

“A Review on Microneedle-Based Transdermal Drug Delivery Systems in Disease Management: Advances, Challenges, and Future Perspectives”

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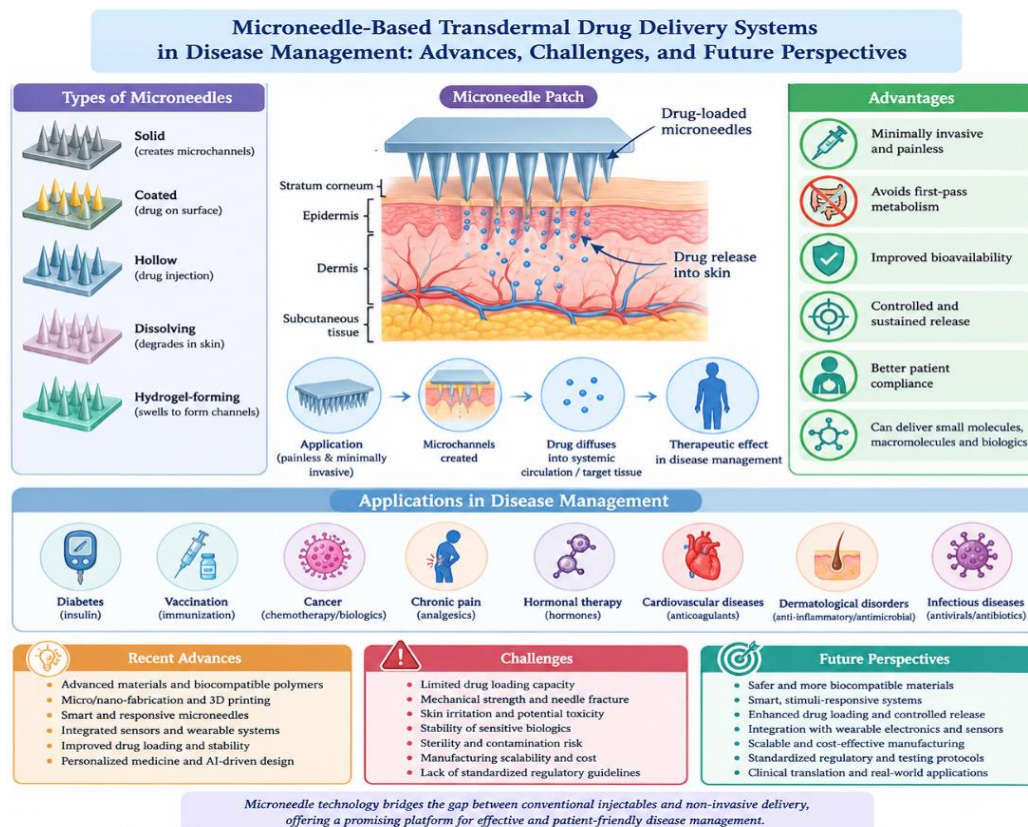
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Abstract: Transdermal drug delivery systems have emerged as an attractive alternative to conventional oral and parenteral routes because they can improve patient compliance, provide controlled drug delivery, and minimize gastrointestinal degradation and hepatic first-pass metabolism. However, the stratum corneum acts as a major barrier to the permeation of many therapeutic agents, particularly hydrophilic molecules, peptides, proteins, vaccines, and other macromolecules. Microneedle-based transdermal drug delivery systems have gained considerable attention as an advanced approach for overcoming this barrier by creating temporary microchannels in the skin and facilitating efficient drug transport with minimal pain and tissue damage. Recent advances in microneedle technology, polymeric materials, nanotechnology, microfabrication, 3D printing, and smart drug-delivery approaches have expanded their potential for the delivery of both conventional and biological therapeutics. These systems have demonstrated promising applications in the management of various diseases, including diabetes, chronic pain, hypertension, cardiovascular disorders, cancer, psoriasis, infectious diseases, vaccination, and other dermatological conditions. Smart and stimuli-responsive microneedle systems further provide opportunities for controlled, personalized, and disease-responsive therapy. Despite their potential, challenges related to drug loading, mechanical strength, needle fracture, skin irritation, biocompatibility, drug stability, sterility, manufacturing scalability, reproducibility, cost, and regulatory requirements remain. This review provides an overview of the development and advances in microneedle-based transdermal drug delivery systems, their role in disease management, therapeutic applications, safety and regulatory considerations, current challenges, and future perspectives. The integration of microneedles with smart technologies, wearable systems, artificial intelligence, and personalized medicine is expected to further enhance their clinical utility and facilitate their translation from laboratory research to practical therapeutic applications.

Graphical abstract:



Keywords: Microneedles(MN), Type 1 diabetes mellitus (T1DM), Anti-Programmed Death-1(APD), cyclosporine A (CyA), Estrogen Replacement Therapy (ERT)

Introduction

Transdermal drug delivery systems (TDDS) have emerged as an attractive alternative to conventional oral and parenteral routes because they can provide controlled drug delivery, improve patient compliance, and avoid gastrointestinal degradation and hepatic first-pass metabolism. However, the major barrier to effective transdermal delivery is the stratum corneum, the outermost layer of the skin, which restricts the permeation of most therapeutic molecules, particularly hydrophilic drugs, macromolecules, peptides, proteins, and other biological therapeutics. Conventional approaches such as chemical penetration enhancers, iontophoresis, sonophoresis, and thermal methods have been investigated to overcome this barrier, but limitations related to irritation, complexity, variable drug delivery, and patient acceptability have restricted their broader application.^(1,2)

Microneedle (MN) technology has emerged as a promising strategy to overcome the limitations associated with conventional transdermal delivery. Microneedles are micron-sized structures capable of creating temporary microchannels across the stratum corneum while minimizing stimulation of the deeper nerves and blood vessels. This approach facilitates the delivery of therapeutic agents into or across the skin with considerably less pain and tissue damage than conventional hypodermic needles. Depending on their design and mechanism of drug delivery, microneedles can be broadly classified into solid, coated, hollow, dissolving, and hydrogel-forming microneedles. These different architectures provide opportunities for delivering a wide range of therapeutic agents, including small molecules, vaccines, peptides, proteins, nucleic acids, and other biologically active compounds.^(3,4)

The development of microneedle-based systems has progressed from simple mechanical enhancement of skin permeation toward sophisticated platforms capable of controlled, sustained, and stimuli-responsive drug delivery. Advances in microfabrication, polymer science, nanotechnology, 3D printing, and smart drug-delivery technologies have enabled the development of microneedle systems with improved drug loading, mechanical strength, dissolution behavior, and therapeutic performance. Their potential applications have expanded to several therapeutic areas, including pain management, diabetes, vaccination, psoriasis, cancer, hormonal therapy, cardiovascular diseases, and various dermatological conditions. In particular, smart microneedle systems, including glucose-responsive insulin delivery platforms, demonstrate the potential of this technology for personalized and responsive therapy.^(5,6)

