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Review Article

Microneedles in Transdermal Drug Delivery: A Comprehensive Review

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Abstract

Transdermal drug delivery systems (TDDS) present a non-invasive and patient-compliant alternative to conventional routes of administration by facilitating drug transport across the skin barrier. Upon topical application to intact skin, the drug permeates the stratum corneum, diffuses through the underlying epidermal and dermal layers, and subsequently reaches systemic circulation via capillary networks. This approach enables controlled and sustained drug release, enhances bioavailability, and circumvents the limitations associated with oral and parenteral delivery, including first-pass metabolism and injection-associated discomfort. The human skin, comprising the epidermis, dermis, and hypodermis, poses a formidable barrier, particularly at the stratum corneum, necessitating the use of advanced penetration enhancement techniques. Among these, microneedle-based technologies have emerged as a promising strategy, offering transient and minimally invasive disruption of the skin barrier. Fabricated from biocompatible materials such as silicon, metals, polymers, ceramics, or sugars, microneedles exist in various designs-including solid, coated, dissolvable, and hydrogel-forming types-each tailored for specific drug release profiles. These systems hold potential not only for therapeutic drug delivery but also for diagnostics and cosmetic applications. Regulatory oversight by agencies like the FDA classifies microneedle-based systems as combination products, requiring comprehensive evaluation including sterility, stability, safety, and performance testing. The development of harmonized regulatory frameworks could further facilitate their clinical translation and market integration.

Keywords: Transdermal drug delivery systems (TDDS), Microelectronics and microelectromechanical systems (MEMS), White adipose tissue (WAT), Microneedle technology, Polymers

Introduction:

In recent years, transdermal drug delivery systems (TDDS) have emerged as a favorable alternative to conventional drug administration methods due to their ability to offer controlled release and enhance patient compliance. Despite these advantages, the skin's outermost barrier-the stratum corneum-restricts the penetration of many therapeutic agents, limiting their effectiveness.¹ To address this issue, microneedle (MN) technology has been developed as a novel, minimally invasive strategy that facilitates drug transport through the skin without causing pain or significant tissue damage. Microneedles are tiny projections, usually between 25 µm and 2000 µm in length, designed to breach the skin barrier and allow efficient drug delivery into the epidermal or dermal layers. They combine the precision of injections with the convenience of transdermal patches, offering a safer and more acceptable option for patients. Various microneedle designs-such as solid, coated, dissolvable, hollow, and hydrogel-forming-enable the administration of different drug classes, including small molecules, biologics, and vaccines. Advancements in microneedle fabrication technologies and biocompatible materials have broadened their clinical applications, making them promising tools in areas like vaccine delivery, chronic

disease treatment, and cosmetic therapy.² This review article aims to explore the current landscape of microneedle-based drug delivery, highlighting their types, working principles, fabrication, therapeutic applications, challenges, and future directions.

Transdermal Drug Delivery (TDD):

Transdermal Drug Delivery (TDD) refers to a technique of administering medications through the skin, allowing them to enter the bloodstream without the use of needles or invasive procedures. This method involves applying a drug-containing formulation onto the surface of healthy skin, from where the active ingredient travels through the outermost layer of the skin, known as the stratum corneum, and continues to move through the underlying layers of the epidermis and dermis.² Notably, the drug does not accumulate in the skin but is absorbed into the dermal microcirculation, making it accessible to the entire body. This delivery approach is considered a pain-free and patient-friendly alternative to traditional drug administration routes like oral or injectable methods. One of the major advantages of TDD is its non-invasive nature, which avoids the discomfort and risks associated with injections, such as infection or needle-related injuries. Furthermore, the skin's large surface area provides an excellent platform for drug absorption,

ensuring that medication can be delivered steadily over time.³

TDD systems help maintain stable drug concentrations in the bloodstream, minimizing peaks and troughs that are common with oral medications. This results in a more consistent therapeutic effect. In addition, these systems often require less frequent dosing, which improves patient adherence, especially in individuals who may forget or avoid taking regular medications due to side effects or the inconvenience of oral or injectable routes. TDD can also enhance the bioavailability of drugs by bypassing the gastrointestinal tract and liver, thereby avoiding first-pass metabolism, which can significantly reduce the effectiveness of certain medications. An emerging and exciting application of transdermal systems is in the area of vaccination. The skin is increasingly being recognized as a promising site for vaccine administration due to the presence of dendritic cells in both the epidermis and dermis. These cells play a crucial role in initiating immune responses, making the skin a strategically beneficial site for immunization. Utilizing the skin's immune capabilities through TDD can lead to effective immune activation even with smaller doses of vaccines.⁴

