Microneedles as a Novel Approach for Transdermal Drug Administration

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***Abstract*—Transdermal drug delivery (TDDS) has become as a promising alternative to conventional administration routes due to its ability to bypass the first-pass metabolism, reduce systemic side effects, and increases patient compliance. However, the skin's outermost barrier, the stratum corneum, limits the passive permeation of most therapeutic molecules, mainly hydrophilic drugs and macromolecules. Microneedle (MN) technology has become significant attention as an innovative strategy to overcome these barriers by creating transient microchannels that enable efficient and minimally lethal drug transport. There are various types of microneedles including solid, coated, dissolving, hollow, and hydrogel-forming have been developed to support the delivery of a wide range of therapeutic agents such as small molecules, peptides, proteins, vaccines, and nucleic acids. Their flexibility extends beyond drug administration to applications in diagnostics, biosensing, dermatological treatments, ocular delivery, and gene therapy. Compared to the other traditional methods, microneedles offer more advantages to the patients such as painless application, reduced infection risk, higher stability for sensitive biologics, and suitability for self-administration. Despite notable progress, challenges remain in terms of large-scale fabrication, mechanical strength, drug-loading capacity, and variability in skin physiology. Continued advancements in materials science, microfabrication, and smart delivery technologies are expected to further enhance microneedle performance and broaden their clinical applicability. Overall, microneedle-based transdermal systems represent a transformative platform capable of improving therapeutic outcomes, expanding drug delivery possibilities, and contributing significantly to the future of patient-centered biomedical innovation.**

***Index Terms*—Stratum Corneum, Microneedle, Hydrogel, Hyaluronic acid, carboxymethyl cellulose,Polymers**

I. INTRODUCTION

Transdermal drug delivery (TDDS) is a route of drug delivery for treating or preventing disease by absorbing drugs through the skin, permeating into the skin and further into the blood circulation. [1] TDDS avoids first-pass effects, prolongs the action of drugs with short half-lives through slow release and avoids fluctuations in blood levels, reduces side effects and improves patient compliance. [2] Microneedles usually consist of micrometre-sized needles (50–900 μm in length) in the form of microneedle arrays that can successfully penetrate the stratum corneum and deliver drugs in a minimally invasive manner below the stratum corneum without damaging blood vessels and nerves in the dermis. [3,4] Transdermal delivery systems (TDS) can provide a convenient and effective means of long-term systemic and/or local drug delivery for a variety of indications that cannot be achieved with oral or parenteral administration. The transdermal route of drug administration refers to the permeation of drug molecules across the layers of the skin, absorption into the bloodstream from the dermis, and subsequent distribution throughout the body. [5]

In recent years, biomedicines microneedles have gained widespread interest in TDDS and have shown brilliant achievements in delivering both chemical small molecules and biomacromolecules whilst being minimally invasive and painless. [6-13] Microneedles can be fabricated with different materials and can be classified into five main types (Figure 1), namely solid

microneedles, coated microneedles, hollow microneedles, dissolving microneedles and hydrogel-forming microneedles (HFMs). [14-16] Among these, HFMs, an attractive type of microneedles first reported in 2012, consist of a swellable polymer (cross-linked hydrogel) that enables the sustained delivery of drugs for long periods of time by either incorporating the drug into the polymer structure during preparation or by loading the drug into a separate reservoir and attaching it to the HFMs. [17]

In the following, the application and evaluation methods of HFMs in TDDS are analysed and discussed in detail.