Despite these advantages, several challenges continue to limit the widespread clinical translation of microneedle-based transdermal systems. These include insufficient drug loading, mechanical failure or fracture, skin irritation, potential toxicity, stability of sensitive biological molecules, sterility and contamination concerns, manufacturing complexity, scalability, batch-to-batch reproducibility, and relatively high production costs. In addition, the absence of universally standardized regulatory requirements and validated testing methods specifically designed for microneedle products remains an important barrier to commercialization and clinical adoption.^(7,8)

Therefore, continued research is required to establish reliable manufacturing processes, improve material biocompatibility and mechanical properties, optimize drug loading and release, and develop standardized safety and regulatory evaluation procedures. Integration of advanced manufacturing technologies, artificial intelligence, wearable devices, and personalized medicine may further enhance the therapeutic potential of microneedle systems. This review discusses the evolution and principles of microneedle-based transdermal drug delivery, major types and fabrication approaches, therapeutic applications, safety and regulatory considerations, current challenges, and emerging future perspectives, with emphasis on their potential to provide effective, minimally invasive, and patient-friendly alternatives to conventional drug delivery systems⁽⁹⁾

Transdermal drug delivery using microneedles

The main driving force behind microneedles is their potential to deliver molecules into the skin in a minimally invasive manner. This objective has led to the use of microneedles for transdermal distribution in a number of particular ways.⁽¹⁰⁾

Transdermal microneedles improve drug distribution across the skin by creating micron-sized pores in the skin. A microneedles patch is a device made of arrays of microneedles on a backing that can be applied to the skin like a bandage.⁽¹¹⁾

With a height of 10–2000 μm and a width of 10–50 μm , a microneedle (MN) is a micron-sized needle that may painlessly pierce through the epidermal layer and reach dermal tissue.⁽¹²⁾

External factors like skin physiology, physiochemical characteristics, and environmental circumstances can affect the MN drug delivery route. The temperature and relative humidity around the application region will contribute for drug delivery. Too little humidity (low humidity) will delay the release of medications to the epidermal layers, while too much humidity (sweat, for example) might alter the osmotic gradient for transdermal drug delivery by interfering with the drug release kinetics due to excess water and other salts.⁽¹³⁾

The length is intended to be both long enough to pierce the SC effectively and short enough to avoid pain receptors.⁽¹⁴⁾

In order to preserve pharmacological activity and the integrity of microneedles—such as their strength, sharpness, and sterility—they must be maintained under certain circumstances.

Anesthetics can be administered via microneedles without the need for needles. They are particularly important in medication delivery since they are painless, minimally invasive, and tiny (100 microns).

(15)

TDD is a non-invasive delivery method that avoids some bioavailability issues that arise from oral drug delivery due to poor absorbability and metabolism issues. It is generally thought to be simple to administer even in more vulnerable age groups, such as pediatric and geriatric patients. The skin is a handy and patient-friendly drug delivery target due to its large surface area and accessibility. The main benefits of transdermal distribution include the elimination of first-pass metabolism, steady delivery, more patient compliance, less systemic medication interactions, sustained drug release, and typically higher therapeutic efficacy.

Few medications that use chemical TDD techniques have been successfully brought to market. Chemical TDD systems like niosomes and nanocrystals are not the ultimate dosage forms and must be transformed into an appropriate dosage form (such as patches, creams, gels, etc.) before being used; this may be the manufacturing complexity of chemical TDD systems that is impeding commercialization. Furthermore, the distribution of hydrophilic macromolecules like insulin and other proteins is severely limited by chemical techniques.⁽¹⁶⁾

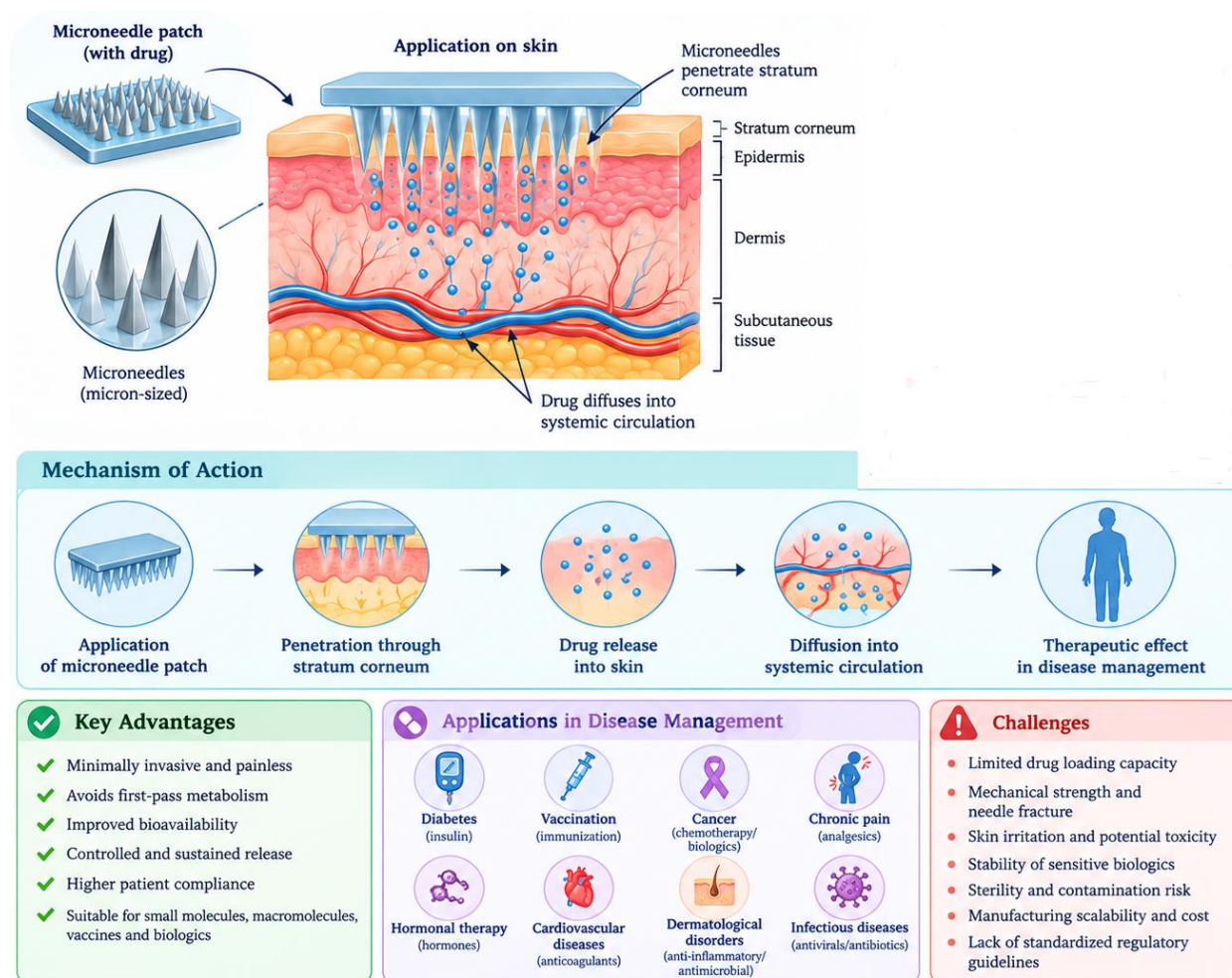


Fig1: Microneedle Based Transdermal Drug Delivery System

History of microneedles

Transdermal medication delivery has a long history dating back to humanity. Three generations of transdermal medication administration have been developed; the third generation has included the application of medical equipment and devices.⁽¹⁷⁾

Microneedle conceptions have changed over time, moving from the use of huge needles to the current,

contemporary design. German dermatologist Dr. Ernst Kromayer used various- sized motor-powered dental burs to treat scars, hyperpigmentation, and other skin conditions in 1905.

