



MICRONEEDLES AS AN EMERGING APPROACH FOR TRANSDERMAL DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW

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ABSTRACT

Transdermal drug delivery systems (TDDS) have gained considerable attention as an alternative to conventional oral and injectable routes of drug administration. Although the oral route is widely preferred for its convenience and patient acceptance, it often faces limitations, including gastrointestinal degradation, poor absorption, and first-pass metabolism. Parenteral administration can overcome some of these issues, but is associated with disadvantages, including pain, risk of infection, and the requirement of trained personnel. These challenges have spurred the development of transdermal drug delivery approaches that enable non-invasive administration through the skin.

Despite several advantages, conventional transdermal systems are significantly limited by the barrier properties of the stratum corneum, which restricts the permeation of most therapeutic molecules. Only a limited number of small, lipophilic drugs can effectively penetrate the skin using traditional patches. To overcome this limitation, microneedle technology has emerged as a promising strategy for enhancing transdermal drug delivery. Microneedles are micron-scale needle projections capable of creating temporary microchannels in the skin without causing significant pain or tissue damage.

This review discusses the structure and barrier function of the skin, mechanisms of drug permeation, and the role of microneedle technology in overcoming these barriers. Various types of microneedles, including solid, coated, dissolving, hollow, and hydrogel-forming systems, are described along with their mechanisms of action. The article also highlights applications of microneedle-based systems in insulin delivery, vaccine administration, and macromolecule transport. Furthermore, the current market developments, advantages, limitations, and prospects of microneedle-based transdermal drug delivery systems are discussed.

Index Terms - Microneedles, Transdermal drug delivery, Skin permeation, Dissolving microneedles, Vaccine delivery, Insulin delivery.

I. INTRODUCTION

Conventional drug delivery systems frequently require repeated dosing and relatively high drug concentrations to achieve the desired therapeutic effect. Prolonged administration may increase the risk of adverse effects and can negatively influence patient compliance. The oral route is the most commonly used method of drug administration because it is convenient, non-invasive, and well accepted by patients. However, oral drug delivery presents several limitations. Many drugs undergo

enzymatic degradation within the gastrointestinal tract, while others cause gastrointestinal irritation or demonstrate poor absorption. In addition, first-pass metabolism in the liver can significantly reduce the systemic bioavailability of certain drugs.

Parenteral administration can overcome some of these limitations and provide rapid therapeutic action. Nevertheless, injectable drug delivery is associated with disadvantages such as pain at the injection site, risk of infection, and the requirement for trained healthcare personnel. Furthermore, needle phobia is frequently observed in both paediatric and adult populations, which may reduce patient acceptance and adherence to therapy. These drawbacks have led researchers to explore alternative drug delivery approaches, including transdermal drug delivery systems (TDDS)[1].

Transdermal drug delivery has emerged as a promising alternative to oral and injectable routes. Historically, therapeutic substances have been applied to the skin for medicinal purposes, and with technological advancements, several transdermal delivery systems have been developed. The first transdermal patch approved for systemic drug delivery was the scopolamine patch in 1979 for the treatment of motion sickness. Later, nicotine patches became widely used and significantly increased the popularity of transdermal drug delivery technology. Currently, transdermal patches are utilised for drugs such as oestradiol, fentanyl, lidocaine, and testosterone. These systems provide several advantages, including avoidance of hepatic first-pass metabolism, sustained drug release, non-invasive administration, and improved patient compliance. Despite these advantages, only a limited number of drugs can be delivered effectively through the skin due to its strong barrier properties, particularly the outermost layer, the stratum corneum[2].

The skin acts as the body's first line of defence against external toxins, pathogens, and environmental agents. The outermost layer, the stratum corneum, is approximately 10–20 μm thick and consists of dead keratinised cells embedded within a lipid matrix that forms a highly effective barrier. This barrier significantly restricts the entry of most therapeutic molecules.