Given the global demand for affordable, easy-to-administer vaccines, particularly in developing nations where healthcare infrastructure may be limited, TDD offers a highly desirable solution.¹ Researchers have been exploring needle-free vaccine delivery technologies, such as patches or topical applications, which can be easily distributed and administered without the need for trained medical personnel. These innovations not only improve accessibility and safety but also reduce the anxiety and pain associated with needle injections. Transdermal Drug Delivery represents a significant advancement in modern therapeutics.⁵ It merges convenience, effectiveness, and safety, offering advantages in systemic drug delivery and vaccine administration. As technology evolves, TDD is likely to play an increasingly vital role in both clinical treatment and global health initiatives, providing a flexible platform for a wide range of pharmaceutical applications.

An Overview of Skin Structure:

The skin, being the largest organ in the human body, plays a vital role in protecting us from a wide range of external threats. It accounts for nearly 16% of an average individual's total body weight and has a surface area of approximately 1.7 m², making it a highly efficient and expansive protective shield. Its functions include acting as a barrier against microorganisms, ultraviolet radiation, harmful chemicals, allergens, and excessive water loss, ensuring both internal stability and defense against environmental damage.

Structurally, the skin is divided into three primary layers: the epidermis, dermis, and hypodermis, each contributing distinctively to the skin's overall function and integrity.⁶

Epidermis:

The epidermis is the outermost layer of the skin and serves as the first line of defense. Its thickness varies depending on the body part-ranging from around 0.8 mm on the palms and soles to thinner regions elsewhere. This layer is composed of multiple layers of epithelial cells, with keratinocytes making up around 95% of the total cell population. These keratinocytes produce keratin, a tough, insoluble protein that provides mechanical strength and resilience.⁷ The outermost portion of the epidermis is the stratum corneum, which directly interfaces with the external environment. It plays a critical role in the skin's barrier function due to its dense structure and low moisture content. The stratum corneum is primarily composed of keratin (about 70%), lipids (around 20%), and water bound within the cells known as corneocytes. This composition helps create a semi-permeable layer that resists water loss and prevents the entry of unwanted substances.⁸

Dermis:

Beneath the epidermis lies the dermis, a thicker region measuring about 2–3 mm in depth. This layer is rich in collagen (about 70%) and elastin fibers, which provide the skin with tensile strength and elasticity.⁹ The dermis is also highly vascularized; its blood vessels deliver nutrients and oxygen to both the dermis itself and the overlying epidermis. Additionally, the dermis houses nerves, immune cells like macrophages, and lymphatic vessels, making it essential for immune surveillance, sensation, and waste removal.⁶

Hypodermis:

The hypodermis, also known as the subcutaneous layer, is the innermost part of the skin structure. It contains a network of fat cells that serve multiple critical roles. Firstly, it acts as a cushion, protecting internal organs and tissues from mechanical shocks. Secondly, it provides thermal insulation, helping maintain body temperature. Lastly, it supports vascular and neural connections between the skin and deeper body structures. Remarkably, nearly 50% of the body's total fat is stored in this layer, along with other essential cells such as fibroblasts and macrophages, which contribute to immune function and tissue repair. The skin is not just a passive covering but a highly organized, multi-functional organ essential for protection, regulation, and sensory communication. Each of its three layers-epidermis, dermis, and hypodermis-works together seamlessly to maintain the body's internal environment and overall health.¹⁰

Routes of Drug Penetration:

Drug movement across intact skin can happen via two primary pathways: the trans epidermal and transappendageal routes. These pathways determine how substances navigate through the skin's complex structure to reach the underlying tissues and eventually enter systemic circulation. The transepidermal route refers to the direct penetration of drug molecules through the layers of the stratum corneum, which serves

as the skin's outermost and most effective barrier. This route includes two mechanisms:

- Intracellular (transcellular) penetration, where molecules pass through the keratin-filled cells (keratinocytes), and
- Intercellular diffusion, where substances move between the cells, navigating through the lipid-rich matrix that holds them together.