The 1970s saw the introduction of the microneedle concept, but it wasn't until the 1990s when this idea was proven through experimentation. In order to alleviate motion sickness, the first transdermal device was authorized in 1979 for the application of a three-day patch containing scopolamine to treat motion sickness.⁽¹⁸⁾

This procedure targeted the cutaneous abnormalities present under the skin which were responsible for depressed scars and wrinkles. The first microneedle for transdermal distribution was proposed in 1998 and was manufactured from silicon wafers by ion etching and photolithography.⁽¹⁹⁾

Hypodermic needles have been used to administer IV medications to patients since the development of hollow needles in 1844. This year, an estimated 16 billion injections will be given globally, making it one of the most popular medical devices.⁽²⁰⁾

In 1998, a unique strategy to transdermal medication delivery that dramatically increased the transport of molecules over skin was demonstrated. When placed into the skin, microneedles made by etching arrays of micron-sized needles into silicon have been demonstrated to significantly increase permeability to calcein by more than 1000 times.⁽²¹⁾

Different materials such as glass, ceramic, metal, and polymers were introduced to create microneedles. In 2004, transdermal medication distribution was accomplished by puncturing the skin using a microneedle array.⁽²²⁾

It prompted the investigation of various fabrication techniques and materials for TDD. Different kinds of MNs include solid, coated, hollow, dissolvable, and hydrogel-forming MNs.⁽²³⁾

TRANSDERMAL DRUG DELIVERY IN DISEASES MANAGEMENT

Transdermal drug delivery in pain management

One of the most extensively studied subjects in the field of minimally invasive controlled drug delivery systems is transdermal drug delivery systems. TDDS may be a suitable substitute for parenteral and oral medication delivery methods. TDDS has several benefits over Some advantages of the oral route include avoiding the medicine's bad taste, if any, and avoiding hepatotoxicity, first-pass metabolism, and gastrointestinal drug degradation. Conversely, hypodermic injections are uncomfortable and carry the danger of spreading illness through the reuse of needles. TDDS, on the other hand, are self-administered, noninvasive, and can be made to release medications over time. They also increase the drug's bioavailability and patient compliance.

There are two types of TDDS: active and passive. When employing active TDDS, any external stimulation like temperature, ultrasound, or low voltage might increase the drug's permeability through the skin. In contrast, passive TDDS does not employ any external stimuli or substances to improve drug penetration.⁽²⁴⁾

Due to its low molecular weight, great potency, and solubility in both fat and water, fentanyl is a perfect medication for transdermal delivery. Patients over the age of two who have grown tolerant to opioids used for moderate to severe persistent chronic pain may be treated with fentanyl patches. Although they can be used to treat severe chronic pain, the British National Formulary for Children does not advocate for their adoption.⁽²⁵⁾

Fentanyl and buprenorphine patches are used in the treatment of cancer and chronic pain. There are several benefits to transdermal opioid administration, which can cause adverse effects like drowsiness, nausea and vomiting, and respiratory depression. Patient compliance is further enhanced by the decreased requirement for dosage administration (72 hourly or weekly). A recently developed iontophoretic patch has the ability to deliver boluses of fentanyl and provide patient-controlled analgesia (PCA).⁽²⁶⁾

Microneedles in chronic pain-associated diseases

The treatment of chronic pain-related conditions like neuropathic pain, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and atopic dermatitis is gaining a lot of attention because of their high prevalence. The transdermal drug delivery system can directly affect the articular cavity and wounded or inflammatory subcutaneous tissues, making it a great pain management technique with high patient acceptance. MNs are the most suitable transdermal formulation for pain treatment. These are used in conjunction with a range of chemical or physical augmentation techniques to address the stratum corneum's blockage, which is the primary barrier to transdermal medication delivery.

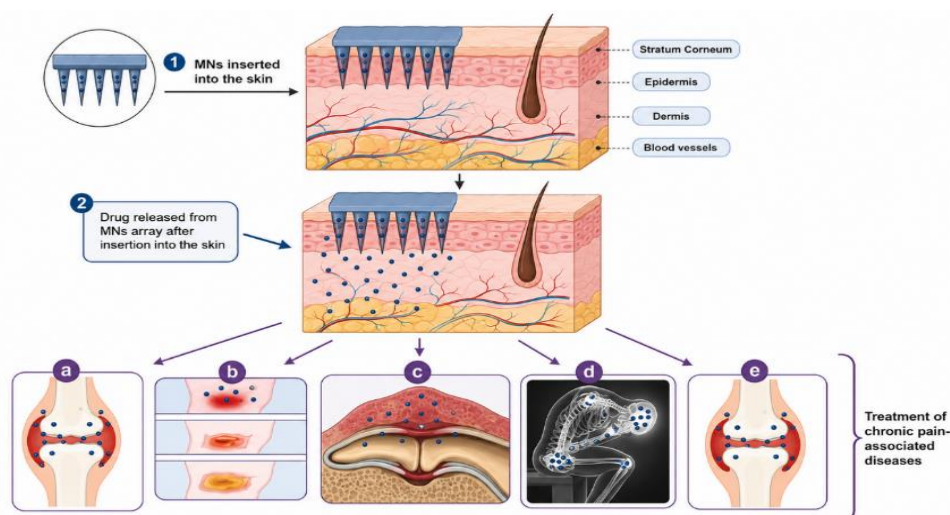


Fig 2: Microneedles in Pain management

When used over an extended period of time, the traditional pain management methods have negative side effects and low patient compliance. Recent developments in drug delivery technology have fundamentally altered how illness is identified, treated, and prevented. Therefore, MNs proven to be a ground-breaking strategy to address the shortcomings of traditional treatments and to ensure patient compliance for their long-term use in the management of pain and inflammation.⁽²⁷⁾

The majority of research on microneedles has focused on manufacturing techniques and evaluated their potential for medication delivery. Despite receiving little attention, the mechanics of microneedle insertion are crucial for real-world applications. Skin can only be penetrated by microneedles with the necessary physical characteristics and geometry. Certain needle designs simply need to be manually inserted.⁽²⁸⁾

When microneedles were first used for drug delivery, the primary objective was either to create hollow microneedles with more advanced capability than traditional hypodermic needles or to increase skin permeability by a solid microneedle pre-treatment. Microneedles are being used in many different sectors, including as intracellular, ophthalmic, and transdermal administration.⁽²⁹⁾

