IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Microneedles In Drug Delivery: A Review

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Abstract: Recently, a novel transdermal delivery technology has garnered significant attention for its effectiveness in administering therapeutics and cosmeceuticals across various applications, such as vaccines, medications, and biomolecules for skin-related issues. The benefits of microneedle patch technology have been thoroughly examined in recent studies, leading to a surge in academic publications in this field. While microneedle patch applications hold considerable promise, they also face certain limitations. This review will address these potential drawbacks, highlighting areas in need of improvement. By focusing on these concerns early, we aim to assist scientists and technologists in addressing these issues promptly and utilizing their resources effectively.

***Keywords*:** microneedles; transdermal delivery; vaccine administration; transdermal patch technology

INTRODUCTION

The skin performs a wide range of functions, serving as a barrier that protects underlying organs from physical, chemical, and microbial threats. Utilizing the skin for drug administration is a promising approach for delivering therapeutics like vaccines, medications, biomolecules, and challenging small molecules. However, the skin's hydrophobic and lipid-rich outer layer limits the bioavailability of these therapeutics. Among the various transdermal drug delivery (TDD) methods, the microneedle (MN) delivery system has gained significant interest from research institutions and companies due to its non-invasive ability to deliver drugs through the skin. The skin’s protective, inflammatory, and immunological properties make the MN system a compelling alternative to traditional delivery methods.[1]

The MN delivery system consists of an array of submillimeter-sized needles (up to 1500 micrometers in length) attached to a support base. This design allows the needles to penetrate the viable epidermis, bypassing the stratum corneum (SC), which is the outermost skin layer. As a result, pharmaceutical compounds can be delivered painlessly since the system does not disrupt the dermal layer, where nerve fibers and blood vessels are primarily located. The MN delivery system has proven effective for administering larger drug molecules (over 500 Da) and various polarities, including small molecules, biomacromolecules (such as proteins, hormones, and peptides), and vaccines for diseases like SARS, MERS, and COVID-19.[2]

Microneedle technology was first conceptualized and patented in the 1950s, but it took several years for its advantages to gain widespread recognition. A pivotal report published in 1998 highlighted the potential of microneedles for vaccine delivery. Since then, the number of investigational studies on microneedles has significantly increased, with over 4,000 patents and research articles produced, and this number continues to grow rapidly. Notably, there has been significant advancement in this field in recent decades.[3,4]

Recently, MN patches have gained rapid momentum in the cosmetic field for skin moisturizing or anti ageing applications. Most commercialised MN patches are composed of hyaluronic acid (HA), which dissolves into the skin after administration. MNs made of HA can moisturise skin tissue and deliver actives for skin improvement via their dissolution. [5,6]

However, the shortcomings of the microneedle (MN) system must be addressed early in the product development process. To assess the future trajectory of this field, key advancements in microneedle research are discussed, along with challenges that could hinder the system's full potential. This brief review places particular emphasis on these limitations, which warrant significant attention. Highlighting these issues at the outset can assist scientists and technologists in resolving them promptly and using their resources effectively.[7]

MICRONEEDLE-BASED DELIVERY APPROACHES

The skin's extensive surface area and accessible location make it an ideal, non-invasive site for delivering therapeutic agents as well as sampling interstitial fluid for biomarker detection. Microneedle (MN)-based delivery and sampling techniques are pain-free, non-invasive, and can be self-administered, offering a promising alternative to traditional hypodermic needles, which enhances patient compliance. In recent decades, research in this area has intensified, leading to the development of microneedles using a variety of materials and designs, including metals, glass, polymers, and hydrogels. Several delivery methods have emerged, with four primary approaches initially proposed and one additional method developed later: [8,9]

1. Poke and Patch (solid MNs)
2. Coat and Poke (coated MNs)
3. Poke and Flow (hollow MNs)
4. Poke and Dissolve (dissolving MNs)
5. Poke and Release (hydrogel-forming MNs)