The stratum corneum is structurally complex, composed of multiple layers of flattened, dead keratinocytes embedded in a lipid matrix.¹¹ These characteristics make it selective, particularly favoring the passage of lipophilic (fat-soluble) substances, though with the right formulation, hydrophilic (water-soluble) molecules may also pass through.

On the other hand, the transappendageal route involves penetration through skin appendages such as hair follicles and sweat glands. Although these structures occupy a small portion of the skin's surface area, they provide shunt pathways that allow quicker access for some drugs, particularly hydrophilic or polar molecules, bypassing the dense stratum corneum. Both pathways offer opportunities for delivering various types of drugs across the skin. Understanding these routes helps in designing effective transdermal drug delivery systems, ensuring that the active ingredients can cross the skin barrier efficiently and exert their therapeutic effects systemically. By tailoring the formulation and targeting the appropriate pathway, drugs with varying properties can be effectively delivered through the skin.¹²

Microneedle-Based Transdermal Medication Administration Methods:

Drug absorption through intact skin primarily occurs via two main pathways: transepidermal and transappendageal routes. In the transepidermal pathway, the drug penetrates directly through the stratum corneum, which is the outermost and most resistant layer of the skin. This route is further divided into two mechanisms: intracellular and intercellular. In the intracellular route, the drug moves through the keratin-filled cells (keratinocytes), whereas in the intercellular route, it diffuses between the cells through the lipid-rich matrix surrounding them. These pathways are crucial for the diffusion of molecules, particularly lipophilic (fat-soluble) substances, although they can also accommodate certain polar compounds.¹³

The transappendageal route, on the other hand, allows drug transport via skin appendages such as sweat glands and hair follicles. This route is especially significant for the movement of hydrophilic or polar drugs, as these appendages provide channels that bypass the dense stratum corneum. Both pathways contribute to effective transdermal drug delivery, depending on the physicochemical properties of the drug and the target depth within the skin. Together, they offer complementary mechanisms for transporting therapeutic agents into or through the skin for systemic or localized effects.¹⁴

Microneedle technology is a novel and promising approach in transdermal drug delivery systems, designed to overcome the limitations posed by the stratum corneum, the outermost barrier of the skin.¹⁵ Microneedles are microscopic needle-like structures that penetrate the stratum corneum and epidermis, allowing drugs to be delivered directly into the dermis where the capillary network is rich and systemic absorption can begin effectively. Based on their structure, composition, and function, microneedles can be categorized into solid, coated, dissolving, and hydrogel microneedles, each with distinct mechanisms of action, materials, and advantages.¹⁶

Solid Microneedles:

Solid microneedles are among the simplest forms in terms of structure and design. These microneedles are made of solid materials and do not contain any drug or excipient within them. Their primary function is to pre-treat the skin by creating micron-sized pores through the stratum corneum and epidermis, temporarily disrupting the skin barrier without reaching deep enough to cause pain or bleeding.

After the skin is punctured with these solid microneedles, a drug formulation—such as a gel, cream, or patch—is applied on the treated skin area. This allows the drug to easily diffuse through the microchannels into the dermal capillaries, significantly enhancing drug permeability and systemic absorption.¹⁷ By bypassing the dense, protective stratum corneum, this method increases bioavailability, especially for molecules that typically have poor skin penetration. Solid microneedles are commonly fabricated from silicon, stainless steel, or polymer. However, for commercial and clinical use, disposable versions are favored to ensure hygiene and prevent cross-contamination.

Coated Microneedles:

Coated microneedles are a further advancement in microneedle systems where the drug is coated directly onto the surface of solid microneedles. Upon insertion into the skin, the drug dissolves off the microneedle and diffuses into the underlying tissues.¹⁸ This method allows for rapid drug release and a quick onset of action, making it suitable for conditions requiring fast therapeutic responses.