Transdermal drug delivery may be greatly enhanced by combining these nanoparticulate systems with microneedles. Combining the solid particles with microneedles facilitates their easier penetration into the skin.

because the medication is enclosed in microneedles. Very little —less than 1 mg is probably the greatest total dose that can be administered. MNPs must be dried throughout the manufacturing process, which explains why they are extremely stable.^(30,31,32)

After being implanted into the epithelium, hydrogel-forming microneedles (HFMs) easily absorb tissue fluid and have enough mechanical strength to pierce the skin [4]. The polymer swells as a result, creating continuous, unhindered hydrogel microchannels that open diffusion portals for drug delivery, enabling the release of the therapeutic agent and the expected therapeutic effects in the body.⁽³³⁾

Transdermal drug delivery systems in diabetes management

In the population, diabetes mellitus is now a prevalent illness. According to basic health research done in 2018, the number of cases of diabetes mellitus in Indonesia increased between 2013 and 2018. People with diabetes require effective therapy to prevent more serious problems and increase their life expectancy, given the growing number of cases of the disease and the significance of managing it properly.⁽³⁴⁾

Insulin-producing beta cells in the islets of Langerhans are destroyed in type 1 diabetes mellitus (T1DM), which results in a complete lack of insulin. However, it is classified as Type 1B diabetes mellitus or idiopathic diabetes when no autoimmune mechanism of beta-cell destruction and no other known cause of insulin deficiency are found.

About 90% to 95% of people with diabetes have type 2 diabetes mellitus (T2DM), formerly known as non-insulin-dependent diabetes mellitus. Relative insulin deficiency and insulin resistance brought on by genetic or environmental factors are seen in this kind of diabetes.⁽³⁵⁾

Insulin, insulin analogs, and non-insulin hypoglycemic medications that contain insulin sensitizers, insulin secretagogues, glucose regulators, and gene therapy make up the majority of anti-diabetic medications.

The primary physiological roles of insulin and its analogs are to control the metabolism of protein, fat, and sugar in vivo and to keep blood glucose levels within normal limits. They can stimulate the target cell membrane carriers in muscle and adipose tissue to transport glucose in plasma into cells, speed up the synthesis of glycogen in muscle and liver cells, and prevent the breakdown of glycogen and the production of PEP carboxykinase.

Patients with postprandial hyperglycemia are best suited for these insulin analogs, which can be administered 0–15 minutes prior to or just after a meal with excellent compliance.⁽³⁶⁾

Insulin Patch Technology

An adhesive device that contains medication molecules is called a transdermal insulin patch. To distribute the appropriate medication dose in the systemic channel at predetermined intervals, this device can be attached to the skin's surface. In order for the medicine particles administered through the stratum corneum to effectively diffuse through lipid molecules, transdermal treatment with this kind of patch must be thin, smooth, flexible, and homogenous.

There are 121 microneedles with a height of 600 mm in a single 6 mm insulin patch. Insulin nvinylpyrrolidone (NVP) with in-situ photopolymerization at 4°C, the enzyme glucose oxidase, a polymer that dissolves at 29–30°C, and NVP as a solvent are all present in each microneedle.

When blood sugar levels rise and glucose fills the fake vesicles, the insulin patch begins to function. This is followed by the activation of the glucose oxidase enzyme, which transforms glucose into gluconate. Due to the conversion of hydrophobic to hydrophilic 2-nitroimidazole molecules, this process necessitates a constant supply of oxygen and frequently results in moderate hypoxia in individuals with diabetes mellitus.⁽³⁷⁾

The traditional techniques of taking blood glucose levels involve using needles to pierce the skin. These needles have been proven to be very painful and have been proven to damage tissue. These Miniature Needles (MNs) may provide a solution to these challenges by providing a minimally invasive skin interface device. One of the biggest challenges in transdermally delivering insulin is the size of the molecule, which is very large (~50 Å across) and cannot pass through the stratum corneum. By using MN technology, it is possible to create miniature pores in the stratum corneum through which insulin can be delivered.

In order to ensure pain-free and proper insulin delivery into the stratum corneum from the MNs, the lumen diameter of the needle should be between 10 and 100 µm in diameter. Therefore, it stands to reason that using arrays creates a more effective means of promoting fluid flow. Increased numbers of MNs within an array create a greater linear flow of insulin delivered into the stratum corneum.

The use of MN to deliver insulin into the stratum corneum would have zero pain and be more stable for longer periods. Therefore, more frequent administration of short half-life insulin is possible with the MN.^(38,39)

Employment of microneedle in insulin patch

There are numerous studies on formulating insulin patches with microneedles. The materials utilized have differing properties; needle length, diameters, and excipients are also varied so that the differences between microneedle formulations can be studied, and modifications to the formulation to achieve optimal results can be evaluated. The two most common treatment options for managing diabetes at this time are oral medications and insulin injections. Although there has been much research completed on using microneedles to create transdermal insulin patches, a considerable portion of research is being conducted concurrently on the pharmacological properties and clinical challenges associated with this mode of administration. The studies reviewed in this document characterize the various formulations and properties of insulin patches employing microneedles.⁽⁴⁰⁾

A popular technique for delivering medication through the skin that makes taking it easier is the use of microneedles. They have been shown to significantly help people with health issues and come in a variety of forms and materials. In conclusion, microneedles are adaptable instruments that have the potential to greatly improve medical results.⁽⁴¹⁾

A number of tactics, such as penetration enhancers, creative formulation designs, and physical procedures, could improve transdermal and intradermal medication delivery. Microneedles are now the most dependable and efficient way to administer drugs transdermally, according to several studies conducted in academic institutions and businesses. It has been claimed that micron-sized needles (Microneedles, 25–2000 µm long) can precisely and reversibly disrupt the function of the skin barrier by penetrating skin layers and producing multiple microchannels in the skin.⁽⁴²⁾

Glucose-Responsive MN-Array Patch Systems for Diabetes Treatment

Previous studies have shown that insulin can be delivered through MN-array patches. MNarray patch systems are simple and painless but they do not provide any means to sense glucose levels; therefore, it is necessary to

check blood glucose levels consistently and apply MN-array patches at the appropriate time to ensure normal blood sugar levels are maintained.

As the blood glucose level (BGL) increased, oxygen was consumed from the enzymatic metabolism of glucose to gluconic acid by glucose oxidase, creating a local hypoxic condition and enabling the hydrophobic to hydrophilic transition. This, in turn, triggered disassembly of the vesicles causing release of insulin. The in vitro study showed the GRVs have a rapid reversible release of insulin between normoglycemic and hyperglycemic conditions. Additionally, one MNarray patch can be effectively applied to the dorsum of a mouse's skin, reduce BGLs to a normal level in 30 minutes, and maintain normoglycemic levels for up to four hours in diabetic mice.⁽⁴³⁾

PSORIASIS

Its challenging to treat psoriasis due to recurrence and treatment resistance. Methotrexate (MTX), cyclosporine A (CyA), and retinoic acid are the first-line medications for psoriasis in systemic therapy. These medications work well, but they have negative side effects like hypertension, hepatotoxicity, and impaired renal function.

