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DESIGN AND FABRICATION OF MICRONEEDLE FOR CONTROLLED DRUG RELEASE

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ABSTRACT

Microneedle (MN) technology has emerged as a minimally invasive and effective substitute for conventional injectable and oral drug delivery systems. Although the approach has been widely explored, its clinical translation remains restricted because of limitations such as insufficient drug-loading capacity and challenges in achieving optimal therapeutic levels. Dissolvable and biodegradable microneedles are primarily applicable for low-dose treatments, including immunization and delivery of Highly potent medications. Microneedles provide a novel strategy for transdermal drug administration by overcoming the protective barrier of the epidermis. These micro-sized projections create temporary channels within the skin, thereby reducing barrier resistance and enhancing drug permeation. The technology has gained considerable interest in biomedical research due to its capability to deliver various therapeutic agents, including biological molecules, vaccines, pharmaceuticals, and other medicinal compounds, through the skin. Microneedle systems have demonstrated applications in vaccine delivery, systemic therapy, and cosmetic treatment. Continuous advancements in this technology highlight its potential to improve therapeutic effectiveness and patient adherence through safe and efficient transdermal drug delivery.

Keywords: *Microneedle Technology, Transdermal Drug Delivery, Types of Microneedle, 3D Printed microneedle.*

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1. INTRODUCTION

The skin, the largest organ of the human body, covers approximately 1.5–2.0 m² and constitutes about 15% of total body weight. It serves as a protective barrier against microbial, chemical, and physical stressors. Transdermal drug delivery is a noninvasive and patient-friendly approach that offers advantages such as pain-free administration, improved compliance, controlled drug release, and avoidance of first-pass metabolism. However, the skin's barrier function, particularly the stratum corneum, limits the permeation of many therapeutic agents. To overcome this challenge, various chemical and physical enhancement techniques have been developed. Among these, microneedle patches have emerged as a promising transdermal drug delivery platform. Microneedles enable painless and minimally invasive delivery by creating microchannels that bypass the stratum corneum, resulting in improved drug bioavailability and therapeutic efficacy [1].

Furthermore, drug release profiles can be tailored through microneedle design and formulation. Extensive research has been conducted on microneedles fabricated using diverse materials and manufacturing techniques for the delivery of pharmaceuticals and cosmetic agents.

2. HISTORY AND EVOLUTION OF MNS

The concept of using microdevices for biomedical applications was first introduced in 1921 by Robert Chambers, who developed steel microdevices for injection and suction purposes in vitro in cells [2]. Each development reflects significant progress in MN technology, addressing safety, functionality, and application specific needs. Fig. 3 provides an overview of key milestones in the development journey of MNS, highlighting pivotal advancements in their evolution. From an application perspective, MNS were first employed for delivering small molecules in 1998, genetic materials in 2002 and vaccines in 2002 using solid

MNs. In 2003, the delivery of nanoparticles and macromolecules was reported using solid and hollow MNs. MNs have since expanded beyond drug delivery; in 2005, MNs were explored in cosmetics for inducing percutaneous collagen production. While hollow MNs have been utilized for blood extraction and glucose monitoring since 2000, they were employed in 2005 for dermal interstitial fluid (ISF) extraction for the same purpose. While initially designed for transdermal drug delivery, MNs have since been adapted for additional routes, including ocular, oral, intra myocardial, and vaginal, among others.

3. PRINCIPLES OF MICRONEEDLE TECHNOLOGY

2.1 Design and Framework

Microneedles are tiny needles, typically ranging from 50 to 900 micrometers in length and a few micrometers in diameter, designed to create micro channels in the skin without reaching deeper nerves, thereby minimizing pain. These microneedles are often arranged in arrays on a patch to cover a larger surface area and ensure uniform drug delivery.

2.2 Formulation Components

Microneedles can be fabricated from various materials, each chosen based on the intended application and the desired mechanical and biocompatibility properties. Common materials include

Polymers: Biodegradable polymers like poly lactic acid (PLA), polyvinylpyrrolidone (PVP), and carboxymethyl cellulose (CMC) are commonly employed in the fabrication of dissolvable and hydrogel-based microneedles [3].