The coating process typically involves dip-coating, where microneedles are dipped into a drug-containing solution.¹⁹ By controlling the depth and duration of the dip, the amount of drug deposited on the microneedle can be adjusted. However, uniform coating is essential to ensure accurate dosing. The formulation must have sufficient viscosity to form a stable film on the needle surface and maintain adherence during storage and insertion. Additionally, the drug should ideally be concentrated near the microneedle tip, which first enters the skin, to optimize delivery efficiency. Despite their effectiveness, coated microneedles are limited by drug-loading capacity, especially for treatments that require high doses. While multiple coating cycles can increase the amount of drug delivered, this also increases complexity and material usage.²⁰

Dissolving Microneedles:

Dissolving microneedles represent a sophisticated drug delivery system made entirely of biodegradable or water-soluble materials embedded with the active pharmaceutical ingredient. These microneedles are designed to completely dissolve in the skin, leaving no sharps waste and eliminating the risk of needle reuse or injury. Typically, they are fabricated using a solvent casting method, where drug-polymer mixtures are poured into molds and allowed to solidify. Common polymers include carboxymethyl cellulose (CMC), methyl cellulose, and sugars like trehalose and sucrose, which are safe, biocompatible, and capable of forming rigid structures with embedded drugs.²¹

In these microneedles, the tip portion, which enters the skin first, contains the drug and must exhibit sufficient mechanical strength to penetrate the skin without breaking. It also requires low viscosity to fill mold spaces effectively without forming air bubbles. The base of the microneedle, which may not contain any drug, can be composed of either a mechanically weaker or water-insoluble material, which helps anchor the needle during application. Recent innovations have aimed at reducing patch wear time by facilitating quick separation of microneedle tips from the base upon skin insertion. Some studies have developed insertion-responsive microneedles that break off instantly upon insertion, thus minimizing discomfort. However, these designs face limitations when high doses of drugs are needed, and research continues to increase drug-loading capacity in dissolving microneedles without compromising structural integrity.²²

Hydrogel-Forming Microneedles:

Hydrogel microneedles are constructed from crosslinked hydrophilic polymers that swell upon exposure to skin fluids but do not dissolve.²³ These systems are designed for sustained drug delivery, where the drug is incorporated throughout the microneedle tip, base substrate, and even the backing patch. Once inserted, these microneedles absorb moisture from the skin, swell, and form a continuous conduit through which drugs diffuse gradually into the skin. Because of their hydrogel nature, they are particularly suitable for delivering larger doses of drugs over extended periods, a feature that makes them attractive for chronic conditions requiring long-term administration. The main advantage of hydrogel microneedles lies in their high drug-carrying capacity and sustained release profile. However, they require longer patch-wearing times due to the slow rate of drug diffusion.² Moreover, formulation stability and mechanical robustness during insertion are critical factors that need to be optimized for effective performance.

Selection and Processing of Materials:

Microneedles are cutting-edge transdermal drug delivery systems that bypass the skin's outer barrier-the stratum corneum-by creating microscopic pathways for drugs to enter the systemic circulation.²⁴ One of the key aspects that determine the functionality, safety, and efficiency of microneedles is the material used in their

construction. The choice of material directly affects their mechanical strength, biocompatibility, drug-loading capacity, and method of delivery. Microneedles have been developed using a wide range of materials such as silicon, metals, ceramics, biodegradable polymers, carbohydrates, and even natural sources²⁵. Each material offers distinct properties that influence the microneedle's performance, production process, and application.

Silicon-Based Microneedles:

Silicon is one of the earliest and most studied materials for microneedle fabrication. It is a widely used material in the microelectronics and microelectromechanical systems (MEMS) industries due to its precision and compatibility with micromachining processes. In microneedle production, silicon allows for the formation of solid, hollow, or coated structures. The mechanical properties of silicon vary with its crystalline orientation, with elastic moduli ranging from 50 to 180 GPa, making it strong enough to penetrate the skin. However, silicon has significant limitations. It is brittle in nature, which may lead to fracture during skin insertion, potentially causing safety concerns. Additionally, silicon microneedles require complex, multi-step fabrication techniques that are time-consuming and expensive, making large-scale manufacturing difficult.²⁶ For this reason, although silicon is excellent for prototyping and research, it is less preferred for commercial use.