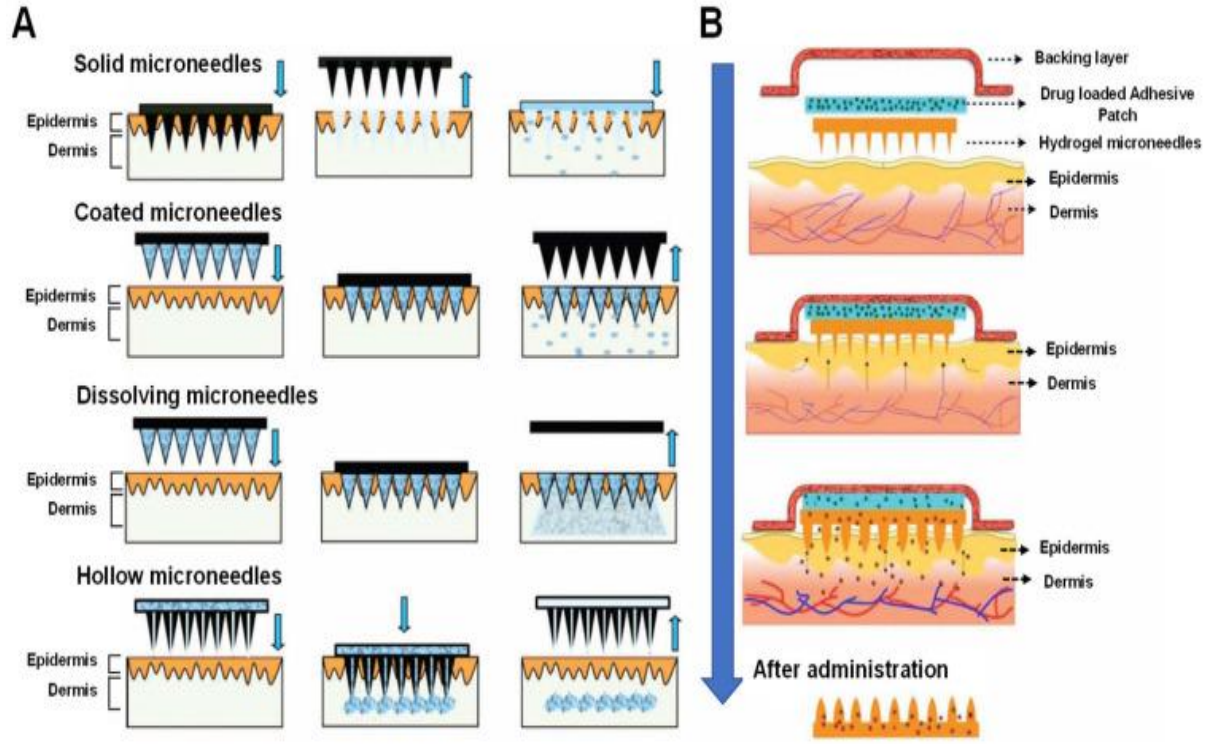


Figure 1: Schematic representation of methods of traditional (A) and hydrogel (B) microneedles mediated drug delivery across skin (arrows point to the order of operations). The figure was adopted from ref [11] with permission from WILEY-VCH VERLAG GMBH & CO. KGAA

Transdermal drug administration and biosensing has become more widely accepted in recent years. The skin typically exhibits a triple-layered structure, with outermost epidermis, middle dermis, and the innermost subcutis. The dermis is fully vascularized and possesses sweat glands, hair follicles, nerve endings, and lymph vessels. This layer of tissue facilitates the local absorption of drugs. The intercellular lipid bilayer of the stratum corneum, the uppermost layer, constitutes the rate-limiting layer for the migration of hydrophilic drug molecules across it. [18-20] Transdermal drug delivery overcomes the disadvantages of intravenous administration, offering various merits such as better compliance and reduced systemic drug interactions. [21] Microneedles (MNs), a promising minimally invasive transdermal drug delivery method, have drawn significant interest and attention in biomedicine in recent years. [22-23]

Microneedle technology is a unique modern transdermal therapy approach that consists of a patch with tiny, micron-sized needles attached to it which are designed to load vaccines, drug molecules, proteins, genes, antibodies, nanoparticles, and many more. [24] Microneedles can be used to successfully overcome the limitations associated with conventional treatment methods in cancer, while offering patients painless gains as they are advantageous from diagnosis to treatments and even theragnostic. Figure 2 shows a schematic illustration of how cancer patients could gain without pain using microneedles.