To overcome the barrier properties of the skin in TDDS, several permeation enhancement techniques have been developed. Hydrophilic drugs generally diffuse through intracellular regions, whereas lipophilic drugs mainly pass through intercellular lipid pathways. Several factors, including molecular weight, polarity, solubility, and drug dose, influence the efficiency of transdermal drug delivery. Therefore, the physicochemical properties of the drug and appropriate formulation design play crucial roles in determining successful transdermal delivery.

The human skin consists of three major layers: epidermis, dermis, and subcutaneous tissue. The outermost epidermal layer, particularly the stratum corneum, acts as the principal barrier to drug penetration. As a result, only molecules with molecular weights below approximately 500 Da and moderate lipophilicity can effectively permeate through intact skin. Various techniques such as sonophoresis, ultrasound, and ionic liquid-based approaches have been explored to enhance transdermal permeation. However, many of these techniques involve complex equipment, higher cost, and limited efficiency. Consequently, the development of advanced transdermal drug delivery strategies has become essential to improve therapeutic outcomes[3,4].

Microneedle technology has emerged as a minimally invasive approach designed to overcome the skin barrier. Microneedles are microscopic needle structures typically ranging from 25 to 2000 μm in length that create temporary microchannels in the skin, allowing drug molecules to reach the epidermal and dermal layers with minimal discomfort and tissue damage. Different types of microneedles, including solid, coated, dissolving, hollow, and hydrogel-forming systems, have been developed to enable the delivery of small molecules, biologics, and vaccines. Advances in fabrication techniques and biocompatible materials have significantly expanded the potential applications of microneedle technology in modern drug delivery systems[5].

II. SKIN STRUCTURE AND BARRIER FUNCTION IN TRANSDERMAL DRUG DELIVERY

Overview of Skin Anatomy

The skin is the largest organ of the human body and covers approximately 20 square feet of surface area. It receives nearly one-third of the body's circulating blood supply and performs several important physiological functions, including protection, thermoregulation, and sensory perception (Fig. 1) [3].

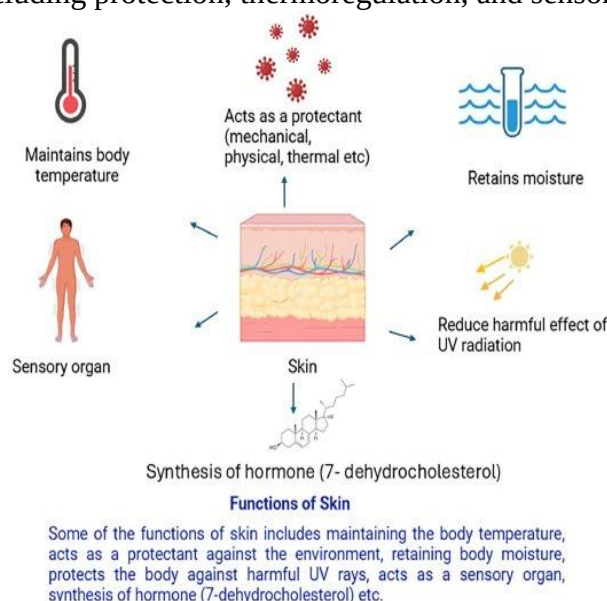


Figure 1: Structure of human skin. [3]

Structurally, the skin is composed of three primary layers: the epidermis, dermis, and subcutaneous layer (Fig. 2). The epidermis forms the outer protective barrier of the body and plays a critical role in preventing the entry of foreign substances and excessive water loss. Beneath the epidermis lies the dermis, which contains connective tissue, blood vessels, lymphatic vessels, and nerve endings that support the structural and functional integrity of the skin. The innermost layer, the subcutaneous tissue or hypodermis, primarily consists of adipose tissue that provides insulation, energy storage, and mechanical support.

In transdermal drug delivery systems (TDDS), drug molecules must penetrate the outermost layer of the epidermis, known as the stratum corneum, to reach deeper skin layers and ultimately enter systemic circulation. The stratum corneum acts as the primary barrier to drug permeation due to its highly organised lipid matrix and densely packed keratinised cells.