Metals: Materials such as stainless steel and titanium are frequently utilized in the production of solid and coated microneedles because of their high mechanical strength and long-lasting stability.

Silicon: Microneedles composed of silicon are produced using microelectromechanical systems (MEMS) techniques, which enable accurate manufacturing and uniform needle structure.

4. CLASSIFICATION OF MICRONEEDLES

A typical microneedle has the shape of a tapered sharp tip with a length of 150–1500 μm , a width of 50–250 μm , and a tip thickness of 1–25 μm [4].

5. BASED ON VARIATIONS IN DRUG DELIVERY

5.1 Solid microneedle

Solid microneedles are a system that consists of microscale tapered sharp tips composed of a single material without any drugs or excipients. Solid microneedles operate on a "poke and patch" principle, creating microchannels in the skin that improve drug permeability by enabling direct diffusion into the dermal layer. Studies on rat skin show that these micropores can remain open for up to 72 hours under occlusive conditions.

5.2 Coating microneedles

In coated microneedles, the surface of a solid microneedle is coated with a water-soluble matrix, allowing the drug to dissolve rapidly into the skin upon microneedle insertion. The coating formulation must form a film on the microneedle surface and maintain adhesion during storage and skin insertion.

5.3 Dissolving Microneedles

Dissolving microneedles are made from biocompatible materials that dissolve upon insertion into the skin, releasing the encapsulated drug [5]. This type is ideal for single-use applications and eliminates the need for needle disposal. MNs dissolve into the skin thereby releasing the conjugated therapeutic agent.

5.4 Hydrogel-Forming Microneedles

Hydrogel-forming microneedles absorb interstitial fluid from the skin and swell, forming a hydrogel matrix that can release drugs in a controlled manner over an extended period. Hydrogels are cross-linked hydrophilic polymer networks capable of absorbing water, resulting in swelling and responsiveness to diverse stimuli.

6. CLASSIFICATION OF STIMULI-RESPONSIVE MICRONEEDLES

In addition to the aforementioned microneedles, there are stimuli-responsive polymer microneedles that can be activated by external factors to release the desired drug [6]. The MNs are designed to evenly and effectively encapsulate the active bioactive agents,

1. pH-Responsive MNs
2. Photoresponsive MNs
3. Thermal Responsive MNs
4. Electroresponsive MNs
5. Ultrasound-Responsive MNs

7. DIFFERENT FABRICATION METHODOLOGIES FOR MICRONEEDLE

7.1 Microelectromechanical System (MEMS)

It is a fabrication technique used for hollow and solid microneedles. It prepares molds for dissolving microneedles. During the pattern transfer stage, a two-dimensional design from a mask is imprinted onto a substrate that is coated with a photoresist layer [7]. Etching procedures are broadly classified into two categories: wet etching and dry etching.

7.2 Micro mouldings

Micromolding is used to produce different types of polymers, including natural polymers like pectin and synthetic or semi-synthetic polymers such as PVA and PVP. The 2D shape of a microneedle is generated through cutting on a flat metallic sheet using a laser. Injection Molding including Laser Cutting and Drawing Lithography.

7.3 Microstereolithography (μSL)

Micro-stereolithography (μSL) is a rapid, high-efficiency manufacturing method used to create three-dimensional (3D) micro-scale structures through a layer-by-layer additive process. This method works by precisely controlling the hardening of a liquid resin using light-induced polymerization.

7.4 Photolithography

Photolithography is a technique used to exquisitely invent solid and hollow microneedles. This fabricates silicon microneedles or dissolving or hydrogel microneedle by means of making an inverse mold based on the structure the structure of microneedle.

8. DRUG DELIVERY BY MICRONEEDLE

8.1 proteins

Protein-based therapeutics are widely utilized in oncology, immunization strategies, and management of hereditary disorders. Microneedle-based systems are actively explored to enhance the delivery performance of protein therapeutics. Several proteins, such as insulin, desmopressin, erythropoietin, lysozyme, glucagon, glucagon-like peptide-1, parathyroid hormone, and growth hormone.