Ceramic Microneedles:

Ceramic materials are another important class used in microneedle fabrication. They are known for their excellent chemical resistance, compressive strength, and long-term stability. Ceramic microneedles are usually fabricated through micro molding techniques, which are cost-effective and offer good scalability.²⁷ Alumina (Al_2O_3) is the most commonly used ceramic due to its inertness and strength. These microneedles are often used in the 'coat and poke' method, where drugs are coated on solid ceramic needles that pierce the skin to deliver the active agent. Other biocompatible ceramics such as calcium sulfate dihydrate and calcium phosphate dehydrate have also been investigated for their favorable mechanical and drug-loading properties. Furthermore, hybrid materials likeOrmocer® a combination of organic monomers and silicon alkoxides have been used to create microneedle arrays with tailored mechanical and functional properties. Ceramics offer the potential for creating safe and durable microneedles, especially in drug delivery systems requiring structural stability.²⁸

Metal Microneedles:

Metals are among the most reliable materials for microneedle fabrication due to their high mechanical strength and biocompatibility.²⁹ Common metals used include stainless steel, titanium, palladium, and nickel. Stainless steel is frequently employed in the medical industry for hypodermic needles and is known for its strength and durability. Titanium is widely used in biomedical implants due to its light weight, corrosion resistance, and compatibility with human tissues. In microneedle design, titanium serves as a strong yet

slightly less robust alternative to stainless steel, making it ideal for drug delivery systems and biosensors. These metal microneedles are typically fabricated by pressing or laser machining and are capable of consistent skin penetration.³⁰ Their robustness makes them suitable for both clinical and diagnostic applications. However, their non-degradable nature means they are better suited for reusable or externally removed systems rather than for dissolvable or bioresorbable microneedles.³¹

Carbohydrate-Based Microneedles:

Carbohydrates offer a unique approach in microneedle design, focusing on biodegradability and ease of fabrication. These microneedles are produced using hot-melt molding processes, where the carbohydrate is melted and cast into molds created using metal or silicon master templates. Drugs can be incorporated directly into the molten carbohydrate mixture before molding. Once applied to the skin, these microneedles dissolve upon insertion, releasing the encapsulated drug into the tissue.³² Common carbohydrate materials include sucrose, maltose, and trehalose. These microneedles are highly biocompatible and are especially effective for short-term or rapid-release drug applications, such as vaccines or insulin. However, their mechanical strength is relatively low, limiting their use in deeper skin penetration or in areas with high skin resistance.³¹

Polymeric Microneedles:

Among all material types, polymers offer the most versatility and are widely researched for the development of dissolvable and hydrogel-forming microneedle systems.³³ Although polymers generally have lower mechanical strength than metals or ceramics, they possess greater flexibility, toughness, and tunability. Biocompatible polymers can be engineered to degrade in the skin after drug release, eliminating the need for removal. Examples of natural polymers used include carboxymethyl cellulose (CMC), amylopectin, hydroxypropyl cellulose (HPC), and dextrin. These are capable of forming microneedles that dissolve after penetrating the skin, enabling efficient delivery of various drugs.

Biodegradable synthetic polymers such as polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), and chitosan have been extensively used in microneedle design.³⁴ These polymers can encapsulate a wide range of therapeutic agents, from small molecules to large biomolecules and even nanoparticles. They offer advantages such as controlled drug release, minimal toxicity, and customizable degradation rates, making them ideal for long-term therapeutic applications, including hormone delivery, cancer treatment, and chronic disease management.