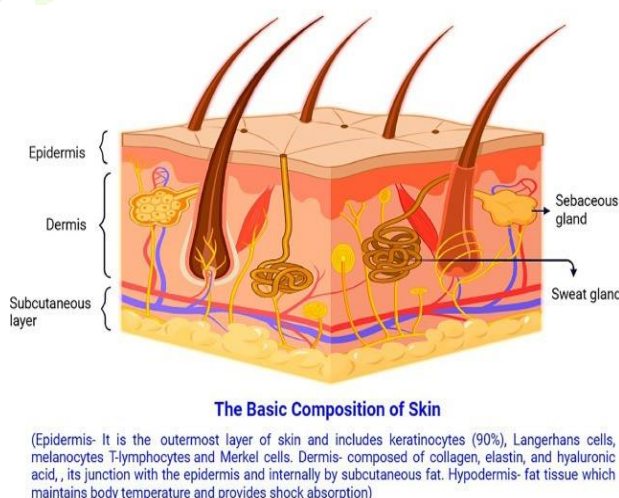


Figure 2 : Layers of the skin. [3]

Pathways of Drug Permeation Through Skin

Drug permeation through the skin occurs primarily via three pathways: transcellular, intercellular, and transappendageal (Fig. 3)[7].

In the transcellular pathway, drug molecules pass directly through the keratin-filled cells and lipid membranes of the stratum corneum. This pathway generally favours lipophilic compounds that can partition into the lipid domains of the cell membranes.

The intercellular pathway involves diffusion through the lipid matrix located between corneocytes. This route is considered the most common pathway for drug permeation and is typically utilised by hydrophilic or low-molecular-weight molecules that diffuse through the tortuous lipid channels.

The transappendageal pathway occurs through skin appendages such as hair follicles and sweat glands. Although these appendages occupy only a small fraction of the total skin surface area, they may play an important role in the transport of polar or ionizable compounds as well as larger molecules.

Drug absorption through the skin is influenced by several factors related to both skin properties and the drug's physicochemical characteristics. Factors such as skin thickness, hydration level, anatomical site of application, and age can significantly affect drug permeation. Similarly, drug properties, including molecular weight (generally less than 500 Da), lipophilicity, melting point, and ionisation state, influence diffusion across the skin barrier[6,7].