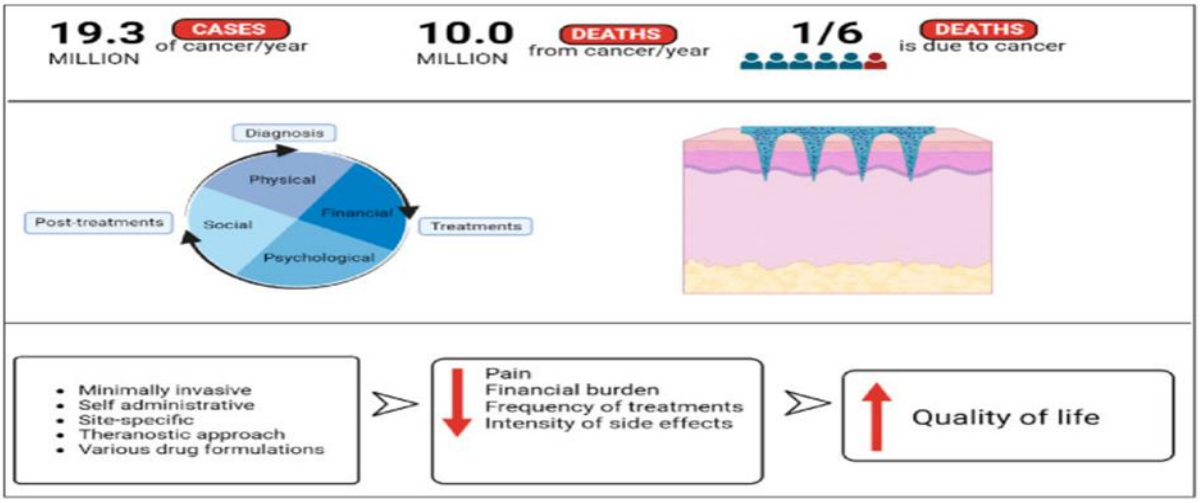
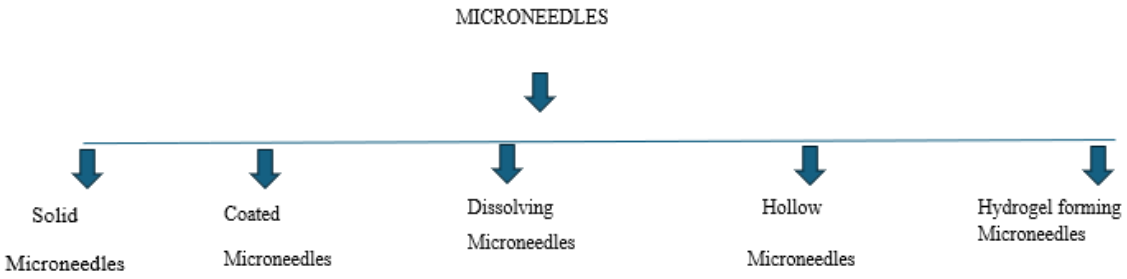


Figure 2.: Schematic illustration of how the advantages of microneedles technology could reduce the common negative effects involved in cancer therapy and increase the quality of life of cancer patients (created using BioRender.com).

Microneedles are also a self-administrative device that could transdermal uptake interstitial fluid, deliver drugs, vaccines, etc., in a minimally invasive and painless manner. [25-26] The concept of using microneedles (MNs) for transdermal drug delivery was first patented by Gerstel and Place in 1976. Since the advent of advanced microfabrication technology in 1998, the first silicon MN array was produced using ion etching and was used for transdermal drug delivery. [27] MNs are designed for transdermal drug delivery of various drugs, including small molecules, [28] proteins, [29] peptides, [30] and nucleic acids. [31] Transdermal delivery systems (TDS) can provide a convenient and effective means of long-term systemic and/or local drug delivery for a variety of indications that cannot be achieved with oral or parenteral administration. The transdermal route of drug administration refers to the permeation of drug molecules across the layers of the skin, absorption into the bloodstream from the dermis, and subsequent distribution throughout the body. [32]

II. CLASSIFICATION OF MICRONEEDLES

Microneedle technology has evolved significantly to accommodate diverse therapeutic needs. Based on their structure, mechanism of drug release, and material composition, microneedles are generally classified into five main types: solid, coated, dissolving, hollow, and hydrogel-forming microneedles. Each type offers unique advantages and is suited for different drug delivery strategies. [33-34] Microneedles are classified into following ways,



Solid microneedles

Solid microneedles are mainly made from metal, silicon, or polymers and are used to create microchannels in the skin through which drug molecules can later diffuse. This "poke-and-patch" approach involves pre-treating the skin with microneedles followed by application of a drug loaded patch or topical formulation. Although simple in

design, solid microneedles require a twostep process and may not ensure uniform drug penetration. [35-37]