Researchers are dedicated to creating novel drug delivery techniques because of the drawbacks of the topical medications currently used to treat psoriasis, such as their poor penetration and adverse effects.

CyA is an effective immunosuppressive agent, but its large molecular size and hydrophobic characteristics make transdermal delivery challenging. A psoriasis animal model was treated with MNPs containing CyA combined with methanol-based hydroxypropyl cellulose. Recent research has explored a number of novel transdermal treatments to enable topical application of CyA.⁽⁴⁴⁾

Researchers have created MNPs to lessen the negative effects of microneedles and increase the effectiveness of MTX treatment for psoriasis. According to research by Ajay K. Banga and colleagues, MTX delivery is more successful when administered beneath MNP-pretreated skin than when control techniques are used. Their group created an MNP in 2008 that was made of soluble maltose and had 56 needles that were 500 micrometers tall.

TDDS and the drug delivery system using microneedles. It can take the place of traditional medication delivery methods, most likely the transdermal technique. The biological treatment is an alternative to conventional treatment for moderate and severe psoriasis, and its greatest benefit is that it is painless.⁽⁴⁵⁾

Cancer

Cancer immunotherapy is a therapeutic approach with activation of immune response against multiple tumor antigens. The skin is a highly active immune defense organ. This includes specific antigen-specific immune response where Langerhans cells and dendritic capture and present antigens under the stratum corneum.

Antigen-coated MNPs are studied to understand antigen-based immunity as MNPs serve as an efficient vehicular tool through the skin for vaccines. For classical transdermal therapeutic vaccines, the ideal antigen model is ovalbumin.

Researchers have also engineered MNPs that deliver promising immunotherapeutic nanoparticle therapeutics directly to melanoma. Recently, a nanoparticle drug prepared with an anti-PD1 antibody inhibited tumor growth. Inhibiting melanoma of escaping the body's immune surveillance system by Anti-PD1 MNP. Ligands on melanoma cells latch onto PD1 at T cell surfaces, effectively short-circuiting immune responses.

In addition, to the best of our knowledge, even though MNs are also applied to anti-breast cancer and anti-ovarian cancer in mice model recently. The rates at which a tumor could be suppressed were higher upon using MNs to deliver the cancer vaccines.⁽⁴⁶⁾

The need to find effective, site-specific treatments is brought on by the unchecked death of healthy cells, chemotherapy-related damage, and acquired immunity against drugs. Modern pharmacological methods for anti-neoplastic medication absorption through the skin help cancer treatments with better pharmacokinetics and fewer adverse effects. The most common kind of transdermal drug delivery method is adhesive dermal patches, which enable the regulated administration of strong antineoplastic medications with improved patient compliance.

However, achieving therapeutic efficacy and expanding the scope of integrating various approaches that can facilitate the development of transdermal administration of anti-neoplastic drugs is crucial, and the development of such an effective transdermal nano-therapeutic system marks a significant turning point in the delivery of anti-neoplastic drugs. Health centers can determine that transdermal formulations are safer and more effective than oral formulations in the near future based on the amount of research and attention.⁽⁴⁷⁾

TDDS IN HORMONAL THERAPY TRANSDERMAL DRUG DELIVERY SYSTEM OF ETHINYLESTRADIOL AND TESTOSTERONE: IN VITRO EVALUATION

Because of its benefits, the idea of administering medications through the skin for the systemic treatment of illnesses is becoming more and more significant . The benefits of TDDS include avoiding hepatic first-pass metabolism, improving therapeutic efficacy, extending the duration of action of powerful medications with brief plasma half-lives, and maintaining a constant drug level in the plasma or serum.

Ethinylestradiol and testosterone both play a significant role in regulating female sexual function. The most common complaints associated with decreased estrogen and/or testosterone levels are decreased desire and libido, vaginal dryness and lack of sexual arousal in postmenopausal females . The estimated proportion of women who can be classified as having low sexual desire ranges from 7 to 33%, depending on the population studied and the definition being used . Due to a hormonal deficiency in postmenopausal women, Hypoactive Sexual Desire Disorder (HSDD) is commonly reported . Estrogen replacement therapy improves sexual function in females in conjunction with testosterone.

This may result in a decline in sexual function in women treated with ERT at a later time . Postmenopausal women who have failed to restore their sexual function with ERT alone can increase their sexual response treated additionally with testosterone . Also, ethinylestradiol and testosterone have many of the appropriate physicochemical and biological qualities to be incorporated into a transdermal patch type delivery system such as small $t_{1/2}$, (in minutes), tiny daily dose in (in $\mu\text{g/day}$) and hepatic first-pass effect upon oral administration.⁽⁴⁸⁾

Transdermal drug delivery in cardiovascular disease

Cardiovascular disease (CVD) remains one of the leading causes of morbidity and mortality worldwide. Traditional treatments, such as oral medications and invasive surgical procedures, have made significant progress in managing CVD. Cardiovascular diseases remain a primary concern.³The need for innovative solutions to enhance the treatment of cardiovascular diseases is clear, and one such breakthrough lies in the domain of transdermal drug delivery.^(49,50,51)

Transdermal drug delivery in Hypertension

Elevated blood pressure (BP), or a systolic reading of 140–150 or higher, is the hallmark of hypertension, a pathological condition. According to the World Health Organization (WHO), hypertension (HTN) is one of the main causes of death and morbidity worldwide, contributing to around 9 million deaths annually. Significant research has connected high blood pressure (BP) to a number of conditions, including heart failure and cardiovascular diseases. Additionally, angina pectoris, chronic renal disease, diabetes mellitus, and atrial fibrillation are all thought to be significantly increased by hypertension. Diabetes and hypertension are thought to frequently coexist.⁽⁵²⁾

Despite their benefits, many antihypertensive medications have limited penetration due to the skin's inherent barrier function. To get around this, enhancement techniques have been developed to boost drug bioavailability and therapeutic efficacy. These techniques include chemical penetration enhancers (like terpenes and fatty acids), physical methods (like microneedles and iontophoresis), and novel formulation approaches (like nanoparticles and liposomes). By optimizing the distribution of antihypertensive medications, these improvements may help patients with MDRHTN better control their blood pressure.⁽⁵³⁾

Despite the skin's extremely selective barrier, its large surface area and the painless simplicity of transdermal administration have made transdermal drug delivery a fast growing modality that promises improved bioavailability, adherence, and efficacy with fewer adverse effects. Transdermal antithrombotic distribution is still difficult, despite recent research into superficial topical antithrombotic compositions, particularly for wound healing. Transdermal drug delivery systems (TDDS) are nevertheless appealing choices for medications with poor water solubility, rapid gastrointestinal degradation, substantial presystemic metabolism, or low oral bioavailability. By avoiding first-pass metabolism, TDDS can help bedridden patients, stabilise plasma concentrations, enable on-off management, and frequently permit lower daily therapeutic doses than oral delivery, reducing systemic side effects like bleeding and stomach discomfort.⁽⁵⁴⁾

Angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) are some of the most commonly prescribed medications for hypertension.