Regulation of the Microneedle Patches:

Microneedle (MN) patches have emerged as promising tools for the transdermal delivery of a wide range of therapeutic agents, including hormones, vaccines, enzymes, mRNA, and small molecules that are otherwise difficult to administer. However, their pathway to regulatory approval is complex. The U.S. Food and Drug

Administration (FDA) has raised concerns over the quality of submissions related to microneedle-based combination products.³⁵ The main areas needing improvement include stability testing, content uniformity, risk management, sterility validation, and manufacturing consistency. As the number of MN-based therapeutic products continues to rise, their regulatory submission must be treated as a combination product-involving both the drug and the device. This adds complexity, as developers are required to provide detailed information covering all aspects of the product, such as formulation stability, active pharmaceutical ingredient (API) migration, mechanical performance of the patch, microbial safety, and manufacturing validation. Inadequate documentation in these areas often leads to delays or rejection of applications.³⁶

Currently, each microneedle product must undergo individualized, product-specific approval, which significantly slows down the regulatory process. This fragmented approval strategy hampers timely commercialization, preventing many potentially beneficial products from reaching the market. To overcome this, there is a growing call for the integration of current Good Manufacturing Practices (cGMP) with standardized quality control systems. Well-defined regulatory guidelines that address essential factors such as microneedle design, drug formulation, sterilization methods, and packaging standards could streamline the approval process. Moreover, regulators suggest that microneedle device development can be advanced independently from the drug or vaccine formulation. This separation could simplify regulatory submissions and help incorporate microneedle technology more rapidly into pharmaceutical supply chains. For successful clinical translation, developers must support their products with comprehensive data from in vitro experiments, animal studies, and clinical trials to demonstrate safety, efficacy, and repeatability. Regulatory challenges remain, ongoing efforts to refine submission guidelines, merge quality standards, and clarify approval processes will accelerate the entry of microneedle patches into the transdermal drug delivery market.³⁷

Advantages of microneedles in transdermal drug delivery:

Research into enhancing skin permeability for drug delivery began as early as the 19th century. One of the primary challenges remains the skin's outermost layer, the stratum corneum, which is composed of dead cells and poses a major barrier to the penetration of macromolecules. Despite this, transdermal delivery methods provide significant advantages over conventional routes such as intramuscular, subcutaneous, or intradermal injections, mainly due to their non-invasive, pain-free nature and ease of application.

Microneedles have emerged as a promising solution to this barrier. These tiny projections can painlessly penetrate the stratum corneum to enable the delivery of large biomolecules directly into the skin.³⁸ The skin is made up of three primary layers: the stratum corneum,

the viable epidermis, and the dermis. While the stratum corneum prevents large molecules from entering, the viable epidermis, which contains living cells and allows the passive diffusion of skin interstitial fluid (SIF), is considered ideal for transdermal drug absorption. Notably, SIF has also gained attention as a potential biomarker for point-of-care (POC) diagnostic and prognostic applications.²⁹ The dermis contains a rich network of blood vessels and nerve endings, which further supports systemic drug distribution once substances cross the upper layers. Microneedle systems overcome the natural barrier of the skin by offering a minimally invasive, efficient, and pain-free alternative for the transdermal delivery of therapeutic agents, enhancing both drug efficacy and patient compliance.

Applications of microneedles:

The skin acts as a natural shield against external elements while also serving as a functional route for administering bioactive substances. This dual function makes it highly valuable in both molecular diagnostics and therapeutic treatments. Microneedle technology, originally developed for treating various diseases, has rapidly evolved and is now utilized in immunotherapy, disease detection, and even cosmetic applications.

Disease treatment:

Biotherapeutic agents such as peptides, proteins, hormones, and natural compounds often face challenges in administration due to the first-pass metabolism that occurs when taken orally.³⁹ Although hypodermic injections provide an alternative, they are associated with discomfort and pain. In this context, microneedle patches have emerged as a promising, minimally invasive option that allows for self-administration, eliminating the pain of traditional injections. These microneedle systems primarily support transdermal drug delivery, offering a safe, efficient, and user-friendly route for treating various diseases.⁴⁰

Diabetes Treatment:

Managing diabetes, especially type 1 and type 2, often involves frequent insulin injections, posing a challenge to patient comfort and compliance, along with the constant risk of hypoglycaemia. To address this, Yu et al. introduced a glucose-responsive microneedle patch that can regulate blood sugar levels by releasing insulin in response to glucose concentration. This system utilizes glucose oxidase, an enzyme that converts glucose into gluconic acid, triggering insulin release-offering a painless, rapid, and controlled approach for type 1 diabetes.