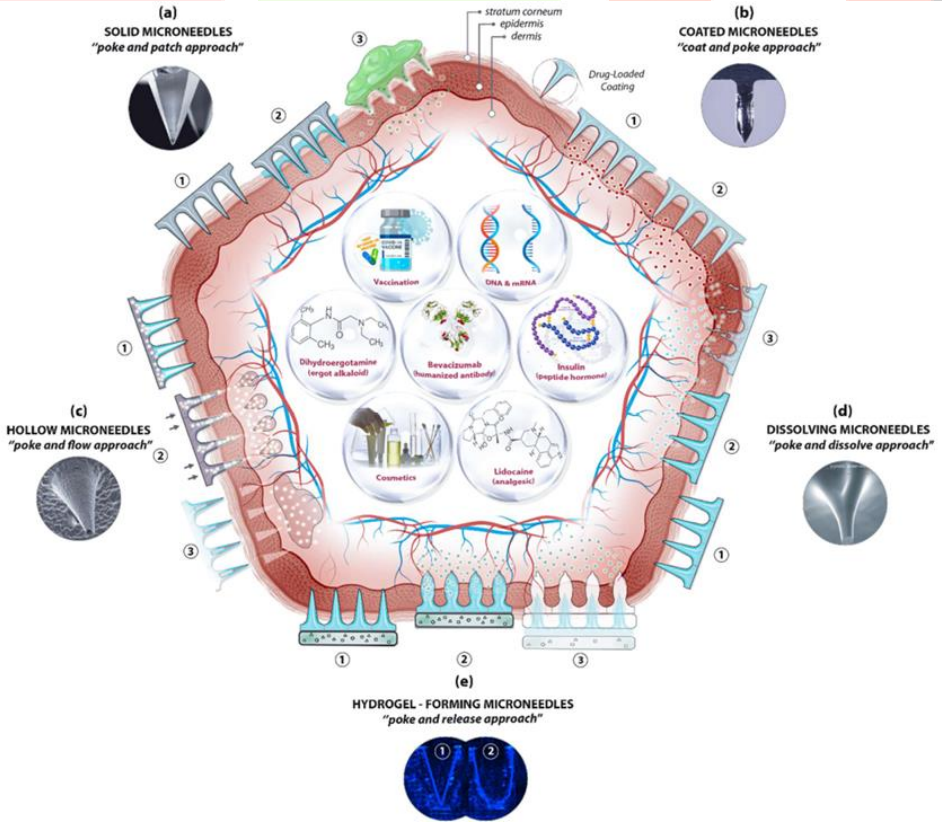

Fig 1: A schematic diagram of microneedle (MN)-based drug delivery approaches with the cross section of the upper layer of the skin.

The "poke and patch" approach involves using a solid microneedle (MN) patch to create small holes in the skin, followed by the application of a drug on the skin's surface. The initial fabrication of solid MNs was done using silicon to deliver calcein through excised human skin in vitro. However, issues such as cost, fragility, biocompatibility, and complex manufacturing processes have led researchers to explore other materials like metals, ceramics, and polymers for improved outcomes. Although producing solid MNs is straightforward—since it doesn't require loading or coating—the main limitations include the two-step administration process and challenges with accurate dosing due to the need for drug reformulations, along with safety concerns. The delivery of proteins, hormones, and vaccines using solid MNs has been extensively reviewed elsewhere.[10]

Coated microneedles are created by applying therapeutic agents to the surface of solid MNs made from materials such as metal, silica, or polymers. The "coat and poke" approach allows for effective drug delivery, provided that the formulations are stable and uniformly applied. The drug formulation must be water-soluble and compatible with layer-by-layer coating techniques. Selecting an appropriate coating method is crucial for successfully generating coated MNs. This approach has been used to deliver vaccines, insulin, hormones, and other macromolecules. Recently, coated MNs have also been employed for ultra-sensitive detection of protein biomarkers in an immunized mouse model. For example, polystyrene microneedles coated with a primary antibody were developed to capture inflammatory biomarkers in interstitial fluid, achieving an improved detection limit. A key advantage of coated microneedles is their ability to protect bioactive molecules during production, ensuring their bioactivity. Additionally, coating is a simple and controlled method to enhance microneedle functionality, especially for sampling and isolation tasks. However, common limitations include the potential reduction in microneedle strength and penetration ability due to small doses and loaded cargo.[11-14]

The "poke and flow" approach utilizes hollow MNs to deliver relatively large quantities of therapeutic agents into the skin, addressing the dosing limitations associated with solid MNs.[15] Hollow MNs allow for controlled flow and dosing via diffusion, pressure, or electronic methods (e.g., pumps) and can be integrated into lab-on-chip devices. They can effectively deliver biomacromolecules, including proteins, vaccines, mRNA, and diagnostic agents[16,17], and can also be used for biomarker isolation, such as glucose[18] and ECG measurements.[19] However, the construction of hollow MNs is complex and can face challenges such as clogging, drug leakage, structural fragility, and the need for a larger tip diameter, which may hinder insertion.