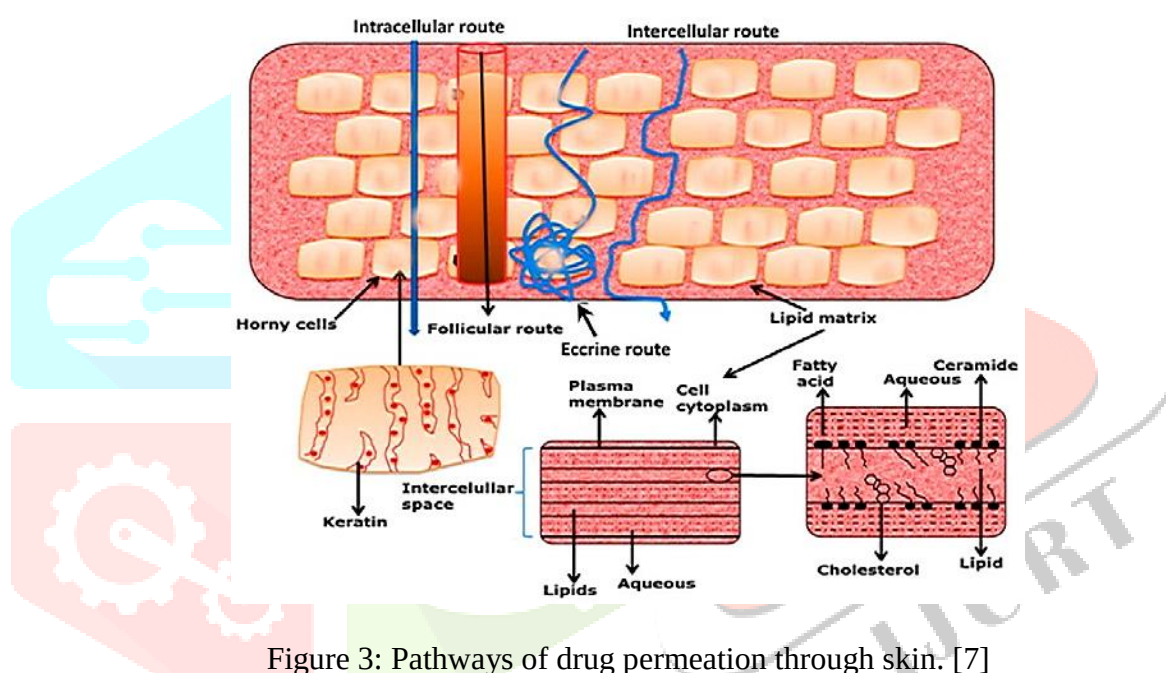


Figure 3: Pathways of drug permeation through skin. [7]

Mechanical Disruption of Skin Barrier

Various strategies have been developed to enhance transdermal drug delivery, including chemical penetration enhancers, advanced formulation approaches, and physical techniques. Among these, microneedle technology has gained considerable attention as one of the most effective methods for enhancing drug permeation across the skin barrier [6].

Microneedles typically range from 25 to 2000 μm in length and are designed to penetrate the stratum corneum without reaching deeper nerve endings, thereby minimising pain during application. Upon insertion into the skin, microneedles temporarily disrupt the stratum corneum and create microscopic channels that facilitate drug transport across the skin barrier. These microchannels significantly increase skin permeability, allowing therapeutic agents to reach the epidermal and dermal layers, where they can subsequently diffuse into systemic circulation[6].

III. COMPARISON OF TRADITIONAL TDDS VS MICRONEEDLE-ENHANCED TDDS

Table 1: Comparison of traditional TDDS and microneedle-enhanced TDDS [8]

Parameter	Traditional TDDS	Microneedle-Enhanced TDDS
Basic Mechanism	Drugs diffuse passively across the skin	Microneedles create microchannels enabling drug entry
Skin Barrier Interaction	Limited by the stratum corneum barrier	Penetrates the stratum corneum
Drug permeation efficiency	Low permeability	Permeability increases significantly
Drug types delivered	Small lipophilic molecules	Proteins, peptides, vaccines, DNA
Pain and invasiveness	Non-invasive	Minimally invasive, generally painless
Delivery control	Limited control over penetration	Controlled delivery possible
Dose limitation	Restricted due to the skin barrier	Larger doses possible
Applications	Hormones, nicotine patches	Vaccines, biologics, macromolecules
Device structure	Simple adhesive patch	Patch containing microneedle arrays
Delivery depth	Limited penetration	Drug delivered to the epidermis or dermis
Technological complexity	Simple manufacturing	Requires microfabrication

IV. MATERIALS USED IN MICRONEEDLE FABRICATION

Microneedles are fabricated from a variety of biocompatible materials depending on their mechanical strength, structural stability, and intended drug-delivery function [11].

The commonly used materials include silicon, metals, polymers, and ceramics.

Main materials used in microneedle fabrication include:

1. **Silicon:** One of the earliest materials used for microneedle fabrication because it allows precise microfabrication and accurate control of needle geometry.
2. **Metals:** Materials such as stainless steel, titanium, and nickel are commonly used due to their high mechanical strength and excellent ability to penetrate the skin.
3. **Polymers:** Biodegradable polymers such as PVA, PVP, PLA, and PLGA are widely used in dissolving and hydrogel-forming microneedles because of their good biocompatibility and ability to dissolve after drug delivery.
4. **Ceramics or glass:** These materials are sometimes used due to their high stability and structural strength.