To get around the problems with their traditional dose form, numerous attempts have been undertaken worldwide at the laboratory level to study skin penetration and create transdermal treatment systems of different ARBs, ACEIs, and other anti-hypertensive.

Due to a number of well-known benefits, such as: (i) avoiding pre-systemic metabolism; (ii) allowing lower daily doses; (iii) reducing the frequency of dosing; (iv) blood or plasma levels of the drug can be kept within the therapeutic window for extended periods of time; (v) prolonging drug action; and (vi) less inter- and intra-patient variability, the idea of delivering drugs via transdermal route for systemic treatment of diseased states. Due to the growing number of medications that can be administered through the skin to the systemic circulation in clinically effective doses, the TTS has grown significantly during the last ten years.

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Transdermal drug delivery in vaccines

TDDSs solve a number of issues related to oral or hypodermic injection drug administration. TDDSs are less intrusive, painless, and self-administered by the patient. Additionally, this technique enables prolonged drug release to enhance the pharmacokinetic profile. Compared to previous approaches, TDDSs are more practical and economical. However, a significant hurdle to the efficacy of TDDSs and their potential for widespread

clinical application is the impermeable skin barrier. Transdermal drug diffusion is particularly hampered by the intact stratum corneum.

Skin diseases

Conventional drugs do not satisfactorily penetrate the stratum corneum of the skin. This weak point limits their therapeutic efficacy. As a result, transdermal drug delivery is widely used in the treatment of various skin diseases, and the use of MNs is receiving great attention in the treatment of various skin diseases, including hair loss, psoriasis, and acne. Presently, MNs have been approved for clinical trials related to cosmetic medicine.⁽⁵⁶⁾

Transdermal drug delivery (TDD) has drawn a lot of attention over the past 20 years due to its many benefits over traditional drug delivery methods, such as pre-established dosages, ease of handling, and patient self-administration. However, the oral route of drug delivery has a number of disadvantages when it comes to therapeutic compounds with limited solubility, permeability, and degradation. Because most medications taken orally go through first-pass metabolism and face numerous biological and physical obstacles, their oral bioavailability varies widely. When administering medications with a limited therapeutic index and low bioavailability, parenteral drug delivery is the most efficient method, especially when patient compliance cannot be guaranteed (e.g., comatose patients). However, certain tools and sterilizing methods are needed for the production and administration of parenteral formulations.

When administering medications with a limited therapeutic index and low bioavailability, parenteral drug delivery is the most efficient method, especially when patient compliance cannot be guaranteed. Additionally, the requirement for an inexpensive, non-invasive vaccination approach, especially in developing nations, has prompted a great deal of research into the creation of straightforward needle free substitute systems, such transdermal drug delivery (TDD).

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Challenges and Future Perspectives of Microneedles

According to Barry Citation (2001), the transdermal device market is estimated to be worth \$2 billion, or 10% of the \$28 billion drug delivery market in the United States. These numbers are startling given that only nine more medications have been approved since the FDA licensed the first transdermal patch in 1979. The physicochemical limitations placed on skin delivery are highlighted in this brief list of "deliverables."

Transdermal drug delivery has grown at a robust 25% annual rate, surpassing both the inhalation market (20%) and oral drug delivery (2%) . As new devices are developed and the number of transdermal medications on the market grows, this number will undoubtedly increase in the future. The use of the skin as a route of administration for the treatment of various conditions will increase with the development of such devices.⁽⁵⁷⁾

TDDS is a non-invasive delivery approach that is generally regarded as being easy to administer even in more vulnerable age groups, such as pediatric and geriatric patients, whilst circumventing some bioavailability concerns that arise from oral drug delivery due to poor absorbability and metabolism concerns. The huge surface area and accessibility of the skin make it a convenient and patient-friendly drug delivery target. Elimination of first-pass metabolism, stable delivery, improved patient compliance, reduced systemic drug

interactions, sustained drug release, and generally greater therapeutic efficacy are all key advantages of transdermal delivery. ⁽⁵⁸⁾

The quest to deliver medications from different plant sources to their target sites for treatment in the body has advanced significantly in recent years, and many delivery systems have been used successfully. Nevertheless, there are many obstacles and limitations to what these systems can accomplish in treatment.

The use of much smaller particles for delivery to the human biological system is a solution to the problems associated with using much larger particles. Some of these delivery systems use large particles as carriers, which are not particularly favourable for treatment because they can constitute challenges such as poor absorption and solubility, in vivo instability, poor bioavailability, target-specific delivery complications, and several adverse side effects upon administration.

The drug delivery and Nano medicine area of research has become a very fascinating area of research in modern science, and in the past years, it has received a lot of attention in terms of research, experimentation, and many clinical trials. ⁽⁵⁹⁾

Regulatory bodies will need data that proves the safety of the device in contact with the skin, either in the short- or long-term. Thus, in order for any of these novel drug delivery systems to succeed and compete with existing ones in the market, the safety, efficacy, portability, user-friendliness, cost-effectiveness, and marketability of the device must be addressed. ⁽⁶⁰⁾

The injectable form of the drugs is non-specific and can produce substantial systemic toxicities based on the traditional oral doses. TDDS is currently emerging as a powerful tool in the management of skin diseases. The government is strictly controlling the development and commercialization of new TDDS products, in addition to promoting TDDS trials. ⁽⁶¹⁾

Recent advances and future perspectives of smart microneedles

Wearable technology has revolutionized both personal wellness and healthcare by offering convenient and reasonably priced options for ongoing patient monitoring. It can provide real-time data on a person's health using non-invasive or minimally invasive methods, making it a desirable option for healthcare monitoring.

1.PDMS-based microfluidics

Polymers are widely used for microfluidic devices to manipulate small volumes of fluids because of their biocompatibility, flexibility and low-cost. The techniques for the fabrication of polymer based microfluidic devices are soft lithography, hot embossing and injection moulding. Soft lithography is the most common. Polydimethylsiloxane (PDMS) is the most widely used polymer for the fabrication of microfluidic devices. Other polymers used for the fabrication of microfluidic devices, besides PDMS, are polystyrene (PS), polyether ether ketone (PEEK), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polymethylmethacrylate (PMMA), cyclic olefin copolymer (COC), polycarbonate (PC), and polyetherimide (PEI). ^(62,63)