The "poke and dissolve" approach involves using water-soluble therapeutic agents that are delivered into the skin through biodegradable and cost-effective polymers. Commonly used materials for dissolvable MNs include hyaluronic acid, sucrose, polylactic/glycolic acid (PLA/PGA), and chitosan. These biomaterials are often employed due to their tunable properties and functionalities, leading to the development of carbohydrate-based microarrays with great potential for innovative drug administration, detection, and biological responses.[16] There has been a rapid increase in articles focused on the production of polymeric MNs. Unlike silicon or metal delivery systems, dissolvable MNs break down upon contact with the skin's interstitial fluid, releasing their therapeutic cargo for local or systemic effects. Most soluble MNs to date have been made using polymers and simple sugars through casting or micromolding techniques, effectively encapsulating and storing therapeutic loads.

The therapeutic agents are encapsulated within the scaffold of dissolvable microneedles (dMNs) and are delivered to the target area after skin insertion via a polymer erosion mechanism, leaving no biohazardous waste behind. For example, successful applications of dMNs in vaccine delivery have been demonstrated, with sucrose and fish gelatin-based microneedles used for this purpose.[20] In a Phase I trial, influenza virus vaccines delivered via microneedle patches (MNPs) were found to be both immunogenic and safe. This method addresses some drawbacks of solid MNs, such as sharp waste, the need for a pump with hollow MNs, and the high costs and complex layering processes associated with coated MNs. However, dMNs have their own limitations, including low mechanical strength, reduced dosing capacity, and uncertain penetration abilities.[21]

Recently, soft materials such as swellable polymers—including poloxamer[22], PEG-crosslinked poly(methylvinyl ether-co-maleic acid), and silk fibroin modified with phenylboronic acid/acrylamide[23]—have been employed to create hydrogel-forming MNs. These polymers absorb interstitial fluid into their three-dimensional matrix upon insertion into the skin, facilitating the delivery of therapeutic agents through the micro-conduits formed. Notably, the responsive delivery of therapeutic applications, such as glucose-responsive insulin, eliminates the need for constant glucose monitoring by relying on physiological signals. Hydrogel-forming MNs have also been explored for diagnostic applications, including glucose detection[24] and lithium monitoring[25]. The delivery timing can be fine-tuned by adjusting the polymer degradation rate, ranging from minutes to days. Nonetheless, the low strength and limited drug capacity of hydrogel-forming MNs present challenges that must be addressed for viable commercial applications in the near future.

CHALLENGES OF THE MICRONEEDLE DELIVERY SYSTEM

Transitioning microneedle (MN) technology from research labs to industry presents an exciting yet challenging endeavor. To effectively translate this innovative technology into viable products for the market, several key questions and challenges must be addressed promptly. In the following sections, we will explore these challenges and the active strategies that can be employed to overcome them, which could significantly influence the future of the field and its commercial applications. Figure 2 summarizes the main issues and concerns regarding the development of a microneedle-based delivery system.