In general, the selection of microneedle material depends on factors such as mechanical strength, biodegradability, biocompatibility, and the desired drug-release mechanism.

V. STRUCTURE AND MECHANISM OF ACTION OF MICRONEEDLES

Principle of Microneedle Technology

The stratum corneum represents the major barrier to transdermal drug delivery due to its highly organised lipid matrix and low permeability to hydrophilic and high-molecular-weight molecules. Conventional transdermal patches are therefore limited to small molecules with moderate lipophilicity. Microneedle technology was developed as a minimally invasive technique that mechanically disrupts the stratum corneum barrier without causing significant pain or bleeding. Microneedles are micron-

scale projections, generally ranging from 25 to 2000 μm in length, that are capable of penetrating the superficial layers of the skin. The penetration depth of microneedles is sufficient to breach the stratum corneum while remaining shallow enough to avoid stimulation of deeper nerve endings and blood vessels. Consequently, microneedle insertion is generally painless and does not result in significant tissue damage.

After insertion, microneedles form temporary microchannels in the skin. These channels bypass the stratum corneum barrier, allowing drug molecules to diffuse into the epidermis and dermis. Due to the skin's natural repair mechanism, the microchannels typically close within a few hours[9,10].

Mechanism of Microneedle Drug Delivery

Microneedle-mediated drug delivery enhances transdermal permeation by mechanically disrupting the skin barrier[7,10].

1. Formation of microchannels

When microneedles are applied to the skin surface, they penetrate the stratum corneum and create microscopic aqueous channels. These channels serve as direct pathways for drug molecules to reach deeper layers of the skin.

2. Reduction of skin barrier resistance

The formation of microchannels bypasses the dense lipid matrix of the stratum corneum, thereby reducing diffusional resistance and enhancing drug permeation.

3. Modes of drug transport

Drug delivery following microneedle insertion can occur through several mechanisms, including:

- Passive diffusion through the microchannels
- Pressure-driven flow in hollow microneedle systems
- Polymer dissolution in dissolving microneedle systems

4. Factors affecting drug delivery

The efficiency of microneedle-mediated drug delivery depends on several parameters, including needle length, density, insertion force, geometry, material composition, and the physicochemical properties of the drug.

5. Delivery of macromolecules

One of the major advantages of microneedle technology is its ability to deliver large biomolecules such as proteins, peptides, DNA, vaccines, and insulin, which cannot normally penetrate the intact skin barrier.

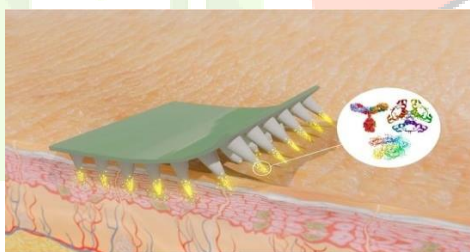


Figure 4 : Mechanism of microneedle-mediated drug delivery. [7,11]

VI. CLASSIFICATION OF MICRONEEDLES

Microneedles can be classified into several types based on their structure and mechanism of drug delivery[12].

Table 2: Classification of Microneedles Used in Transdermal Drug Delivery

Type of Microneedle	Description
Solid Microneedles	Made from metals, silicon, or polymers. Used for skin pretreatment. After insertion, they create temporary microchannels in the stratum corneum, and a drug formulation (gel, cream, patch, etc.) is applied over the treated area. This is known as the poke-and-patch technique. Easy to fabricate and enhances drug permeation, but requires two-step administration and pores close quickly due to skin healing.
Coated Microneedles	The drug is coated on the surface of the microneedles. After insertion, the coating dissolves in interstitial fluid, releasing the drug into the skin. Allows single-step delivery and is suitable for molecules like proteins, peptides, DNA, and vaccines. However, drug loading capacity is limited (≈ 1 mg).
Dissolving Microneedles	Fabricated from water-soluble sugars or biodegradable polymers such as PVP and PVA. The drug is encapsulated within the needle matrix. After insertion, the microneedles dissolve in the skin, releasing the drug directly into the tissue. Patient-friendly and leaves no sharp waste, but may have lower mechanical strength.
Hollow Microneedles	Contain a central lumen through which liquid drug formulations are delivered directly into the skin. They can be prefilled or connected to an external reservoir. Provide precise control of dose and delivery rate, but fabrication is complex, and lumen blockage may occur.
Hydrogel-Forming Microneedles	Made of cross-linked hydrocolloid polymers attached to a drug reservoir (patch, film, tablet). After insertion, they absorb interstitial fluid and swell to form a hydrogel network, allowing controlled diffusion of the drug into the skin. Needles can be removed without leaving residues, but they may exhibit limited mechanical strength.