8.2 Vaccines/antibodies

Vaccines are traditionally administered through subcutaneous injections. However, microneedle-based vaccine delivery systems have recently gained attention due to their ability to stimulate strong antibody-mediated immune responses. To enhance immune responses further, immunomodulatory agents such as granulocyte-macrophage colony-stimulating factor (GM-CSF) [8].

9. 3D PRINTING-BASED TECHNIQUES

It is possible to develop micro needles with multifaceted 3D structures. It encompasses various techniques such as liquid crystal display (LCD), projection-based printing (PBP), continuous liquid interface production (CLIP), stereo lithography (SLA), two-photon polymerization (TPP), [9]. Investigate the impact of various 3D-printing parameters on the efficacy of the transdermal drug delivery method. The parameters include temperature.

10. APPLICATIONS OF MICRONEEDLES

10.1 Chronic Disease Management

Microneedle technology offers a minimally invasive and pain-free approach for managing chronic diseases such as diabetes, reducing dependence on frequent conventional insulin injections.

10.2 Pain Management

It is providing targeted treatment with minimal systemic side effects. This approach is beneficial for managing chronic pain conditions such as arthritis and neuropathy [10]. Microneedles can deliver both small molecule analgesics and larger biologic therapies.

10.3 Cosmetic Application

Within the cosmetic field, microneedles are employed to administer anti-aging compounds, including hyaluronic acid, peptides, and other dermal rejuvenating agents. These systems enhance the penetration and bioavailability of active ingredients.

10.4 Gene Therapy

Microneedles enable the transdermal administration of nucleic acids, such as DNA, RNA, and small interfering RNA (siRNA), for therapeutic gene regulation. This

strategy offers significant potential for the management of genetic disorders and other diseases through molecular-level intervention.

10.5 Wound Healing and Wound Dressing

The therapeutic success of many factors used in chronic wound management has been limited due to inadequate delivery to the targeted wound site. Zhang and colleagues developed an innovative wearable, self-powered microneedle platform.

11. CHALLENGES AND LIMITATIONS OF MICRONEEDLE

Microneedle drug delivery systems are made from organic and inorganic materials, with polymers being the most widely used due to their biocompatibility, biodegradability, and mechanical stability [11]. Stimuli-responsive microneedles enable sustained, controlled, or on-demand drug release at target sites by responding to internal or external triggers, improving therapeutic efficacy while reducing pain and side effects.

12. PROSPECTIVE INNOVATIONS

12.1 modernizing manufacturing approaches

The development of economically viable and scalable production methods is essential to improve the accessibility of microneedle technologies. Manufacturing approaches such as additive manufacturing, micromolding, and continuous roll-to-roll fabrication techniques offer promising solutions and warrant further investigation [12].

12.2 Enhancing structural and functional drug stability

Designing formulations that preserve drug stability within microneedle systems during storage and administration is crucial for maintaining therapeutic effectiveness [13]. Strategies such as encapsulation techniques, incorporation of cryoprotective agents, and the use of stabilizing excipients are currently being extensively investigated [14].

12.3 Clinical trials

Carrying out comprehensive clinical investigations is essential to confirm the safety, effectiveness, and appropriate usage parameters of microneedle-based systems across diverse therapeutic applications [15].

12.4 others

Repeated application of microneedle patches at the same skin site may lead to complications such as irritation, allergic reactions, and localized inflammation [16]. Moreover, maintaining the long-term stability and structural preservation of the therapeutic agents loaded within microneedles is a critical consideration.

13. CONCLUSION

The biomedical research sector has experienced growing interest in designing and manufacturing drug delivery systems that can be controlled or triggered according to therapeutic requirements. This article reviews different fabrication techniques used for microneedle production, classifies the various types of microneedles, and discusses the materials employed in

their development, with particular emphasis on their biomedical applications. Microneedle technology demonstrates significant promise in revolutionizing drug delivery systems, representing a rapidly advancing area for continuous research and technological progress [17]. Microneedle technology has advanced toward scalable manufacturing, and drug delivery systems based on microneedles are anticipated to enter the pharmaceutical and cosmeceutical markets in the near future [18].

14. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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None

16. DECLARATION COMPETING INTEREST

The authors have no conflicts of interest to declare.

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