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A REVIEW ON LONG-ACTING TRANSDERMAL MICRONEEDLES AS AN EMERGING DRUG DELIVERY SYSTEM

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ABSTRACT

Over the past 20 years, there has been a growing interest in microneedle (MN)-assisted drug delivery technologies. It is a competitive substitute for conventional hypodermic needles due to its advantages of self-management and low invasiveness. MNs enable regulated and prolonged release by penetrating the stratum corneum and delivering active substances through the cutaneous layer. Long-acting polymeric MNs can improve patient compliance and treatment results by lowering the frequency of administration, especially when managing chronic diseases. Long-acting MNs can also lessen adverse effects and gastrointestinal responses, underscoring their potential therapeutic utility. Recent developments in long-acting polymeric MN design and applications are reviewed in this paper. We also address the challenges of large-scale manufacturing and regulatory considerations for polymeric MN systems, as these factors are crucial for the effective clinical translation of MN products.

Keywords: Transdermal, Microneedles, Long-acting system, Novel drug delivery.

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INTRODUCTION

Transdermal drug delivery systems (TDDS) have become more and more common in recent years for both local and systemic drug delivery. Systemic medication administration is made possible by the delivery of active components into the circulatory system via cutaneous tissue [1,2]. However, only a small number of highly lipophilic tiny molecules (with log p values between 1 and 3, a molecular weight of less than 500 Da, and a low melting point) can benefit from TDDS due to the stratum corneum's (SC) poor permeability [3]. Usually found on one side of a patch or the bottom layer of a supporting substrate, microneedles (MNs) are made up of several micron-sized projections that range in size from 25 to 1,000 microns [4]. As a physical permeation-enhancing technique, MNs can penetrate the stratum corneum and create reversible microchannels in the skin's surface layer, significantly enhancing drug permeability and penetration [5–7]. This approach avoids the invasiveness associated with conventional injections, improving patient acceptance and

compliance.

Since the concept was first introduced in 1976, six major categories of MNs have been developed: solid, coating, hollow, swell, dissolving, and biodegradable [8]. Recently, the applications of MNs have expanded into drug delivery, cosmetic medicine, and medical devices, with specific applications illustrated in Figure 1. The materials used to create MNs can be divided into inorganic materials and polymers. Inorganic materials, such as silicon and metal, are commonly used to produce solid or hollow MNs [9–12]. However, these inorganic materials often exhibit low biocompatibility and are prone to fracture, which can lead to intradermal biohazard residues. In contrast, biodegradable polymers have emerged as the preferred materials for MN preparation due to their excellent mechanical properties, biocompatibility, and low production costs. These biodegradable MNs can safely degrade in vivo, even in the event of breakage within skin tissues, eliminating the risk of sharp biohazardous waste.

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In recent years, advancements in slow-releasing polymers and nano/micro-particle drug delivery technologies have transformed microneedles (MNs) from traditional rapid-release mechanisms to long-acting release systems [13]. MNs can currently be used to deliver a wide range of medications, including chemical substances and macromolecular biological medications like proteins and vaccinations. Chronic patients generally need long-term medication, yet they often don't take it as prescribed. The risk of toxicity can be increased by conventional rapid-release administration methods, such as daily oral pills or injections, which can result in large variations in plasma drug concentrations. Additionally, missed or delayed dosages might result in inadequate illness management, as is the case with diabetics' blood glucose control and women of reproductive age's contraception. By assisting in the maintenance of steady plasma medication concentrations, long-acting delivery methods lower the possibility of systemic toxicity. For patients with chronic illnesses, long-acting MNs are therefore expected to improve self-management and extend therapeutic efficacy [14].

Polymeric MNs can facilitate long-acting drug release by modifying the degradation profiles of polymer excipients and the diffusion rates of encapsulated drugs. This review emphasizes the benefits of polymeric MNs in treating chronic diseases, summarizes four key design strategies for long-acting MNs, and explores their mechanisms of action across various disease areas. We conclude by addressing the challenges associated with this technology and the potential for transitioning from laboratory research to clinical application in the future.

DESIGN STRATEGIES OF LONG-ACTING POLYMERIC MICRONEEDLES

By continually releasing medications over a lengthy period of time, long-acting polymeric microneedles (MNs) provide long-lasting medicinal effects. Four typical design approaches for long-acting polymeric MNs can be summed up as follows based on the characteristics of the primary polymer materials (such as dissolving, biodegradable, or swellable) and the kinds of drug reservoirs (nano/microparticles or back-layer): (A) dissolving MNs filled with nanoparticles or microparticles; (B) biodegradable polymeric MNs; (C) swellable polymeric MNs; and (D) back-layer reservoir polymeric MNs. The benefits and drawbacks of several long-acting polymeric MN design techniques are also discussed [15, 16].