For type 2 diabetes, Chen et al. developed an innovative pH-sensitive microneedle patch made from alginate.⁴¹ This patch incorporates two types of mineralized nanoparticles: copper phosphate containing glucose oxidase (m-GOx), which detects elevated glucose and produces H⁺ ions, and calcium phosphate encapsulating exendin-4 (m-Ex4), a therapeutic peptide that is released in response to acidity. This intelligent patch eliminates the need for repeated daily injections and enables effective blood glucose regulation.

Additionally, Lee et al. created a wearable electrochemical system capable of monitoring sweat parameters like pH, glucose, and temperature.⁴² This device can transcutaneously release metformin, a commonly used antidiabetic drug, and offers a new direction for personalized and real-time diabetes management.

Obesity:

Obesity results primarily from the accumulation of white adipose tissue (WAT), while brown adipose tissue (BAT) helps in energy expenditure. Researchers have explored transdermal methods to target WAT.⁴³ Dangol et al. formulated a hyaluronic acid (HA)-based dissolving microneedle patch containing caffeine. Applied to mice on a high-fat diet, it significantly reduced weight by enhancing caffeine's skin absorption. Further, Zhang et al. developed an HA-based microneedle patch for localized obesity treatment. It encapsulated rosiglitazone (Rosi), a browning agent, in dextran nanoparticles, combined with glucose oxidase and catalase. This setup created a localized acidic environment that transformed WAT into BAT, helping reduce fat accumulation and improve insulin sensitivity. These microneedle innovations provide targeted, pain-free, and efficient solutions for chronic metabolic disorders.⁴⁴

Immunobiological administration:

Traditional vaccination techniques, such as hypodermic, intramuscular, and intradermal injections, often cause discomfort and are associated with needle-related anxiety.⁴⁵ These drawbacks have driven the development of needle-free delivery systems, including liquid jet injectors and microneedles, which offer a less painful and more patient-friendly alternative.

Among these innovations, microneedle arrays have shown great potential in enhancing vaccine administration. These tiny needles can create temporary microchannels in the skin, allowing efficient transport of vaccine molecules. Dissolving microneedles, which break down after insertion, require precise optimization to ensure full skin penetration and timely dissolution. For instance, Li et al. demonstrated that maltose-based microneedles could deliver monoclonal antibodies within just one minute, significantly reducing the time compared to conventional solid microneedles that may require up to 24 hours.

Sullivan et al. developed biocompatible polymer microneedles embedded with inactivated influenza virus vaccines to enhance immune responses.⁴⁶ Similarly, Raphael and colleagues focused on refining formulation ratios to stabilize vaccines during delivery. Nanoparticle-based vaccines have also gained attention, offering controlled release of protein antigens. Notably, combining nanoparticle carriers with hollow microneedles has proven to be an effective method for targeted intradermal vaccine delivery.

In another study, De Groot et al. utilized ceramic nanoporous microneedle arrays to improve the transport efficiency of diphtheria and tetanus toxoids.⁴⁷ These advanced systems offer several key benefits over

conventional methods: they are painless, portable, easy to use for individual administration, and capable of delivering vaccines rapidly. Moreover, the introduction of a triple formulation strategy for hepatitis B has been proposed to extend the longevity and effectiveness of microneedle-based vaccinations. Overall, microneedle technologies represent a significant advancement in immunization practices, addressing both patient comfort and delivery efficiency.

Cosmetic field:

The integration of microneedle technology into the cosmetic field has seen remarkable advancements in recent years, leading to the development of a variety of innovative cosmeceutical products. These applications can be broadly categorized into two areas: stimulating the skin's natural healing process and enhancing the delivery of active cosmetic ingredients.² Microneedles work by creating temporary micro-channels in the skin, which not only enhance the absorption of skincare actives but also activate the skin's natural wound healing responses. Importantly, this method does not cause severe skin irritation, redness (erythema), or post-inflammatory hyperpigmentation, making it a safe and gentle option. This approach enables efficient and targeted delivery of active cosmetic compounds, thereby improving both efficacy and safety. One notable development in this area is the creation of a cosmetic microneedle patch loaded with retinyl retinoate and ascorbic acid, designed for anti-wrinkle effects. Unlike traditional products, this patch avoids side effects such as allergic reactions, offering a safer alternative for sensitive skin.⁴⁸