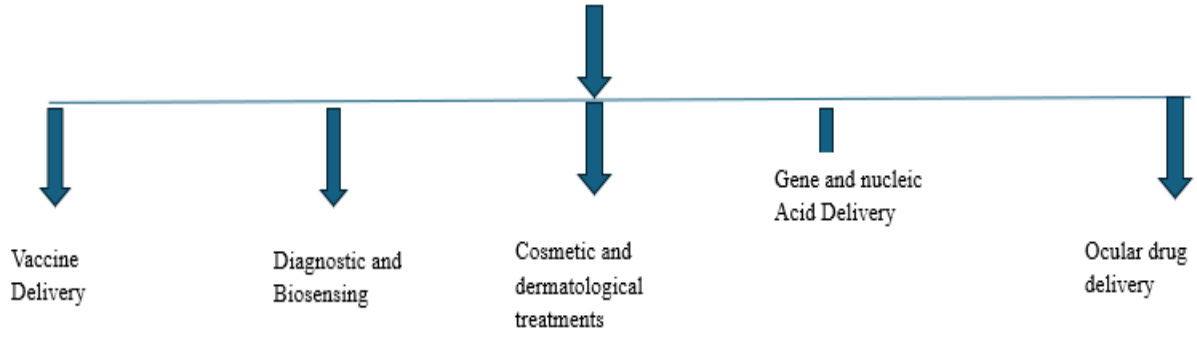
Coated Microneedles:
Coated microneedles are fabricated by applying a thin layer of drug formulation onto the surface of solid microneedles. Upon insertion into the skin, the drug coating dissolves rapidly, allowing for immediate drug release. This type is suitable for delivering potent drugs and vaccines in small doses. However, limitations include low drug-loading capacity and challenges in achieving uniform coating across needles. [38]

Dissolving Microneedles:
Dissolving microneedles are made from biodegradable and water-soluble polymers such as hyaluronic acid, carboxymethyl cellulose, or polyvinylpyrrolidone. These microneedles encapsulate the drug within their structure and dissolve completely upon skin insertion, eliminating biohazardous sharp waste. They are ideal for sustained release and single-step administration, with excellent safety profiles. [39-40]

Hollow Microneedles
Hollow microneedles resemble traditional hypodermic needles on a microscale and deliver drugs in liquid form through a central bore. They allow controlled infusion of larger drug volumes, making them suitable for biologics and vaccines. However, they are more complex to manufacture and may be prone to clogging or mechanical failure during insertion.

Hydrogel-Forming Microneedles
Each microneedle type presents unique design opportunities and formulation considerations. Selection depends on factors such as drug stability, dose requirement, duration of therapy, and patient compliance. As research progresses, hybrid and multifunctional microneedle systems are also being developed to combine the strengths of various types.

III. HOW AND WHERE THE MICRONEEDLES ARE USED OTHER THAN TDDS



Vaccine Delivery
Microneedles deliver vaccines into the skin layers in immune cells {epidemic and dermal}, producing a strong immune response with minimal invasiveness.[41]
It is used in Skin {intradermal delivery}
Example: Influenza, measles, and COVID 19

Diagnostic and Biosensing
Microneedles extract interstitial fluid or detect biomarkers directly in the skin for real-time monitoring. [42]
It is used in Skin (for glucose, lactate, or drug level monitoring).
Example: Glucose-sensing microneedle patches for diabetes.

Cosmetic and Dermatological Treatment
Microneedles create micro-injuries to stimulate collagen production or enhance absorption of cosmetic ingredients. [43]
It is used in Facial and body skin.
Example: Treatment of acne scars, wrinkles, and pigmentation.

Gene and Nucleic Acid Delivery:
It is used to Deliver DNA, RNA, or mRNA into cells for gene therapy or DNA vaccination. [44]

It is used in Skin or mucosal tissues.

Ocular Drug Delivery

Short microneedles are used to inject drugs into or across ocular tissues. [45]

It is used in Sclera, cornea, or subconjunctival space.

Example: Delivery of Anti-VEGF drugs for macular degeneration.