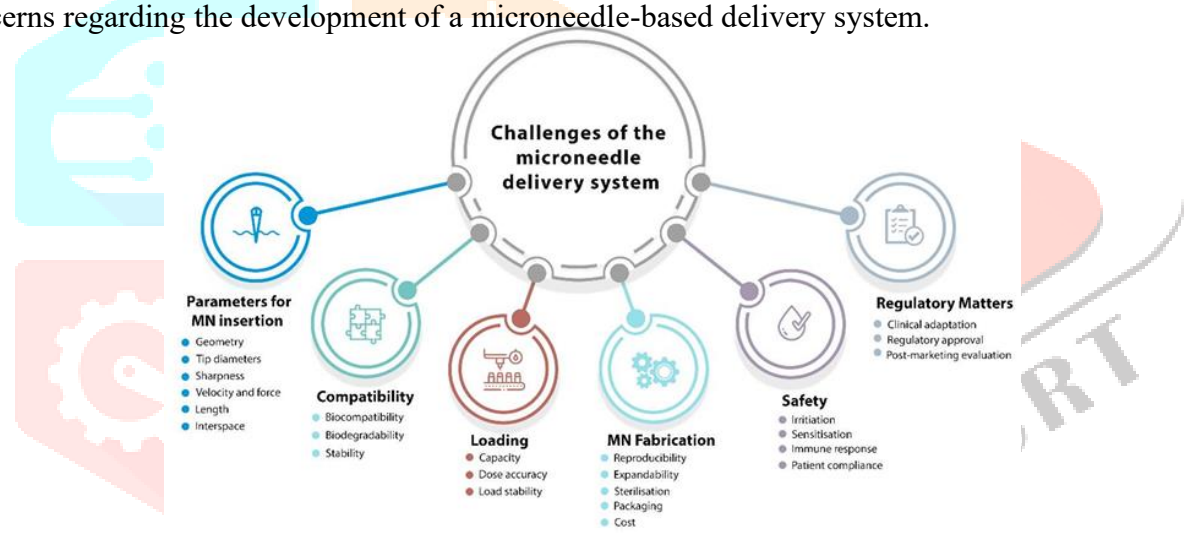

Fig 2: Factors effecting development of microneedle-based delivery system

Parameters Affecting MN Insertion

The ability of microneedle (MN) patches to effectively puncture the skin is crucial. When considering this aspect, it's essential to account for the skin's characteristics, which can vary across different body regions and between individuals. The insertion and penetration behavior of MNs, which must overcome the skin's elasticity, is influenced by several parameters, including geometry, base and tip diameters, length, and interspacing (center-to-center spacing). A "one-size-fits-all" approach is not feasible during the design and development of any MN application. The infiltration and active delivery performance of MNs are closely related to their geometry, materials, management methods, and the characteristics of the skin tissue. Depending on the target medications and applications, the mechanical strength, insertion depth, and drug release profile of microneedles can be finely tuned by adjusting their shape and composition.[26-28]

- **Geometry**

The geometry of MNs is a critical parameter to consider early in the development process. Recent studies indicate that the mechanical strength and penetration capabilities of MNs are influenced by the geometric structure of microneedle arrays. Simulations have demonstrated a linear relationship between mechanical strength and the number of vertices in the microneedle base (e.g., triangular, square, and hexagonal). Triangular and square microneedles tend to achieve better insertion depths due to their sharper edges compared to hexagonal designs. Cone-shaped MNs have been identified as ideal for delivering ovalbumin and achieving transcutaneous immunization, resulting in enhanced needle insertion and quicker disintegration for a more potent immune response. Additionally, recent innovations have suggested incorporating hemispherical convexities in the lower half of cone-shaped dissolving MNs to improve drug flux and reduce the risk of inadequate delivery.[29-31]

- **Tip Diameter and Sharpness**

Tip diameter significantly affects MN insertion. Relatively blunt MNs (with tip diameters of 60–160 micrometers) require higher insertion forces (0.08–3.04 N) and are directly related to the frontal area of the tip. For effective penetration, MNs with sharper tips (less than 15 micrometers in diameter) facilitate smoother access to the skin, which is particularly critical in vaccine delivery to ensure precise targeting of Langerhans cells in the epidermis or dendritic cells in the dermis for a robust adaptive response. While sharper tips reduce the required puncture force, they may also compromise the structural strength of the MNs, increasing the risk of breakage.[32,33]

- **Application Velocity and Force**

In addition to tip diameter, application velocity and force are vital parameters in the MN delivery system. Studies have shown that penetration depth varies significantly (from 10% to 80%) and increases with higher application velocity and force. Various patch configurations have yielded consistent penetration force requirements per microneedle. For instance, a 25-microneedle array with a tip radius of less than 100 nanometers requires an insertion force of about 10 mN per microneedle for effective skin penetration. Independent studies have confirmed that insertion forces of 15–20 mN and 15–30 mN per microneedle are necessary for effective insertion, translating to a total applicator force of 0.1–3 N for arrays of 10–100 microneedles. Although these forces are relatively low, maintaining consistent application may necessitate controlled application techniques or specialized devices. [34-37]

