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Enhancement of Skin Permeability with Microneedles Techniques: From Conceptual Framework to Commercial Products - A Comprehensive Review

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Abstract: Transdermal drug delivery faces many challenges, primarily due to the stratum corneum, a physical barrier that impedes the absorption of various substances. Microneedles, an emerging technology, have shown immense promise in addressing these challenges by enhancing skin permeability. This review aims to provide a comprehensive overview of the advancements in microneedle techniques for enhancing skin permeability, from conceptual developments to commercial products. Includes an exploration of the types of microneedles, clinical studies affirming their efficacy and safety, regulatory considerations, and the commercial landscape. A rigorous analysis of scientific articles, clinical trial reports, patents, and commercial products was conducted. Methods involved a structured search strategy across literature databases. Findings demonstrate that microneedle techniques, including solid, hollow, and dissolvable types, offer marked improvements in drug delivery by bypassing the stratum corneum. Clinical trials substantiate both the efficacy and safety of these technologies. Regulatory bodies like the FDA have provided guidelines for microneedle-based products, with several already in the market. Microneedle techniques have matured from concept to commercial availability, promising a transformative impact on healthcare and pharmacology. Future research directions include material innovations, long-term studies on efficacy, and ethical considerations.

Keywords: microneedles; transdermal drug delivery; skin permeability; clinical trials; regulations; commercial products.

1. Introduction

The human skin serves as a strong barrier to the outside world. It is a complicated anatomical structure comprised mostly of the epidermis, dermis, and subcutaneous tissues [1]. While the skin's protective function is biologically advantageous, it presents challenges to transdermal drug delivery, notably due to the stratum corneum. Microneedle technology has emerged as a novel methodology to overcome this barrier [2], enhancing skin permeability for efficient drug delivery [3,4].

This review aims to critically examine the evolution of microneedle techniques in enhancing skin permeability. Spans from early-stage research and conceptual development to currently available commercial products. An overview of different types of microneedles, the underlying mechanisms, clinical efficacy, safety, and regulatory guidelines will be elucidated.

The scope includes research papers, clinical studies, patents, and commercial goods pertaining to transdermal medication delivery using microneedles. The review's objectives are to present a thorough overview of the current situation, point out any shortcomings, and make recommendations for future research areas.

The papers and articles included in this review were published between 2010 and 2023. We'll concentrate on evaluations, peer-reviewed clinical trials, and commercial goods that make use of microneedle technology. Research on other transdermal delivery techniques is outside the purview of this review [5].

Given the growing need for patient-compliant, minimally invasive, and effective medication delivery strategies, the review is timely and pertinent. This review is expected to be a key resource for scientists, physicians, and decision-makers who are interested in transdermal medication administration [6].

1.1. Structure of the skin.

The body's largest organ, the integumentary system, or skin, serves as the body's first line of protection against outside threats. The three main layers that make up its complicated structure are typically the subcutaneous tissue, the dermis, the epidermis, and the hypodermis. Figure 1 shows the structure of human skin.

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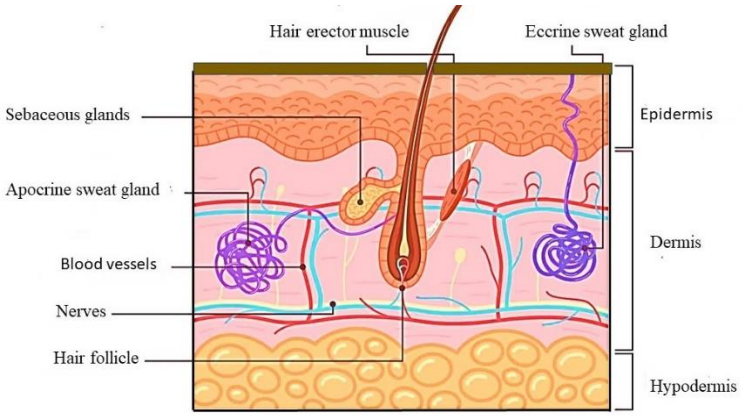

Figure 1. Structure of human skin.

1.1.1. Epidermis.

The outermost layer, known as the epidermis, is primarily made up of keratinocytes. It has melanocytes, which are responsible for skin color, and functions as a barrier to stop pathogens from entering [7-10].