Nano/microparticle-loaded dissolving microneedles

Water-soluble polymer materials such as hyaluronic acid (HA), polyvinylpyrrolidone (PVP),

polyvinyl alcohol (PVA), chondroitin sulfate (CS), and glucan are commonly used as matrix excipients for nano/microparticle-loaded dissolving MNs. Drugs are encapsulated in the soluble matrix of the needle tips using slow-release methods, such as microspheres and nanoparticles. When combined with MN delivery systems, these slow-release nano/microparticles—which can be composed of liposomes, metal nanoparticles, or nanocrystals—allow for sustained release. The matrix excipients of this kind of MN completely dissolve in a matter of seconds or minutes after being inserted into the skin, leaving behind deposits of microspheres or nanoparticles that act as a drug reservoir [17-20].

Biodegradable polymeric microneedles

Biodegradable polymers have garnered significant attention due to their bioavailability and the precise control they offer over the degradation rate in drug delivery systems. These polymers are utilized for delivering antibiotics, growth hormones, and vaccines in various forms, including microcapsules, films, and fibers. Biodegradable polymeric microneedles (MNs) combine the features of traditional MNs with implantable drug deposits. The polymers used in these MNs can be categorized into natural options, such as chitosan and silk fibroin, and synthetic options like PLGA and polylactic acid (PLA). While these synthetic polymers are nearly insoluble in the interstitial fluid of skin tissue, they degrade slowly over time. The drug release profile is closely tied to the polymer degradation rate; therefore, adjusting the physical and chemical properties of the polymer, such as molecular weight and block molar ratios, can facilitate the desired release period for different drug types. Additionally, it is advantageous to manufacture MNs using double-layer or multilayer techniques, allowing the biodegradable cone needle tips to detach quickly from the backing layer after application to the skin, thereby reducing application time. Chitosan is frequently chosen as a material for biodegradable polymeric MNs due to its excellent biodegradability. This method increased the immunogenicity of the inactivated influenza vaccine and fostered long-lasting protective immunity in mice by providing prolonged antigen exposure and immunological stimulation. Because of its inherent qualities, including as biocompatibility and biodegradability, which make it appropriate for MN production, PLGA is also frequently used for continuous drug release [21-24].

Swellable polymeric microneedles

Swellable polymeric microneedles (MNs) are typically created by crosslinking hydrophilic polymers. The methods for polymer cross-

linking generally include chemical cross-linking and physical incubation under UV radiation or high temperatures. These swellable MNs do not dissolve or degrade within the skin tissue. Instead, they absorb interstitial fluid from the skin, causing the needle tips to swell and form hydrogel channels that facilitate drug diffusion. Consequently, swellable MNs must always be applied directly to the skin during administration. The kinetics of drug release are primarily influenced by factors such as drug solubility, the degree of cross-linking, the swelling properties of the polymer, and polymer-drug interactions. Typically, these MNs are designed as an integrated type so that the base plate can also function as a drug reservoir, allowing for the delivery of milligrams of drug to small areas. Furthermore, this type of MN can be completely removed after application, addressing safety concerns related to polymer and degradation product residues [25-29].

Back-layer reservoir polymeric microneedles

When back-layer reservoir polymeric microneedles (MNs) are applied to the skin, the needle tips are used to form drug penetration channels. The size of the needle tips, however, could not be sufficient for the proper drug

loading required for long-term administration. To improve the drug loading capacity of MNs for prolonged drug delivery, external drug reservoirs or the MN base layer are crucial. Usually, swellable or dissolving polymers are employed to make the needle tips. As was already indicated, swellable needle tips allow for continuous medication distribution from the reservoirs by preventing the skin microchannels from closing [30-32]. The purpose of long-acting formulations is to maintain medications at therapeutic levels for as long as necessary while undergoing therapy. extended-acting polymeric microneedles (MNs) are perfect for a variety of medications, including biomacromolecules, medications with extended half-lives or low bioavailability, and medications administered locally. Long-acting MNs for controlled drug release have the potential to greatly improve therapeutic effects, minimize systemic exposure toxicity, lower the frequency of administration, and increase medication compliance in patients with chronic illnesses. Their uses in diabetes, vaccinations, cancer, skin conditions, and contraception are covered in the sections that follow.