- **Length**

The thickness of the stratum corneum (SC) and other skin layers varies among individuals, which can affect the depth of microneedle (MN) insertion. The effectiveness of drug transport through the skin after applying an MN patch largely depends on how deeply the tissue is perforated. For drugs that are relatively small and possess high diffusion capabilities, creating surface pores with microneedles may suffice for therapeutic effects. However, if the goal is rapid delivery into the bloodstream, it may be advantageous to create pores that penetrate deeper into the dermis, where capillaries are located. This could explain the variety of microneedle lengths reported in studies. In addition to shorter microneedles, some research has explored longer microneedles (up to 1000 micrometers) to enhance insulin permeability through the skin.[38]

- **Interspace (Centre-to-Centre Spacing)**

The skin's topographical diversity allows it to withstand significant deformation before penetration occurs. To create effective delivery with a high-density array of microneedles (e.g., more than 500 per cm^2), a considerable number of punctures must be generated, requiring substantial energy. As the density and number of microneedles increase, so does the force needed to penetrate the skin, which can lead to heightened discomfort for the patient. This may necessitate the use of a larger or stronger application device for certain

scenarios. Additionally, increasing the width, length, and density of the needles can result in larger and more numerous puncture sites, allowing for greater medication diffusion. However, closely spaced needles may also lead to a "bed-of-nails" effect, which can complicate insertion and affect comfort.[34]

Biocompatibility, Biodegradability, and Stability

Biocompatibility is a critical safety consideration for microneedle (MN) systems intended for clinical use. To ensure MN products are safe for human exposure, various tests are conducted to assess biocompatibility based on contact durations: less than 24 hours, between 24 and 30 hours, and more than 30 hours. For the first two durations, tests for cytotoxicity, sensitization, irritation, and intracutaneous reactivity are performed. For the longer exposure period, additional tests for genotoxicity and subacute/subchronic systemic toxicity are recommended.

Biodegradability is highly desirable in microneedle materials, as biodegradable polymers can be safely degraded and removed from the body. Recent efforts in MN fabrication have increasingly focused on using biodegradable polymeric systems. One significant advantage of these polymeric microneedles is their ability to encapsulate medications within the microneedle matrix, allowing for controlled release through biodegradation or dissolution in the skin's interstitial fluid.[39]

Stability of the microneedle structures and their cargo is essential, particularly when involving sensitive therapeutics such as proteins and peptides. The capability to manufacture MNs from aqueous polymeric mixtures at room temperature—without the need for heating—helps maintain the stability of the incorporated medications. Stability assessments typically involve storing MNs and their cargo at various temperatures (25°C, 4°C, -20°C, 40°C, and 60°C) and conducting analytical evaluations. Generally, the protein cargo within MNs exhibits enhanced storage stability and longer shelf life due to the rigid glassy matrices, which restrict molecular mobility and limit exposure to atmospheric oxygen. The incorporation of stabilizers like trehalose and sucrose can further improve stability.[40]

Water management is particularly important under non-vacuum storage conditions, as excess moisture can compromise both the stability of the drug cargo and the mechanical integrity of the MNs. Dissolvable MNs, in particular, are sensitive to surrounding humidity, necessitating a dry and cool storage environment to ensure prolonged stability and shelf life.[41]

Loading Capacity and Dosage Accuracy

Loading Capacity: Coated microneedle devices typically deliver a bolus dose of around 1 mg of medication. In contrast, hollow microneedles facilitate continuous infusion or "on-demand" dosing. However, their effectiveness can be hindered if the central exit becomes blocked by compressed skin tissue after insertion. Despite the potential of MNs to penetrate the skin, challenges remain in ensuring optimal drug delivery and dosage accuracy, highlighting the need for ongoing research and development in this area. The effectiveness of microneedle technology largely relies on the passive diffusion of biological formulations into the skin, which can limit the ability to deliver large dosages effectively. A significant portion of the dose may remain on the skin's surface, leading to concerns about application timing and the lack of real-time monitoring of dose delivery. This hesitance is particularly notable in clinical scenarios like vaccine distribution, where consistent dosages are essential. Recent studies have demonstrated that administering vaccines directly into the epidermis and dermis can elicit strong immune responses using much lower doses compared to traditional intramuscular injections. However, this benefit could be compromised if only a small percentage of the administered vaccine penetrates the skin. While this challenge is not insurmountable, vaccines, in particular, necessitate a minimum dosage to effectively trigger immunity, making it more challenging to achieve adequate delivery through passive diffusion alone.[42,43]