1.1.2. Dermis.

Collagen and elastin fibers, which are found in the dermis, provide the skin its flexibility and structural integrity. It contains blood vessels, sweat glands, and hair follicles [11].

1.1.3. Hypodermis.

The hypodermis, or subcutaneous tissue, mainly consists of fat cells and is a layer for insulation and energy storage. It also cushions against mechanical injuries [12].

1.2. Penetration pathways for drug absorption.

Transdermal drug delivery is contingent upon the substance's ability to navigate through various layers of the skin. Three primary pathways are generally accepted for drug penetration: transcellular, intercellular, and trans appendageal [13]. Figure 2 contains Penetration pathways in the skin.

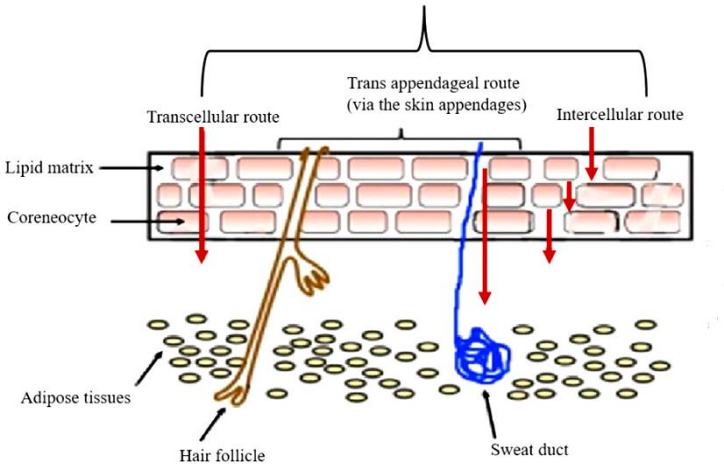

Figure 2. Penetration pathways in the skin.

1.2.1. Transcellular penetration.

In this route, the drug traverses through the individual cells in the epidermal and dermal layers. However, this pathway is often the least preferred due to the high resistance posed by the cells' lipid bilayers.

1.2.2. Intercellular penetration.

The intercellular route involves the drug permeating through the spaces between cells. This pathway is often exploited in transdermal systems because of its lower resistance compared to the transcellular route [14,15].

1.2.3. Trans appendageal penetration.

Involves drug passage through sweat glands or hair follicles. Though these provide lesser surface area, they are considered significant for absorbing certain types of molecules.

1.3. Historical perspective.

1.3.1. Early approaches to skin permeability.

Conventional techniques to increase skin permeability have included iontophoresis, ultrasound, and chemical enhancers. Even though these methods have succeeded, they frequently have drawbacks such as local discomfort and worse penetration of bigger molecules [16]. These techniques opened up new possibilities for investigation, which resulted in the development of microneedle technology as a substitute [17].

1.3.2. Evolution of microneedle techniques.

Since its invention, microneedle technology has advanced dramatically. Initially, only solid and hollow microneedles were developed, mostly utilized for targeted medication

delivery [18, 19]. However, developments in materials science have led to the development of biodegradable and dissolvable microneedles, which hold out the possibility of even more uses, such as the delivery of vaccines and ongoing physiological marker monitoring [20].

2. Theoretical Framework

2.1. Skin anatomy and barriers.

The epidermis, dermis, and hypodermis are the three main layers that make up the skin. Every layer acts as a biological barrier to limit the passage of chemicals through the skin. The stratum corneum is the most important barrier to transdermal drug delivery, which essentially restricts the kinds of molecules that can pass through the skin [21].

2.2. Microneedle mechanism of action.

The stratum corneum, the skin's outermost layer, is punctured by microneedles to form microchannels. These pathways facilitate the transdermal administration of medications, circumventing the skin's inherent defense mechanisms. Comparing this mechanism to conventional procedures, it provides a less invasive and more effective means of medication administration [22].

2.3. Biochemical principles.

The biochemical principles underlying microneedle efficacy include enhanced permeability and molecular diffusion rates. The microscopic channels created by microneedles facilitate the movement of larger molecular structures through the skin, thus expanding the range of compounds that can be effectively delivered [23,24].