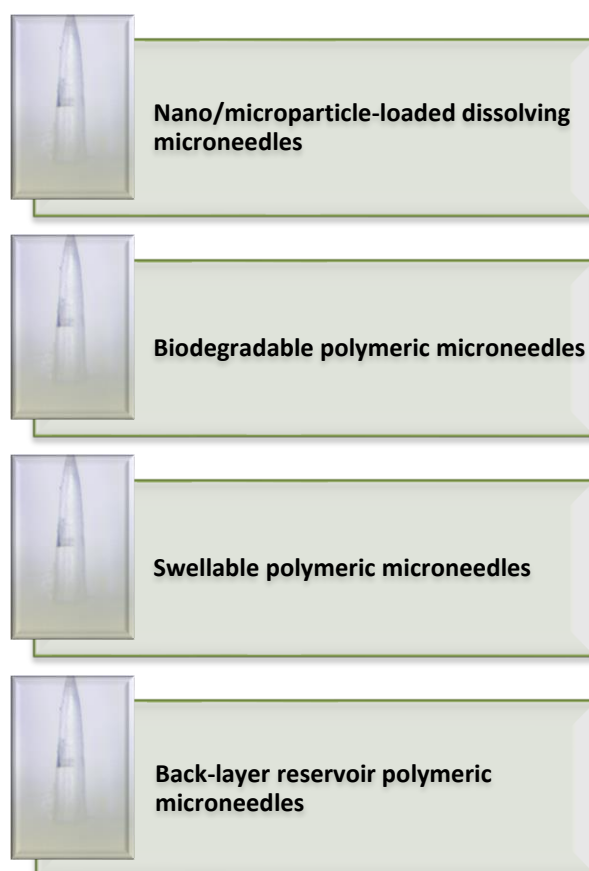


Figure 1: Design strategies of long-acting polymeric microneedles.

APPLICATION OF LONG-ACTING POLYMERIC MICRONEEDLES

Diabetes

Diabetes is a common chronic disease characterized by blood glucose disorders. Frequent subcutaneous insulin injections are the most common treatment for effectively controlling blood glucose levels. Utilizing MNs for insulin delivery can reduce medical waste and address issues such as injection pain, needle fear, and adverse reactions at the injection site. A possible method for controlling diabetes using insulin delivery systems is the use of smart glucose-responsive MN patches. A smart insulin MN made of silk fibroin binding semi-interpenetrating network hydrogels was described by Chen et al. A two-layer approach was used to enhance the preparation process: the base layer was made entirely of silk fibroin, while the needle-tip layer included both silk fibroin protein and phenylboric acid/acrylamide hydrogel. The reversible binding interaction between glucose and borate in aqueous solution is the basis for this responsive system. Because of this, the MNs can respond to hyperglycemia by releasing insulin on their own, much like a healthy pancreas [33-37]. Dual-responsive MNs, which depend on glucose and hydrogen peroxide concentrations to regulate insulin release rates, have been developed as early as 2018. In the future, integrating electronic messaging technology with wearable insulin-MN patches could enhance their appeal. The reliance on repeated hypodermic injections for vaccines is one of the biggest barriers to increasing global vaccination coverage and protection. The MNs delivery method using nano/ microparticle-encapsulated vaccines provides a novel method of different vaccine delivery systems for skin immunization. Mazzara et al reported vaccine MNs containing PLGA controlled-release particles to achieve the same performance as traditional prime-boost immunity of conventional hypodermic injections.

Contraception

The high rate of unwanted pregnancies places significant emotional and financial strain on women and society. Long-acting contraceptives can enhance family planning and offer flexible protection to women who are fertile. The vaginal ring, implants, and long-acting injections are examples of long-acting contraceptives available on the market. However, because they are all invasive, medical specialists must administer or remove them. Therefore, better self-administered long-acting contraceptives are desperately needed to give women more options and convenience. Despite offering up to one week of contraceptive protection, the transdermal patch is noticeable and interferes with daily hygiene due to its continual administration. These issues might be resolved by long-acting polymeric MNs. Offering a new option for female contraception is critically

crucial, particularly in underdeveloped nations. The innovative long-acting contraceptive MN patches were well received by women and suppliers. They all got over their worries about discomfort after talking more about how utilizing MNs felt on their skin [38-41].

Cancer

Conventional cancer treatments, such as radiation, chemotherapy, and surgery, might harm healthy tissues in addition to malignant cells. Compared to invasive drug delivery techniques (such intravenous infusion), MN drug delivery has demonstrated unique benefits in the treatment of superficial tumors, and its minimally invasive treatment features are more appealing. Long-acting MNs can reduce systemic toxicity by directly accumulating medications into superficial tumor lesions and achieving regulated release. Additionally, its sustained-release characteristics can lower the likelihood of tumor recurrence, improve drug compliance, and decrease the need for frequent medical visits [42-44].

