer solution or applied as part of a patch. Various physicochemical characterizations can be performed on the loaded drug, depending on the formulation type, including measurements of particle size, polydispersity index, viscosity, and zeta potential [50]. For patches that are applied after pre-treatment, tests for drug release, adhesion, and permeation are conducted. The size, internal structure, and crystallinity of liposomes or nanocarriers can be analyzed using techniques such as dynamic light scattering, X-ray scattering, and transmission electron microscopy. Stability studies under various temperature, pH, and simulated in-vivo conditions (such as with cell lines or tissues) are also crucial. Other necessary tests include solubility studies, drug content analysis, in-vitro release tests, and biocompatibility assessments [5,15].

8.2. Dimensional Evaluation

Several methods are employed to evaluate the geometry of microneedles, including measuring the tip radius, length, and height. Common techniques for this purpose include optical or electrical microscopy, with 3D imaging providing more accurate insights into needle geometry, which helps in quality control. Scanning Electron Microscopy (SEM) and confocal laser microscopy are often used. SEM utilizes a focused electron beam to interact with the sample's atoms, producing signals that provide detailed information about the surface topography and composition. Confocal laser microscopy, on the other hand, generates high-resolution images [51,52].

8.3. Mechanical Properties or Insertion Forces

A microneedle needs to be sharp and slender to ensure it can easily penetrate the skin, while also being strong enough to prevent breakage once inside the skin. Mechanical tests are essential to evaluate the force at which a microneedle loses its structural integrity and the force required for insertion. The ratio of these two forces, known as the "safety factor," should be as high as possible for safe and efficient design [53].

8.4. In-vitro Skin Permeation Studies

A diffusion cell apparatus is typically used to study the drug's permeation through the skin. Pig ear skin is commonly employed for these experiments, with the skin mounted between a receptor and donor compartment. The cumulative permeation profiles of skin treated with microneedles are compared with untreated skin [54].

8.5. In-vivo Animal Model Studies

Hairless rats are often used for in-vivo studies, with appropriate anesthesia techniques applied to ensure animal welfare. One key parameter considered during these studies is trans-epidermal water loss (TEWL), which is measured both before and after microneedling. The DelfinVapometer is typically used to assess this parameter [54].

IX. APPLICATIONS

9.1. Oligonucleotide Delivery

Oligonucleotides, which are short DNA or RNA sequences, are challenging to deliver to their intracellular target sites. As a result, various techniques have been explored to improve their delivery. One such approach involved using microneedles to deliver a 20-mer phosphorothioated oligodeoxynucleotide. Solid microneedles made of materials like stainless steel or titanium were employed in the "poke with patch" method. This method enabled a greater amount of the drug to reach its target compared to untreated skin. Additionally, combining iontophoresis with the microneedle approach resulted in more effective delivery than iontophoresis alone [2,57].

9.2. Vaccine Therapy

Vaccines are biological preparations that provide active acquired immunity against specific diseases. They typically contain a killed or weakened form of a pathogen, its toxins, or one of its surface proteins. By stimulating the immune

system, vaccines help protect the body from future infections. The microneedle approach has been found to be effective in vaccine delivery [29,30].

Microneedles have been used to deliver DNA vaccines, leading to significantly stronger immune responses compared to traditional injections [58]. Efforts have also been made to develop microneedle patches for administering vaccines such as the influenza vaccine [59]. Hollow microneedles, which require lower doses than intramuscular injections, have been used for the administration of vaccines like anthrax and rabies [8].

Ogai and colleagues fabricated hollow microneedles from poly-glycolic acid to improve vaccination efficiency via the intradermal route. By targeting the upper dermis, microneedles enable more precise drug delivery, resulting in higher antibody titers after vaccination compared to subcutaneous injections on the 15th day [60]. Additionally, dissolving microneedles have been explored for intradermal vaccination, further enhancing the potential for effective vaccine delivery [61].

9.3. Peptide Delivery

Peptides, when taken orally, are often degraded by enzymes, making transdermal delivery an attractive alternative. However, the skin's barrier limits the amount of peptide that can pass through. Microneedles offer a solution to this challenge by enhancing the penetration of peptides through the skin.

Desmopressin, a synthetic form of vasopressin, is a potent peptide hormone used to treat conditions such as diabetes insipidus, bedwetting in children, and hemophilia A. Studies on delivering desmopressin using microneedles have shown that this method is safe and more efficient than other delivery routes [2].