Dosage Accuracy

Ensuring dosage accuracy in microneedle (MN) delivery systems, especially for continuous drug delivery, is crucial. Various strategies involving separable microneedles have been proposed to reduce the duration the patch is worn and facilitate rapid formulation removal. However, delivering protein drugs such as insulin, erythropoietin, glucagon, growth hormones, and parathyroid hormones poses challenges due to their

susceptibility to degradation. These issues can be mitigated by incorporating stabilizers and optimizing the entire manufacturing process, including storage conditions, polymer concentration, sterilization, and packaging. Solid microneedles often struggle with precise drug delivery, while coated microneedles can deliver accurate dosages but have limited loading capacity due to their small surface area. Dissolvable microneedles made from hydrophilic, biocompatible, and biodegradable materials can encapsulate drugs effectively, allowing for controlled release without producing residual debris. This method also enhances the penetration of nanoparticles through the skin barrier. Research into various analytical techniques for tracking nanomaterials in vitro and in vivo has shown promise in improving drug delivery accuracy.[44,45]

Skin Irritation and Recovery

The skin's immunogenic nature means it can respond significantly to MN-delivered therapeutics, potentially leading to mild, temporary erythema depending on the drug's size, composition, and type. Evaluating skin irritation, sensitization, and immune response is essential for the safety assessment of MN products during clinical trials. This evaluation typically requires animal testing before advancing to human trials. However, the skin's strong immune response may provide advantages for MN-based vaccine delivery if other challenges are adequately addressed.

Cost of Microneedle Fabrication

The current microneedle manufacturing processes must evolve to enable large-scale production for therapeutic applications. While extensive economic evaluations of this technology are still lacking, it is anticipated that, like many emerging technologies, the clinical application of microneedles may be costly due to complex fabrication, storage requirements, and lengthy regulatory approval processes.[46-48]

Sterilization of the Microneedle Patches

Sterilization of microneedle (MN) patches is a critical consideration in their development for commercial applications. Choosing an appropriate sterilization method is essential, particularly when the cargo includes sensitive ingredients such as biomolecules, vaccines, or peptides. Common sterilization techniques like moist heat, gamma radiation, and ethylene oxide may adversely affect both the active ingredients and the integrity of the microneedles themselves.

Despite the reduced risk of bioburden from MNs compared to traditional hypodermic needles, regulatory bodies often mandate complete sterilization to ensure user safety. The choice of sterilization method is influenced by the materials used for MN fabrication:

Solid MNs(made from metals, silicon, or glass) can be effectively sterilized using dry heat, moist heat, or gamma radiation.

Coated MNs that deliver fragile biological ingredients require careful selection of sterilization methods to preserve the stability and activity of the coatings.

Dissolving MNs (composed of carbohydrates and polymers) present the greatest challenge, as sterilization can impact both the drug load and the morphological, physicochemical, and mechanical properties of the MNs.[49]

Research has demonstrated that while no measurable bioburden was detected when following aseptic preparation, traditional sterilization methods such as moist and dry heat can damage formulations. Conversely, gamma irradiation at a sterility assurance level (SAL) of 10^{-6} is effective for hydrogel-forming MNs without causing structural damage, although it can degrade certain model drugs like ovalbumin and alter the appearance of ibuprofen.[50,51]Alternative sterilization methods, such as ethylene oxide and electron beam sterilization, have shown promise as less destructive options. Additionally, innovative approaches like embedding silver nanoparticles in carboxymethyl cellulose (CMC) MNs have been proposed for self-sterilization, ensuring that the MNs remain free from microorganisms until the skin has healed.[52]. Given the limited available literature, extensive research is needed to optimize sterilization processes for

MN-based products before they can be commercially produced and approved. The challenges of endpoint sterilization are particularly significant, as maintaining aseptic conditions during manufacturing can be both complex and costly.