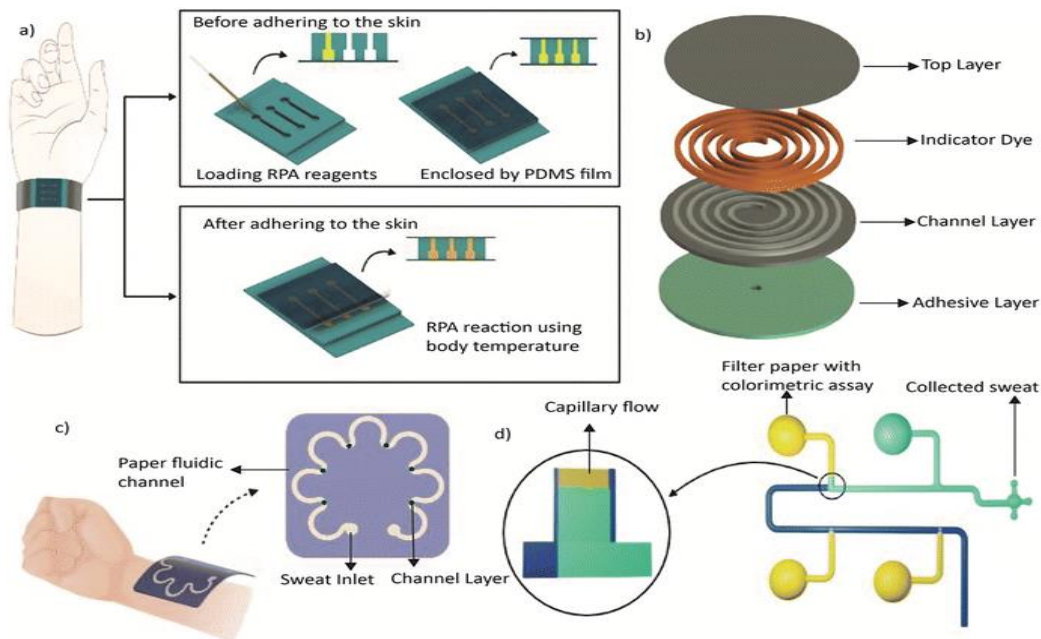


Fig3: Schematic representation of a wearable microfluidic sweat-sensing patch

2.Advanced manufacturing technologies

The development of microneedle systems heavily relies on the progress of manufacturing technologies that allow precise control over geometry, scalability and functional integration. Simple designs can be fabricated using traditional techniques but these often lack in terms of throughput, customization and material compatibility. In response, emerging advanced manufacturing techniques including 3D printing, lithography based processes, and laser micromachining provide higher flexibility and resolution to create complex, multi-material, and application-specific microneedle architectures. This section discusses state of the art manufacturing techniques that are driving the next generation of microneedle innovations. ^(64,65)

Table 1: Microneedle advanced fabrication techniques, their advantages, limitations, and pharmaceutical applications.

Fabrication Strategy	Technique Method /	Advantages	Limitations	Applications
Mold-Based Fabrication	Conventional Four-Step Method	Provides high precision and reproducibility. Suitable for large-scale production and fabrication of multicomponent microneedles. Easy to handle and widely	Limited flexibility and adaptability. Drug wastage may occur during fabrication. The process depends heavily on molds and involves time-	Most widely used method for laboratory, large-scale, and industrial manufacturing of microneedles.

		adopted in industry.	consuming, technically demanding steps.	
	Surface Coating Modification	Simple and controlled process that protects sensitive bioactive agents. Enables accurate drug loading and is suitable for mass production.	Restricted by mold design and lacks versatility. Requires multiple processing steps and specialized techniques.	Commonly used for loading vaccines, proteins, and other bioactive compounds onto microneedles.
	Mold Filling by Imprinting	Ensures accurate fabrication while maintaining the stability of sensitive therapeutic agents.	Requires additional equipment and remains dependent on molds. Drug loss can occur, and the process is relatively time-intensive.	Used when precise incorporation of bioactive materials into microneedles is required.
	Mold Filling by Spin Coating	Offers precise and uniform drug distribution while protecting active pharmaceutical ingredients.	Needs specialized spinning equipment and remains limited by mold geometry. The process can be lengthy and technically complex.	Suitable for drug-loaded microneedles requiring uniform coating or distribution.
	Mold Filling by Infiltration or Spraying	Allows accurate drug loading and preserves sensitive bioactive substances during fabrication.	Requires extra instrumentation and still relies on mold structures. The fabrication process can be complicated and time-consuming.	Applied in the preparation of bioactive or therapeutic microneedle systems.
Mold-Free Fabrication	Drawing Lithography	Flexible, cost-effective, and efficient	Lower precision compared to mold-based	Useful for fabricating bioactive

		technique. Does not rely on molds, minimizes drug loss, and simplifies fabrication steps.	methods. Mainly produces single-layer, cone-shaped microneedles and requires technical expertise.	microneedles with simplified manufacturing procedures.
	Droplet-Born Air Blowing	Mild and less damaging fabrication process. Offers flexibility, reduced drug wastage, and simplified manufacturing without molds.	Limited accuracy and mainly suitable for producing single-layer conical microneedles. Technique requires skilled operation.	Suitable for incorporating sensitive biological materials into microneedles.
	Centrifugal Lithography	Economical and gentle fabrication method with flexible design capability. Simplified processing and reduced material loss.	Produces mainly unilayer conical structures and has lower precision compared to mold-based fabrication.	Used for preparing drug-loaded microneedles with simplified fabrication processes.
	3D Printing	Highly precise and capable of producing complex and customized microneedle structures without molds. Enables advanced and intricate designs.	Requires expensive high-precision instruments and longer fabrication times.	Ideal for manufacturing sophisticated microneedles with complex geometries and tailored designs.
	Microlens-Integrated Technique	Cost-effective, scalable, flexible, and suitable for automated production. Does not require molds and	Some fabrication steps may involve harsh conditions, and the method is sensitive to	Shows strong potential for large-scale and industrial microneedle manufacturing.

		supports adjustable fabrication.	material selection.	
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3. Personalized medicines

Wearable medical systems have sensors and medicine containers that work together. This means they can check how someone is doing and give them the amount of medicine at the same time. Wearable medical systems are really good for people with diabetes. For instance someone found a way to put small parts that help break down medicines onto a surface to help manage diabetes. Wearable medical systems like these are very helpful for people with diabetes because they can check and treat diabetes at the time. People with diabetes can use medical systems to make their lives easier. Wearable medical systems are good, for diabetes management.

Three dimensional printing is really changing the way we make Micro Needles. This technology lets us build things layer by layer with a lot of detail. So we can make Micro Needles that're exactly the right size and shape for what we need. We can even make them in shapes and designs. This is great because we can make Micro Needles that're just right for each person. Three dimensional printing also works with lots of materials that are safe for people, like special liquids that harden when you shine a light on them and plastics and metals. These materials can make Micro Needles work better.⁽⁶⁶⁾

4. AI integrated patches

Allergic contact dermatitis is a common skin problem that affects about 20% of people. It can really affect the quality of life and productivity of people with contact dermatitis. The usual way to figure out if someone has contact dermatitis is with patch testing. Patch testing is a way to diagnose allergic contact dermatitis but it can take a long time and different doctors may not always agree on the results. As we get technology we can use artificial intelligence to help make the patch testing process better. Artificial intelligence can help make sure the results are consistent reduce mistakes made by people and maybe even make the whole process of diagnosing allergic contact dermatitis easier and more accurate, with patch testing and artificial intelligence.^(67,68)

5. 3D INTEGRATION

Artificial intelligence is changing the way we work with 3D integration. This is because AI can be used to improve the process of stacking and linking integrated circuits or ICs in a 3D arrangement.