Cyclosporine A, a water-insoluble, high-molecular-weight cyclic peptide, is commonly used to treat various skin diseases. Dissolving microneedles loaded with cyclosporine A (600 μm in length and 250 μm in width) were fabricated using a molding process. When applied to porcine skin for 60 minutes, approximately 65% of the microneedles dissolved, delivering $34 \pm 6.5 \mu\text{g}$ of the drug [62].

In another study, Liu et al. developed polyethylene glycol diacrylate-based microneedles loaded with GAP-26, a gap junction blocker. These microneedles utilized a swelling effect to improve peptide delivery, demonstrating enhanced

permeation and confirming the inhibition of keloid fibroblast proliferation and collagen I expression [63].

9.4. Hormone Delivery

Insulin, a peptide hormone used to lower high blood sugar levels, has been effectively delivered via microneedles, showing enhanced efficiency in reducing blood glucose. Li et al. developed solid microneedles and tested their effect on blood glucose levels in diabetic mice. The results demonstrated a 29% reduction in blood glucose within 5 hours, confirming that microneedles improve insulin permeability through the skin [35].

Ye and colleagues explored microneedles integrated with pancreatic β -cell capsules designed to sense blood glucose levels and secrete insulin. However, the patch did not function as expected. To improve functionality, they developed a microneedle matrix containing synthetic glucose signal amplifiers (GSAs), consisting of nanovesicles loaded with glucose oxidase, α -amylase, and glucoamylase enzymes. These amplifiers successfully triggered insulin secretion from the β -cell capsules [65].

A clinical study of parathyroid hormone (1-34)-coated microneedles showed a 3-fold reduction in T_{max} and a 2-fold reduction in apparent half-life ($T_{1/2}$) compared to conventional injection therapy [66]. These findings highlight the potential of microneedles in hormone therapy, with further possibilities for sustained release by incorporating suitable polymers [67]. Additionally, combining microneedles with iontophoresis may offer further improvements in hormone delivery [68].

9.5. Cosmetics

Microneedles are gaining popularity in the cosmetic industry, particularly for enhancing skin appearance and treating blemishes and scars. The microneedle approach has been explored for delivering active cosmetic ingredients such as ascorbic acid, eflornithine, and retinyl retinoate [8]. In one study, melanin was incorporated into phosphatidylcholine liposomes (nanoliposomes), which improved solubility in lipids. The application of this formulation via an e-roller led to a greater amount of pigment reaching deeper layers of the skin, particularly near hair follicles [69]. Enhanced delivery of cosmetic peptides like melanostatin, rigin, and pal-KTTKS through microneedles has also been investigated [70].

9.6. Lidocaine Delivery

Lidocaine, a local anesthetic, can be delivered through microneedles with less pain compared to traditional hypodermic injections, improving patient compliance [29]. Baek et al. coated the microneedle tips with lidocaine, and the microneedles demonstrated consistent in vitro skin penetration and enhanced drug delivery in just 2 minutes, offering a pain-free, rapid solution for local anesthesia [36]. In another study, microneedles coated with PEG-lidocaine dispersions showed improved drug delivery in 3 minutes, compared to a topical formulation [1].

9.7. Pain Therapy

Polymeric microneedles loaded with meloxicam were created using polydimethylsiloxane molds, and in vitro permeation studies showed nearly 100% drug release within 60 minutes. The drug deposition was 63.37%, and a transdermal flux of 1.60 $\mu\text{g}/\text{cm}^2/\text{hr}$ was observed, representing a 2.58-fold increase in permeation compared to the free drug solution [71]. For treating neuropathic pain, which is often difficult to manage, dissolving microneedles were explored. These microneedles delivered a selective calcitonin gene-related peptide (CGRP) antagonist peptide, exhibiting high specificity for the receptors and no skin irritation or side effects. Approximately 75% of the microneedles dissolved within 20 minutes of application [72]. The use of microneedles for pain management presents new opportunities in therapeutic delivery.

9.8. Ocular Delivery

Microneedles are also being explored for targeted drug delivery in the posterior segment of the eye. Iontophoresis was used to deliver nanoparticles through the suprachoroidal space, and when combined with microneedles, more than 30% of the nanoparticles reached the posterior segment of the eye, significantly enhancing delivery compared to iontophoresis alone [73].