IV. IMPORTANCE OF MICRONEEDLES IN TRANSDERMAL DRUG DELIVERY VS OTHERS DRUG DELIVERY METHOD

Parameter	Microneedle-Based Transdermal Drug Delivery	Other Drug Delivery Methods
Invasiveness	Minimally invasive, penetrates only the outer skin layer	Often invasive (e.g., injections) or completely non-invasive but less effective (e.g., oral, topical)
Pain and Discomfort	Painless or minimal discomfort	Injections cause pain; oral drugs may cause gastric irritation
Patient Compliance	High – easy and self-administrable	Lower – requires trained personnel or multiple doses
First-Pass Metabolism	Avoided, as drug bypasses liver metabolism	Occurs in oral route, reducing bioavailability
Drug Absorption	Rapid and efficient through dermal microchannels	Variable absorption depending on route (oral, topical, etc.)
Drug Release Control	Can be designed for controlled or sustained release	Limited control in oral or topical routes
Drug Stability	Suitable for biologics (proteins, peptides, vaccines)	Many degrade in GI tract or during metabolism
Risk of Infection	Low – especially with dissolving microneedles	Higher – injections may cause infection or needle-stick injuries
Waste Generation	Minimal – dissolving types leave no sharps waste	Generates hazardous sharps waste (needles, syringes)
Onset of Action	Rapid due to direct systemic absorption	Oral route slower due to digestion and absorption time
Drug Type Compatibility	Works for both small molecules and large biomolecules	Oral/topical limited mostly to small molecules
Cost and Convenience	Cost-effective for self-use and storage	Requires infrastructure (cold chain, staff, etc.) for injections

Discussion: Transdermal drug delivery systems have gained significant attention due to their ability to bypass the first-pass metabolism, provide sustained drug levels, and increases patient compliance. However, the major things still remain the barrier properties of the stratum corneum, which prevent passive diffusion of many therapeutic molecules, especially hydrophilic drugs and macromolecules. [46] To overcome this, several improvement methods including chemical enhancers, iontophoresis, sonophoresis, and microneedles have been developed to facilitate improved skin permeation. [47] Between these approaches, microneedle-based delivery has emerged as one of the most transformative technologies. Microneedles create temporary microchannels in the skin without reaching pain receptors, enabling the delivery of peptides, proteins, vaccines, and other complex molecules that mainly exhibit poor permeability. [48] Dissolving and hydrogel-forming microneedles further improve safety by avoiding sharp waste and enabling controlled or sustained drug release. [49] Despite significant progress, several challenges persist. Many transdermal systems face limitations in drug-loading capacity, formulation stability, and variability in skin physiology among individuals. Microneedle technologies also require improvements in large-scale manufacturing, mechanical strength, insertion reliability, and long-term safety validation before widespread commercial adoption. [50]

V. CONCLUSION

Microneedles are considered innovative drug delivery systems with unique benefits. They are the perfect

platform for pharmaceutical and biological applications since they have improved pharmacokinetics, safety, and efficacy when delivering active substances to the targeted spot. Some studies have reported that MN-based delivery of antihypertensive drugs improves the transdermal delivery of these drugs. The size and geometry of MNs can be modified based on the disease condition, and a simpler strategy is being pursued to prepare MNs with unique structures and reduced preparation cost. MNs are well-positioned as promising devices that can enhance patient quality of life by exploiting the advantages associated with a variety of biomedical, nanomaterial, nanomedical, and photonic technologies. This is due to the current advancement of novel intelligent treatment platforms and approaches. They are the perfect platform for pharmaceutical and biological applications since they have improved pharmacokinetics, safety, and efficacy when delivering active substances to the targeted spot. They have offered groundbreaking solutions for the delivery of active therapeutic ingredients employing MNs in life-threatening conditions. As a result, specific microneedle devices have made it to the commercial market.

Although microneedle technology has made significant progress in obesity treatment, future research needs to further improvement the safety, efficacy, and optimal dosing regimen of microneedle technology in order to achieve satisfying anti-obesity effects. In addition, combination therapy that integrates MN technology and INT or PTT provides alternative options for obesity treatment with enhanced therapeutic efficacy. The field of long-acting TDS has continued to grow over the last few years with the development of innovative technologies. To evaluate the drug delivery efficiency of transdermal administration by MNs and intravenous injection in a precise, non-invasive, and timely manner, we introduced PACT to record the in-situ responses from drugs, i.e., PA signals from ICGs, at different time slots and quantitatively compared the ICG signal intensities in the glioma tumour region.

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