Regulation of the Microneedle Patches

The regulation of microneedle (MN) patches poses unique challenges, particularly for submissions to the U.S. Food and Drug Administration (FDA). Concerns have been raised regarding the quality of submissions for combination products that employ MNs, specifically in areas such as stability testing, content consistency, risk analysis, sterility validation, and manufacturing processes. MNs offer a promising route for delivering a variety of therapeutic agents—including hormones, vaccines, enzymes, mRNA, and challenging small molecules—through the skin. To gain regulatory approval, it is crucial to demonstrate the efficacy and repeatability of MN devices through comprehensive studies involving cell cultures, animal testing, and clinical trials. Additionally, a nuanced understanding of human physiological conditions, clinical needs, and the usability of MN devices is essential for promoting successful clinical translations. The number of MN-based medicinal products is rapidly increasing, but the submission process for FDA approval is complex. Submissions are considered combination products, which require extensive information regarding product analysis and testing. This includes risk analysis, content uniformity, stability testing (focusing on formulation/API migration and mechanical characteristics), sterility validation, and details about manufacturing processes. The FDA emphasizes that "regulation of combination products must take into account the safety and effectiveness questions associated with each constituent and the product as a whole." The current FDA strategy favors product-specific approvals rather than approvals for specific MN systems, resulting in significant delays that can hinder the commercialization of MN technologies. To facilitate this process, merging current Good Manufacturing Practices (cGMP) with quality control and establishing clear licensing regulations for aspects such as shape, formulation, sterilization, and packaging are crucial. Additionally, clinical development of MN devices could progress independently from drug or vaccine formulations, simplifying regulatory processes and potentially allowing for quicker integration of MN technology into drug supply chains. While only small quantities of active ingredients may reach target delivery sites, this streamlined approach could mitigate some regulatory challenges faced by more complex formulations.[39]

There is also potential for MN devices to be classified under CE marking as medical devices, allowing pharmaceutical companies to invest in the device before committing to the development of the associated medication. Robust guidance is needed to classify MN-based products appropriately; they may fall into categories as medical devices for monitoring/diagnostic purposes, or as combination products (integrating drug and device) or drug products for delivering medications or vaccines. Adapting existing quality control measures for MNs is crucial, as current standards for transdermal patches may not adequately address the unique characteristics of MN products compared to traditional hypodermic needles. If these regulatory concerns can be effectively resolved, the introduction of MN-based products into the transdermal market could soon become a reality. A notable milestone was achieved in 2020 when Zosano Pharma submitted the first new drug application for a pharmaceutical microneedle patch, named Qtrypta. This patch features titanium microneedles coated with zolmitriptan for the acute treatment of migraines, marking a significant step forward in MN technology and its regulatory journey.[53,54]

CONCLUSIONS

The development of marketable microneedle (MN)-based drug delivery products appears imminent. Ongoing extensive research is focused on enhancing the efficient delivery of therapeutics, as there is a pressing need for innovative transdermal delivery methods that cater to hydrophilic molecules, macromolecules, proteins, and conventional medicines for new therapeutic indications.The future of the microneedle industry looks promising, with rapid advancements in knowledge and technology driving industrial progress. MNs have shown effectiveness in several clinical trials, though a significant number of preclinical studies remain. Collaboration among experts from academia, industry, and regulatory bodies is essential to ensure the safe and effective clinical application of MNs, provided that the existing challenges are addressed promptly and

rationally. It is anticipated that microneedle technology will contribute to improved illness prevention, diagnosis, and control, ultimately enhancing the health-related quality of life for patients worldwide. However, the complex and costly production processes, along with various application-related challenges, could impede their clinical translation. This is evident in the limited clinical data available on platforms like "www.clinicaltrials.gov" regarding "microneedle vaccines," highlighting the ongoing difficulties in scaling up MN production. Looking ahead, novel manufacturing techniques—particularly micromachining and 3D printing—hold significant promise for reducing costs and simplifying fabrication processes. These advancements could facilitate the transition of microneedle technologies from research and development stages to practical, widely used therapeutic applications, paving the way for broader adoption in clinical settings.

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