9.9. Cancer Therapy

Cancer treatment remains a major challenge worldwide, and microneedles are being investigated for delivering anticancer drugs. Self-degradable microneedles were studied for melanoma treatment by delivering anti-PD-1 (aPD1) in a controlled, sustained release. Additionally, anti-PD-1 and glucose oxidase-loaded pH-sensitive dextran nanoparticles were delivered via microneedles for enhanced therapeutic effect

[74]. Microneedles have also been explored to improve the delivery of 5-fluorouracil, a topical cream for basal cell carcinoma, with skin treatment via solid microneedles increasing the permeability of the drug by 4.5 times, showing significant inhibition of tumor growth [75]. Bhatnagar et al. studied the delivery of chemotherapeutic agents like tamoxifen and gemcitabine for breast cancer treatment, noting that localized delivery could reduce side effects [76]. Furthermore, polymeric microneedles have been investigated for the localized delivery of anticancer drugs for skin cancer treatment [77].

X. CLINICAL TRIALS AND SAFETY

Numerous pre-clinical studies have demonstrated the effectiveness of microneedles in various applications, but only a few have successfully transitioned to human trials. The first human study on microneedles was conducted by Kaushik et al. in 2001, which aimed to evaluate whether silicon microneedles were small enough to reduce pain compared to a 26-gauge hypodermic needle. The microneedles were applied to the forearms of 12 healthy male and female volunteers. The results showed that microneedles caused less pain than traditional hypodermic needles [79].

Further trials were conducted by Arya and colleagues to assess whether microneedles caused local skin reactions and were well-tolerated by patients. In a study with 15 human subjects, no swelling, pain, or erythema were observed at the application site. Participants were able to self-administer the microneedle patches without the need for an applicator, and they preferred this method over conventional needles [80].

A randomized clinical trial with 21 male participants investigated the enhanced delivery of lidocaine after microneedle pre-treatment. While topical 4% lidocaine cream produced anesthesia after 60 minutes of application, pre-treatment with microneedles resulted in anesthesia within just 30 minutes [81].

An open trial involving 10 patients tested a hyaluronic acid-based microneedle patch for treating psoriasis. The microneedle patch was applied daily for a week over skin treated with calcipotriol-betamethasone ointment. The one-week application significantly reduced psoriatic plaques, proving to be more effective than traditional cream applications [82].

XI. CURRENT RESEARCH, CHALLENGES, AND FUTURE TRENDS

The first microneedles were made from silicon, and early studies aimed to determine whether microneedles could enhance drug delivery through the skin. Initial permeation studies on cadaver skin demonstrated that large molecules like albumin and insulin could be delivered more efficiently with microneedles. Subsequent research confirmed that microneedles offer improved delivery for larger molecules. Today, new and innovative microneedle concepts continue to emerge, showing promise for the future [2].

While microneedles are being explored for a variety of drugs, there are several challenges to overcome before they can be widely commercialized. Extensive clinical studies are required for approval. Key challenges include skin irritation, redness, and allergies, as well as the limited drug capacity that microneedles can hold. Delivering hydrophilic and large molecules through the skin remains a significant hurdle. Additionally, selecting the right materials for fabricating microneedles with adequate mechanical strength and proper insertion force is crucial. The ultimate goal is to enhance drug permeation while minimizing pain. Moreover, it may be challenging for patients to first insert the microneedles and then apply a patch, and there is a risk of infection if skin pores don't close properly after use [1].

Several advancements are being made to improve drug delivery through the skin. Modifications to conventional microneedles, like 3M's flexible hollow microneedle technology, are already being explored. This innovation allows for the direct systemic delivery of larger protein doses, potentially in the hundreds of milligrams [83]. Research into combining ultrasound and transdermal drug delivery is also underway to further enhance skin permeability [84]. These developments indicate that microneedles, with various modifications, are set to revolutionize transdermal drug delivery, opening new avenues for more efficient and targeted treatment methods.

XII. CONCLUSION

Microneedle technology has established itself as a transformative platform in transdermal drug delivery, offering a minimally invasive and highly efficient alternative to conventional methods. By enabling precise transport of both small molecules and macromolecules across the stratum corneum, microneedles expand therapeutic

possibilities while simultaneously improving patient compliance and comfort. Their versatility, reflected in applications ranging from vaccines and peptides to hormones, analgesics, and cosmetic agents, underscores their broad clinical relevance. Nevertheless, key challenges—including scalable manufacturing, optimization of drug-loading capacity, and long-term safety validation—remain to be fully addressed. Ongoing advances in material science, fabrication strategies, and regulatory frameworks are expected to accelerate their clinical translation. With continued innovation, microneedles are poised to redefine drug administration practices, positioning themselves as a cornerstone of next-generation therapeutics.

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