Skin Diseases

The human body's skin serves as a vital barrier of defense. People's quality of life is significantly impacted by chronic skin conditions. Topical treatment is mostly advised for mild instances in order to minimize systemic side effects. However, this approach's therapeutic efficiency is diminished by the stratum corneum's barrier function. According to research, just 20% of the medication could be absorbed into the skin when typical cream was applied to the skin's surface. Due to their safe and effective intradermal medication administration, polymeric MNs have demonstrated notable benefits when used in conjunction with long-acting preparations. Actinic keratosis, acne, hypertrophic scars, and atopic dermatitis are among the skin conditions for which polymeric MNs have been extensively researched to date. Enhancing skin penetration, controlled drug release, targeted drug delivery, and imaging and therapeutic functions are the four design principles for increasing efficacy for the use of MN-based devices in the treatment of skin diseases [45-48]. One to three percent of people have psoriasis, a chronic inflammatory autoimmune skin condition that needs ongoing care.

CHALLENGES FACED BY MN SYSTEMS

MN technology has significant advantages over traditional transdermal drug delivery and has been adopted for clinical use by various researchers. However, the widespread adoption and application of MN technology face challenges related to manufacturing barriers and unclear regulatory pathways.

Manufacturing Challenges

In the preparation of polymeric MNs, factors such as height, shape, spacing, penetration ability, and moisture significantly influence the drug release

profile and are crucial for design and development. Currently, industrial scalability, product quality control, and cost-effectiveness are key factors in the evolution of polymeric MN technology to industrial manufacturing. Micro-molding and lithography are the two types of methods used in the production of polymeric MNs. The micro-molding technique is especially useful for polymeric MNs and requires an external force to fill the mold with the formulation solution. Centrifugation and suction techniques are common filling methods. Without the need for molds, the lithography method prints the master pattern of the MNs' geometry onto the substrate. Innovative techniques such as 3D printing and centrifugal lithography can also be employed. As of now, there are no biodegradable polymeric MNs available in global markets. Under Good Manufacturing Practice (GMP) management, it is essential to establish standardized operating procedures and production process controls to ensure repeatability across multiple batches, which would support the industrial production of polymeric MNs [53-57].

Regulatory Challenges

In 2019, the PATCH organization established the Microarray Patch Centre of Excellence to accelerate MN development efforts. Currently, the clearance procedure for MNs requires individual applications, and there is no comprehensive regulatory framework for specific MN systems, which severely limits the commercialization of MN medical products. The safety profiles and data support for excipients used in MNs often lack rigor, especially for intradermal applications. While the biocompatibility of MNs is currently high, some chemicals in MNs might accumulate in the skin, potentially leading to adverse effects such as granulomas or localized redness. The long-term effects of MNs on the skin still require further investigation. Additional preclinical studies should be conducted to assess pharmacokinetics, pharmacodynamics, and biosafety *in vivo* [58-62]. Early engagement and planning with regulatory authorities are crucial. If shortcomings are identified during later clinical stages, this could significantly delay clinical progress. In order to ensure product quality, consistency, and repeatability, health and regulatory organizations should assist manufacturers in developing production processes and quality standards suitable for this dosage form in accordance

with GMP. Large-scale manufacturers must also adhere to stricter sterility requirements set by regulatory bodies in order to prevent infections. Finally, in order to guarantee dosage consistency and enable successful clinical translation after product development, it is critical from the user's point of view to produce precise descriptions of the administration technique or standard pharmaceutical equipment [63, 64].

CONCLUSION

Long-acting polymeric microneedle (MN) drug delivery systems are a novel platform that combines sustained drug release technology with MN patches. This strategy increases patient compliance, increases the possibility of self-administration among patients with chronic illnesses, and reduces the weariness brought on by daily pill regimens and injection pain. Additionally, by guaranteeing that the medication is constantly administered at a therapeutic concentration, it may reduce the danger of systemic toxicity. Furthermore, research on the use of dissolving MNs to administer doxorubicin for the treatment of skin cancer is presently undergoing clinical trials. However, no long-acting polymeric MNs have yet to enter clinical trials, in contrast to conventional dissolving or coated MNs. Long-acting MN-assisted medication therapy has made great strides, but there are still a number of obstacles to overcome in terms of patient acceptance, regulatory compliance, and large-scale commercial manufacture. Since long-acting polymeric MNs are a relatively new technology, the majority of current research has focused on their structure and potential uses. These systems have shown noteworthy benefits and successful therapeutic results, inspiring continued research. Long-acting medication delivery by MNs appears to have a bright future thanks to ongoing advancements in preclinical and clinical research.

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