As the global demand for effective skincare solutions continues to grow, the commercial production of microneedle-based cosmetic products is also expected to rise. These products are typically available in two forms: patches and rollers. Microneedle rollers, fabricated using soft polymer films through inclined rotational UV lithography, have shown superior performance in enhancing skin permeability. An advanced device, known as DermaFrac™, has also entered the market.⁴⁹ This system combines micro-needling with light-emitting technology that delivers functional wavelengths for a fully customized skincare experience. Designed for personalized cosmetic treatment, it marks the next step in user-specific skincare innovation.

Drug delivery by microneedles:

Proteins:

Protein-based therapeutics are increasingly used in treating cancer, genetic disorders, and for vaccinations.⁵⁰ However, their clinical application is often limited due to low stability, poor absorption, and degradation during administration. To overcome these barriers, microneedle technology is being explored as a promising delivery system for protein drugs like insulin, erythropoietin, desmopressin, lysozyme, glucagon, GLP-1, parathyroid hormone, and growth hormone.⁵¹ Microneedles enable direct transdermal delivery, improving drug bioavailability while minimizing degradation. Despite these advantages, maintaining protein stability during

formulation, storage, and clinical use remains a major challenge. Selecting appropriate materials and stabilizers is crucial for ensuring therapeutic effectiveness.

To address this, Chen et al. developed a microneedle patch responsive to glucose and temperature changes for controlled insulin release in diabetes management.⁵² This system ensures both therapeutic precision and storage stability. Additionally, Lahiji et al. demonstrated that optimizing fabrication conditions-such as using low temperatures, gentle drying methods, specific polymer concentrations, and effective stabilizers-can preserve lysozyme activity up to $99.8 \pm 3.8\%$. These advancements highlight the potential of microneedle technology to revolutionize protein drug delivery, offering minimally invasive, stable, and efficient therapeutic solutions for complex diseases.⁵³

Vaccines/antibodies:

Microneedle-based vaccines have emerged as a promising method to induce robust antibody-mediated immune responses, offering superior localized immunity compared to traditional injections.⁵⁴ These vaccines maintain long-term antigen stability and allow for more flexible storage, making them ideal for broader distribution and use in varied environmental conditions.

Monoclonal antibodies, which specifically target cells and modulate immune activity, are widely used in diagnostics and treatments.⁵⁵ Delivering these antibodies through microneedles can minimize systemic side effects and reduce overactivation of autoreactive T cells, enhancing therapeutic safety and efficacy. However, preserving antibody stability within microneedles remains a key challenge, as protein degradation can reduce efficacy and increase immunogenic risks. To address this, trehalose has been used as a stabilizer during microneedle fabrication. Compared to sucrose, trehalose demonstrated significantly better protection, retaining up to 80% of the antibody's original activity under stress conditions.⁵⁶ Furthermore, the application of immunomodulators such as granulocyte-macrophage colony-stimulating factor (GM-CSF) within microneedles has been shown to prolong immune responses. A third-generation hepatitis B vaccine embedded in microneedles with 15% trehalose exhibited improved thermal stability, lasting 7 days at 40°C and enduring multiple freeze-thaw cycles outperforming conventional liquid vaccines in both stability and immunogenicity.⁵⁷

Conclusion:

Transdermal drug delivery using microneedles offers a promising alternative to conventional drug administration methods. It ensures painless, minimally invasive, and efficient drug delivery through the skin by bypassing the stratum corneum barrier. Microneedles enhance drug bioavailability, improve patient compliance, and eliminate risks associated with hypodermic needles. Various types, such as solid, coated, dissolving, and hydrogel microneedles, offer flexibility in delivering both small and large doses. Biocompatible materials like polymers and metals are used for fabrication. As regulatory pathways evolve, microneedle-based systems are expected to play a significant role in

future pharmaceutical applications, including vaccines, diagnostics, and chronic disease management.

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