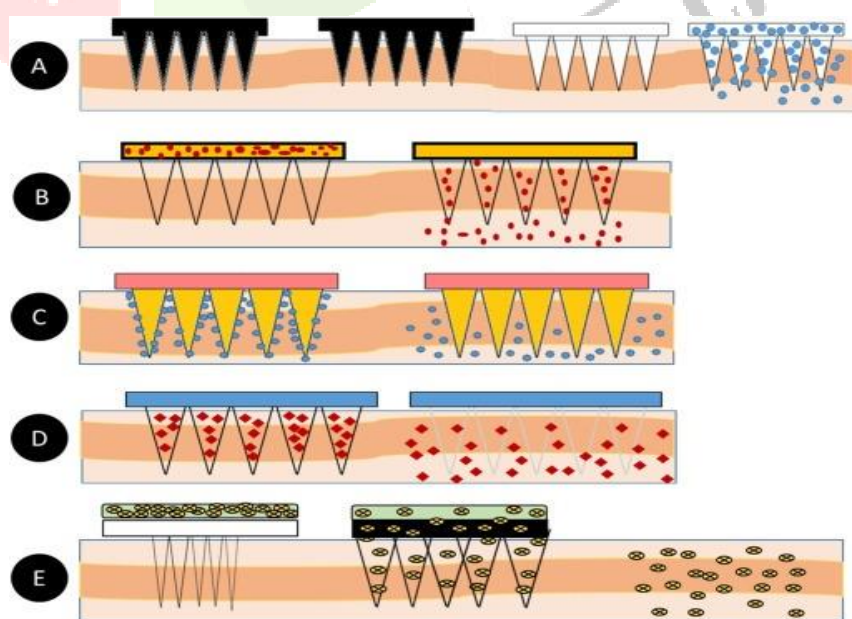


Figure 5 : Types of microneedles: (A) Solid Microneedles; (B) Hollow Microneedles; (C) Coated Microneedles; (D) Dissolving Microneedles; (E) Hydrogel-forming Microneedles. [13]

VII. APPLICATIONS OF MICRONEEDLE-BASED DRUG DELIVERY SYSTEMS

Microneedle-based drug delivery systems have gained considerable attention due to their ability to deliver a wide range of therapeutic agents through the skin in a minimally invasive manner.

1. Insulin delivery

Dissolving microneedle patches fabricated using polymers such as polyvinylpyrrolidone (PVP) provide a minimally invasive platform for insulin delivery. These systems enable rapid insulin release and improve pharmacological response while reducing the need for conventional hypodermic injections[14].

2. Macromolecule and protein delivery

Microneedle systems can efficiently deliver macromolecules such as proteins and peptides that cannot normally penetrate the skin barrier. These systems allow minimally invasive delivery while maintaining drug stability and therapeutic efficacy[14].

3. Vaccine delivery

The skin contains a high concentration of immune-active cells, making it an ideal site for vaccine administration. Microneedle patches can deposit vaccines directly into the epidermis or dermis, resulting in enhanced immune responses[14].

4. Biologic drug delivery

Microneedle patches fabricated from polymers such as gelatin and carboxymethyl cellulose have been investigated for the delivery of biologic therapeutics with improved bioavailability and controlled drug release[15].