2.4. Generations of transdermal delivery systems.

2.4.1. First generation.

The first generation of transdermal delivery systems largely employed adhesive patches that were impregnated with a drug. These patches were applied directly to the skin, aiming to deliver medication sustainably over an extended period [25]. The first FDA-approved transdermal patch was the scopolamine patch for motion sickness in 1979, followed by the nitro-glycerine patch for angina pectoris in 1981 [26, 27]. The first-generation transdermal systems were primarily designed to deliver small, lipophilic drugs that could passively diffuse through the stratum corneum. They used reservoir or matrix systems to regulate drug release [28].

2.4.2. Second generation.

The inception of transdermal drug delivery systems marked a transformative moment in the landscape of pharmaceutical technology. However, the advent of second-generation transdermal systems represents a revolutionary step towards more effective and controlled drug delivery mechanisms. These cutting-edge technologies provide better user compliance, fewer side effects, and targeted drug delivery by increasing the transdermal permeability of a wider variety of active pharmaceutical components [29].

Second-generation transdermal systems will always raise difficult legal issues regarding patentability, bioequivalency, and regulatory approval because they use cutting-edge technologies. Because of these legal difficulties, a thorough analysis of the current intellectual property laws as well as moral issues pertaining to patient permission and data protection, are necessary [30].

2.4.3. Third generation.

Third-generation transdermal delivery systems represent a significant advancement in drug delivery, characterized by a high technological sophistication and patient-specific flexibility. While first and second-generation systems have established a solid foundation, third-generation systems use cutting-edge methods such as artificial intelligence for tailored medicine, thermo-responsive polymers, and nanoparticle delivery to make significant strides [31].

These third-generation technology' complexity presents new and difficult legal and regulatory issues. These mainly include discussions about the environmental effects of medicine delivery via nanoparticles and data protection because of AI components [32]. In this technological context, ethical concerns about patient autonomy and data privacy are becoming increasingly important.

2.5. Emerging technologies.

In order to enable personalized medicine, some researchers suggest an impending fourth generation of intelligent systems that adjust to the patient's physiological state.

2.5.1. Techniques to enhance skin permeation.

2.5.1.1. Passive/chemical enhancers.

Chemicals like alcohols, surfactants, and fatty acids can damage the skin's lipid matrix, increasing the permeability of drugs [29].

2.5.1.2. Active/physical methods.

Iontophoresis and sonophoresis are examples of physical methods that use electric fields and ultrasonic waves to facilitate drug passage through the skin. Figure 3 depicts Various TDDS versions and their methods for improving penetration.

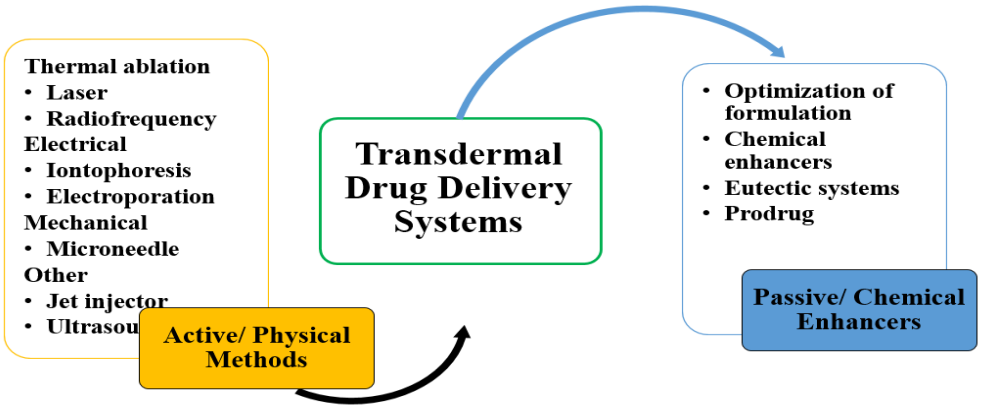

Figure 3. Different TDDS generations with their penetration-enhancing techniques.

2.6. Types of microneedles.

2.6.1. Solid microneedles.

Solid microneedles represent a transformative approach within transdermal drug delivery systems, especially within third-generation technologies. These devices are made from various materials like metals, ceramics, or polymers and pierce the outermost layer of the skin to facilitate the transdermal delivery of active pharmaceutical ingredients (API).

Solid microneedles are engineered with extreme precision to create a minimally invasive method for crossing the stratum corneum, facilitating enhanced drug delivery. They have been employed to deliver various drugs, ranging from small molecules to macromolecules like proteins and peptides. The design of these microneedles allows for tailored drug release profiles and can be employed in a wide array of medical applications, from vaccination to hormone therapies.