There are areas where AI is very important in 3D integration. These include making designs managing heat, testing and finding faults making things work better predicting if things will be reliable and making things work faster.

AI can help make the design of 3D ICs. This is because AI can use algorithms and models to make the design of 3D ICs better which results in 3D ICs that work faster and are more connected.

Also AI can help with testing integration and finding problems. This means that people do not have to get involved much and it makes the process more accurate. Artificial intelligence is very helpful, in 3D integration. The use of Artificial Intelligence in integration is really interesting. It plays a role, in many things like coming up with ideas designing things making the design real, manufacturing, packaging and testing. This helps designers work efficiently and accurately. It is also very reliable.

Artificial Intelligence and 3D integration are really capturing the attention of people who do research and work in this field. They are learning how Artificial Intelligence can help with integration.⁽⁶⁹⁾

Regulatory aspects of microneedles

Microneedle-based drug delivery systems require comprehensive regulatory evaluation to establish their safety, quality, efficacy, and reproducibility before clinical use. Since microneedles combine characteristics of medical devices and drug delivery systems, their regulatory classification may depend on the composition, mechanism of action, intended use, and type of therapeutic agent incorporated into the system. Regulatory assessment generally includes evaluation of the microneedle material, mechanical strength, needle dimensions, drug loading, content uniformity, skin penetration, dissolution or drug release, biocompatibility, sterility, stability, and potential local or systemic toxicity. Particular attention is required for polymeric and dissolving microneedles to ensure that the materials and their degradation products are safe and that the intended dose is consistently delivered. For products containing vaccines, proteins, peptides, nucleic acids, or other biological agents, additional assessment of biological stability, potency, and immunological safety may be necessary. Manufacturing processes must also demonstrate consistency, quality control, sterility where applicable, and batch-to-batch reproducibility. A major challenge is the absence of universally standardized regulatory requirements specifically dedicated to microneedle systems, which can complicate product development and approval. Therefore, harmonized regulatory guidelines and standardized testing methods for microneedle characterization, manufacturing, safety, and clinical performance are needed to facilitate their translation from laboratory research to commercial and clinical applications.⁽⁷⁰⁾

Safety aspects of microneedles

Microneedles are considered a minimally invasive drug delivery system; however, their safety must be carefully evaluated because they penetrate the skin barrier. Microneedle application may cause temporary skin irritation, redness, swelling, itching, or mild inflammation, particularly when excessive insertion force or inappropriate needle dimensions are used. Adequate mechanical strength is essential to prevent bending or breakage of the microneedles, as fractured needles may leave fragments in the skin and cause tissue injury or inflammation.⁽⁷¹⁾

Since microneedles disrupt the skin barrier, proper sterility and manufacturing practices are necessary to minimize the risk of microbial contamination and infection. The materials used for microneedle fabrication should be biocompatible, non-toxic, and should not produce harmful degradation products. Allergic or hypersensitivity reactions to polymers, adhesives, drugs, or other formulation components should also be considered. In addition, accurate drug loading and uniform drug release are important to ensure dose consistency and prevent premature or uncontrolled drug release.⁽⁷²⁾

For dissolving microneedles containing proteins, peptides, vaccines, or other biological molecules, drug stability and biological activity must be maintained during formulation and storage. Repeated application may also result in cumulative skin irritation, inflammation, or sensitization, requiring appropriate long-term safety studies. Therefore, comprehensive evaluation of biocompatibility, mechanical strength, sterility, skin irritation, drug stability, dose accuracy, and long-term effects is essential for the safe and effective clinical application of microneedle-based drug delivery systems.^(73,74,75)

LIMITATIONS OF MICRONEEDLES

Despite their design microneedles need thorough testing for safety and biocompatibility while they are usually tolerated biodegradable parts may cause localized inflammation designing microneedles is a balancing act

between strength and drug stability. microneedles made of polymer often have low fracture stress, which can cause the tip to break during skin penetration.

Dissolving microneedles can release their payload early due to exposure to interstitial fluid especially for biologics. It is hard to keep proteins or nucleic acids stable during fabrication and storage because they degrade at temperatures above 40°C. Even though lyophilisation can keep vaccines stable for up to 6 months at 40°C it also makes production more expensive.

Microneedles have potential. Require careful design and testing to ensure their safety and effectiveness. The stability of microneedles is crucial for their success. Microneedles are being researched for their use, in delivering drugs and vaccines.⁽⁷⁶⁾

Additionally, gut permeability and solubility may naturally restrict the bioavailability of pharmaceuticals, hence limiting drug absorption.⁽⁷⁷⁾

Patients' skin problems or sensitivities may occur. However, there are relatively few cases of microbial contamination following microneedle use, and these are frequently linked to design flaws, component immunogenicity, or microneedle administration.⁽⁷⁸⁾

There are some restrictions on the use of microneedles in cancer therapy due to their site-specific approach, particularly when it comes to diagnostics. Localized drug accumulation, decreased drug penetration, restricted microneedle access to plasma tumor markers, microbial contamination, and local itching are typically the causes of allergic responses or skin inflammation.^(79,80)

Conclusion

Microneedle-based transdermal drug delivery systems have emerged as a promising and innovative approach for overcoming the limitations of conventional drug delivery routes. By temporarily disrupting the stratum corneum and creating microscopic pathways, microneedles can enhance drug permeation while minimizing pain, invasiveness, and patient discomfort. They also offer important advantages such as avoidance of first-pass metabolism, improved bioavailability, controlled and sustained drug release, and the possibility of self-administration.

The development of different microneedle types, including solid, coated, hollow, dissolving, and hydrogel-forming systems, has expanded their applications in the delivery of small molecules, macromolecules, vaccines, and biologics. Their potential has been demonstrated in several therapeutic areas, including chronic pain, diabetes, psoriasis, cancer, hormonal therapy, cardiovascular diseases, vaccination, and dermatological conditions. Recent advances in smart microneedles, glucose-responsive systems, wearable devices, personalized medicine, AI-integrated systems, and advanced manufacturing technologies such as 3D printing further demonstrate the versatility of this technology. Despite these promising advantages, several challenges remain before widespread clinical and commercial adoption can be achieved. These include limitations in drug loading, mechanical strength, stability of sensitive biological molecules, skin irritation, material toxicity, microbial contamination, manufacturing scalability, and the absence of well-established regulatory and quality standards specific to microneedle systems. Overall, microneedle technology represents a significant advancement in transdermal drug delivery and has the potential to bridge the gap between conventional injectable and non-invasive delivery systems. Continued research focusing on safe and biocompatible materials, optimized drug loading, scalable manufacturing, smart and personalized delivery, regulatory standardization, and well-designed clinical studies will be essential for

translating microneedle-based systems from laboratory research into clinically effective and commercially viable products.

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