5. Avoidance of first-pass metabolism

Transdermal drug delivery using microneedles bypasses gastrointestinal degradation and hepatic first-pass metabolism, thereby improving systemic drug availability[15].

6. Controlled and sustained drug release

Biodegradable microneedle systems enable gradual drug release within the skin, helping maintain therapeutic drug concentrations for extended periods[15].

7. HIV vaccine delivery

Microneedles fabricated using materials such as silk fibroin have been explored for HIV vaccine delivery. These systems can encapsulate stabilised HIV antigens and provide sustained antigen release to enhance immune responses[16].

8. Needle-free vaccination

Microneedle patches offer a painless and needle-free vaccination approach, which can improve patient compliance and facilitate easier administration[16].

VIII. CURRENT MARKET STATUS OF MICRONEEDLE-BASED PRODUCTS

Several microneedle-based products have reached commercial markets, while many others remain under clinical development. Selected examples are summarised in Tables 3.1 and 3.2. [17]

Table 3.1 Marketed Microneedle Products

MN Type	Product/Platform	Company	Therapeutic Area	Market Status
Hollow Microneedle (MEMS)	MicronJet™	NanoPass Technologies	Vaccines, Aesthetic treatments	Marketed (FDA 510(k) cleared)

Table 3.2 Microneedle Products Under Development

MN Type	Product Platform /	Company	Therapeutic Area	Status Outcome /
Solid / coated	High-density MN patch	Vaxxas	Influenza (H7N9)	Phase I: TGA manufacturing license secured
Dissolving	Dissolvable MN patch	Micron Biomedical	Measles–Rubella, Rotavirus vaccines	Phase 1/2 trial published (2024); Phase I rotavirus trial ongoing
Solid / coated	emxRNA™ Patch	Kindeva / Emervax	mRNA vaccines	Preclinical; clinical trials expected in 2026
Solid / coated	Qtrypta (M207)	Emergent BioSolutions (formerly Zosano Pharma)	Migraine / Infectious diseases	Development was discontinued after regulatory issues
Solid / coated	Abaloparatide-sMTS	Radius Health / Kindeva	Osteoporosis	Phase III trial failed; program discontinued

IX. ADVANTAGES OF MICRONEEDLE-BASED TRANSDERMAL DRUG DELIVERY

1. Efficient drug delivery through skin

Microneedle systems can successfully penetrate the stratum corneum and deliver therapeutic agents into deeper skin layers. Studies using fluorescently labelled ovalbumin have demonstrated that coated microneedles are capable of transferring drugs into the skin effectively after insertion, confirming efficient transdermal delivery[18].

2. Strong immune response for vaccine delivery

Microneedle patches have shown the ability to induce strong immune responses when used for transdermal vaccine delivery. In vivo studies in mice demonstrated that iontophoresis-driven microneedle patches delivering ovalbumin generated stronger immune responses compared with conventional intramuscular injection[19].

3. Stability at room temperature

Microneedle patch systems loaded with therapeutic molecules have demonstrated long-term stability at room temperature. Studies have shown that certain microneedle formulations can maintain their biological activity and delivery efficiency for extended storage periods[19].

4. Reduced pain and improved patient compliance

Dissolving microneedle systems provide a painless and patient-friendly alternative to conventional hypodermic injections. These systems are minimally invasive and can be self-administered, thereby improving patient compliance and reducing needle-related anxiety[20].

X. DISADVANTAGES OF MICRONEEDLE-BASED TRANSDERMAL DRUG DELIVERY

1. Difficulty in dose formulation

Delivering adequate doses of certain therapeutic agents using microneedle patch systems can be challenging. For example, lipid nanoparticle (LNP)-based vaccines require the incorporation of stabilizing polymers to maintain nanoparticle stability, which may limit the total amount of drug that can be loaded into the microneedle matrix[21].