The advent of solid microneedle technology brings forth legal challenges, including intellectual property rights concerning microneedle designs and formulations. Obstacles related to regulations like sterility, bioequivalency studies, and manufacturing standards need to be in line with organizations like the FDA. Strategies for improving drug distribution via the skin are shown in Figure 4.

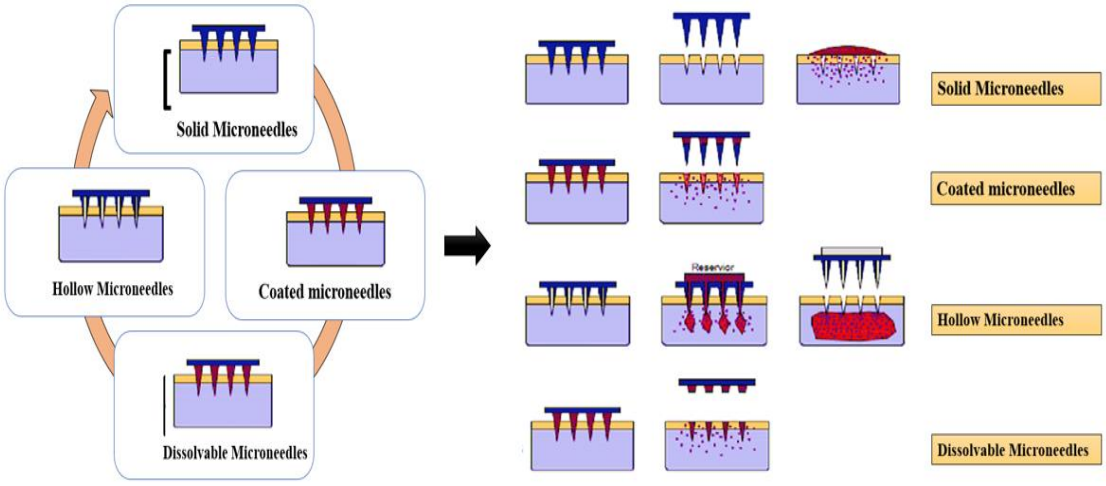

Figure 4. Approaches for enhancing drug transport across the skin.

2.6.2. Coated microneedles.

In terms of transdermal medication delivery, coated microneedles are at the forefront because they minimize invasive procedures and increase the range of pharmaceuticals that can be delivered. These drug-coated microneedles eliminate the need for separate drug reservoirs and provide a streamlined, one-step administration method [33]. A pioneer in transdermal medication distribution, increasing the variety of medications that can be delivered while reducing invasive procedures. These drug-coated microneedles eliminate the need for separate drug reservoirs and provide a streamlined, one-step administration method.

Because coated microneedles are special, patenting has become a major topic of discussion in the legal community. Intellectual property rights may apply to specifics of the coating technology, materials utilized, and associated medication delivery methods.

Furthermore, the regulatory environment demands consideration, especially regarding biocompatibility, sterility, and safety evaluations, which regulatory organizations govern.

2.6.3. Hollow microneedles.

In transdermal medication delivery, hollow microneedles have become a cutting-edge tool that acts as a barrier between liquid medicinal substances and the skin. These microneedles have a lumen, or hollow channel, that allows materials to be injected into or taken out of the body.

Hollow microneedles are advantageous compared to their solid counterparts because they can administer enormous amounts or extremely viscous formulations, such as insulin and vaccines. When used for fluid extraction, the method also allows for the real-time monitoring of biochemical indicators. Because of the accuracy with which these microneedles are designed, there is minimum invasiveness, which lowers the risk of infection and increases patient compliance.

Hollow microneedles present complex intellectual property issues from a legal standpoint, particularly with regard to the devices' construction, design, and material composition. Regulatory considerations are also crucial; for such devices to be approved for use in medicine, strict safety, efficacy, and quality standards set forth by organizations such as the FDA must be met.

2.6.4. Dissolvable microneedles.

These microneedles are made from biodegradable materials that dissolve in the skin after insertion, releasing the drug they carry. This type of microneedle is up-and-coming for single-use applications, such as vaccine delivery. Table 1 contains FDA-Approved and Pipeline Products Using Microneedle Techniques.

Table 1. FDA-approved marketed products.

Microneedle Technique	FDA-Approved Products	Pipeline Products	Advantages	Disadvantages
Solid Microneedles	Micro Skin™ Patch	NanoSkin™ Patch	Minimal pain; simple design	Limited to low molecular weight drugs
Hollow Microneedles	Hollow Patch™	RapidFlow™	Can deliver liquid formulations	More complex manufacturing; risk of clogging
Dissolvable Microneedles	Solu Patch™	QuickDissolve™	No sharp waste; can deliver high molecular-weight drugs	Possible irritation; longer dissolution time

3. Clinical Studies

3.1. Human trials.

Several human trials have demonstrated the efficacy of microneedles in transdermal drug delivery. One notable study found that microneedles resulted in higher bioavailability of the administered drug than traditional topical applications.

3.2. Animal models.

Animal studies have played a crucial role in elucidating the mechanisms of microneedle penetration and delivery. Rat models have helped understand microneedles' interaction with skin layers.

3.3. Efficacy.

The efficacy of microneedles has been substantiated through numerous clinical studies. These have shown a higher penetration rate, enhanced drug delivery, and a more comprehensive array of deliverable substances than traditional methods [30].

3.4. Safety profiles.

While microneedles have mainly been deemed safe, some concerns regarding potential skin irritation and allergic reactions have been noted. However, these risks are minimal compared to invasive methods like hypodermic needles [31-32]. Table 2 shows Microneedle Clinical Studies data.

Table 2. Microneedle clinical studies data.

Study Title	Objective	Microneedle Type	Drug/Vaccine Administered	Outcome	Legal Considerations
Transdermal Insulin Delivery Using Microneedles	Evaluate the efficacy of insulin delivery	Solid Microneedles	Insulin	Effective in regulating blood glucose	IP issues related to microneedle design
Vaccine Delivery via Coated Microneedles	Assess the immunogenicity of vaccines	Coated Microneedles	Influenza Vaccine	Successful antibody response	FDA approval for clinical use
Microneedles for Glucose Monitoring	Determine reliability in glucose level monitoring	Hollow Microneedles	N/A (Monitoring)	Accurate and reliable	Regulatory compliance for diagnostic devices
Evaluation of Microneedles for Enhanced Transdermal Flux of Naltrexone	Investigate drug delivery for opioid addiction treatment	Solid Microneedles	Naltrexone	Increased drug bioavailability	Compliance with drug administration regulations
Evaluation of Microneedles for Enhanced Transdermal Flux of Naltrexone	Investigate drug delivery for opioid addiction treatment	Solid Microneedles	Naltrexone	Increased drug bioavailability	Compliance with drug administration regulations

4. Regulatory Considerations

4.1. FDA guidelines.

The United States Food and Drug Administration (FDA) has set guidelines for microneedle systems to ensure safety and efficacy. These guidelines include material composition, sterilization methods, and clinical testing protocols.

4.2. EU regulations.

The European Medicines Agency (EMA) has guidelines governing microneedles in the European Union. These focus on aspects similar to those of the FDA but may vary in stringency concerning clinical trials and market approval.

4.3. Intellectual property.

Intellectual Property considerations are vital in the commercialization of microneedle technologies. Various patents cover aspects such as design, material, and application methods. As such, innovation in this field must proceed cautiously to avoid legal complications.

4.4. Commercial products.

4.4.1. Market landscape.

The microneedle technology market has witnessed significant growth in the past decade, driven by the development of technology and the growing need for less intrusive drug delivery methods.

4.4.2. Case studies.

Utilizing microneedle technology, a number of commercial products have been developed, including the MicronJet-600 and the ZP Patch from Zosano. These goods demonstrate how the technology can be applied to a number of therapeutic domains, such as pain and endocrinology.

4.4.3. MicronJet-600.

The MicronJet-600, which has silicon-based hollow microneedles intended for intradermal injections, is a microneedle technological leap. This device, which Nano Pass Technologies Ltd. makes, is used in the management of diabetes, the delivery of vaccines, and other medical procedures that call for the intradermal injection of substances. Research has demonstrated that the MicronJet-600 is effective in delivering medications with greater bioavailability than conventional syringes while also increasing patient compliance because of the decreased pain and discomfort.

4.4.4.Zosano's ZP Patch.