2. Reduced mechanical strength without plasticizers

Microneedle formulations prepared without suitable plasticizers may exhibit brittle behaviour and reduced bending strength. This mechanical instability can affect the structural integrity of the microneedles during insertion into the skin and may compromise efficient drug delivery[21].

XI. CHALLENGES IN MICRONEEDLE-BASED DRUG DELIVERY

Despite significant progress in microneedle (MN) technology for transdermal drug delivery, several challenges still limit the large-scale translation of these systems from laboratory research to commercial application. One of the major barriers is related to manufacturing scalability and product consistency. Producing microneedle arrays with uniform quality across large batches is technically demanding. The needles must maintain precise dimensions, sharp tips, and structural integrity during fabrication, as even small variations in geometry can reduce insertion efficiency and affect drug delivery performance.

For dissolving and coated microneedles, maintaining precise control over polymer composition, coating thickness, and drug loading is essential to ensure dose uniformity and consistent drug release. Minor variations in coating thickness may lead to differences in pharmacokinetic profiles, which can compromise therapeutic outcomes. In addition, maintaining the mechanical strength of microneedles during storage and application is important to prevent needle breakage or incomplete insertion into the skin.

Another significant challenge is preserving the stability of incorporated drugs, particularly biologic molecules such as proteins, peptides, and vaccines. These therapeutic agents are sensitive to temperature, moisture, and processing conditions, which can affect their stability and biological activity within the microneedle matrix.

Manufacturing conditions also present challenges. Vaccine-loaded microneedles often require aseptic processing, which is more complex and expensive than conventional sterilisation methods. Furthermore, consistent application of microneedles requires standardised applicator systems to ensure uniform insertion force and minimize variability in drug delivery.

Overall, achieving reliable large-scale production while maintaining structural precision, mechanical robustness, and drug stability remains a major challenge for the widespread adoption of microneedle-based drug delivery systems[18].

XII. FUTURE PERSPECTIVES

Clinical studies have demonstrated that microneedles can penetrate the skin with minimal pain and without causing significant irritation. The temporary disruption of the stratum corneum typically resolves within 8–24 hours due to the skin's natural regenerative capacity. These findings highlight the potential of microneedle systems as a safe and minimally invasive approach for transdermal drug delivery.

Recent research indicates that microneedle-based systems can effectively deliver hydrophilic drugs, biologics, and vaccines that normally cannot penetrate the intact skin barrier. Intradermal vaccine delivery using microneedles has shown immune responses comparable to conventional intramuscular injections, suggesting their potential for dose-sparing vaccination strategies.

Microneedle-based insulin delivery systems have also demonstrated promising outcomes in regulating blood glucose levels with minimal discomfort, indicating their potential to replace conventional injections in certain therapeutic applications. However, the successful commercialisation of microneedle technologies will require careful regulatory evaluation, particularly for drug-coated and dissolving microneedle patches that are classified as combination products.

Overall, ongoing advances in fabrication techniques, formulation strategies, and regulatory frameworks are expected to accelerate the development and clinical translation of microneedle-based transdermal drug delivery systems for future healthcare applications[10].

XIII. CONCLUSION

Microneedle-based transdermal drug delivery systems represent an innovative and promising strategy to overcome the limitations of conventional transdermal drug delivery methods. By creating microscopic channels in the skin, microneedles facilitate the efficient delivery of a wide range of therapeutic molecules, including peptides, proteins, vaccines, and other biologics. These systems combine the advantages of transdermal patches with the efficiency of injectable drug delivery while minimising pain and improving patient compliance.

Various types of microneedles, including solid, coated, dissolving, hollow, and hydrogel-forming systems, have been developed to address different therapeutic requirements. Despite the promising potential of this technology, challenges related to large-scale manufacturing, drug stability, and regulatory considerations remain. However, ongoing research and advancements in fabrication techniques and formulation strategies continue to enhance the feasibility and clinical applicability of microneedle systems.

Overall, microneedle technology has significant potential to transform transdermal drug delivery and may play an important role in future pharmaceutical and biomedical applications.

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