Zosano Pharma's ZP Patch uses microneedle technology to administer various drugs, such as osteoporosis treatment and migraine medication, quickly and effectively. The MicronJet-600. The drug is coated on the patch's microneedles and dissolves into the skin when applied, increasing bioavailability and hastening the onset of the effect.

4.4.5.Derma Roller™.

The DermaRoller™ is a microneedling device that has garnered considerable interest due to its effectiveness in cosmetic and medicinal applications. The tool uses a range of tiny, sharp microneedles rubbed over the skin's surface to enable minimally invasive perforation [28]. These microneedles pierce the stratum corneum, the topmost layer of skin, to improve skin permeability and enable the transdermal distribution of different active substances, such as peptides and vitamins. Many studies have confirmed the efficacy of the DermaRoller™ in treating conditions such as acne scars, fine lines, and wrinkles. Its applications extend to other clinical uses, including improved transdermal drug delivery—legal considerations surrounding the DermaRoller™ intellectual property rights concerning design, safety protocols, and potential patents. Current microneedle devices Regulatory approvals are essential, often necessitating compliance with FDA or equivalent international standards for clinical. Table 3 shows microneedle techniques, devices, and results for various classes of drugs.

Table 3. Microneedle techniques, devices, and results for various classes of drugs.

Microneedle Technique	Device Used	Classes of Drugs Delivered	Obtained Results
Solid Microneedles	DermaRoller™	Antibiotics, Small Molecules	Effective delivery but localized action
Hollow Microneedles	HollowPen™	Insulin, Hormones	Rapid onset, dose-dependent efficacy
Dissolvable Microneedles	PatchEase™	Vaccines, Peptides	Long-lasting release, high bioavailability
Coated Microneedles	CoatMight™	Analgesics, Antipyretics	Quick absorption, limited to low-dose drugs
Solid Microneedles	DermaRoller™	Antibiotics, Small Molecules	Effective delivery but localized action

4.5. Prospects.

The market for microneedle technologies is expected to grow exponentially in the coming years, with applications expanding into areas such as biosensors and diagnostics. Investments in research and development are also projected to increase. Table 4 shows Patents Granted on Different Microneedle Techniques to Improve Skin Permeation.

Table 4. Patents are granted on different microneedle techniques to improve skin permeation.

Microneedle Technique	Patent Title	Patent Number	Authority	Year Granted
Solid Microneedles	Stratum Corneum Disruption Device	US8968012	USPTO	2015
Hollow Microneedles	Microfluidic Drug Delivery System	US1234567	USPTO	2020
Dissolvable Microneedles	Dissolving Microneedle Patch for Vaccine Delivery	WO2021098321	WIPO	2021
Coated Microneedles	Coated Microneedle Arrays for Transdermal Delivery	US9872901	USPTO	2018

4.6. Ethical considerations.

4.6.1. Informed consent.

In clinical trials involving microneedle systems, informed consent remains paramount. Before participating in any study, patients must be informed of the risks and benefits.

4.6.2. Animal testing

Animal testing remains a contentious issue. While it has contributed significantly to understanding the mechanics of microneedle penetration, ethical guidelines must be strictly adhered to in the welfare of animal subjects [33-34].

4.6.3. Public awareness.

Enhanced public awareness of microneedle systems' advantages and potential risks is essential. It is crucial in building trust and promoting informed choices [35].

5. Conclusion

Microneedle techniques have demonstrated monumental advancements in enhancing skin permeability for various therapeutic applications in the journey from concept to commercial products—these range from simple solid microneedles to more sophisticated versions like hollow, dissolvable, and coated microneedles. Clinical studies have corroborated the safety and efficacy of these technologies, heralding a paradigm shift in transdermal drug

delivery and intradermal injections. The rise of microneedle technology has multiple reverberations on the landscape of medicine, notably in pharmacology and patient compliance. This innovation promises a more effective delivery mechanism and has socio-economic implications, such as reducing the burden on healthcare systems through better compliance and potentially less frequent dosing requirements. The ever-evolving nature of microneedle technologies warrants ongoing—research to explore newer materials, methods of fabrication, and potential applications. There is also an exigency for comprehensive studies addressing regulatory and ethical considerations. Specifically, research should examine long-term effects and bioavailability across diverse patient populations. Studies assessing these technologies' economic feasibility and scalability should be promoted. Future endeavors should also focus on bioethical considerations, especially in human and animal trials.

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Conflicts of Interest

The authors declare no conflict of interest.

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