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INVISIBLE YET PAINLESS: THE RISE OF MICRONEEDLES TRANSFORMING DRUG, VACCINE AND PHARMACY DELIVERY

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Abstract

Microneedle (MN) technology has emerged as a promising strategy for transdermal drug delivery by combining the advantages of hypodermic injections and conventional transdermal systems. MNs are minimally invasive, painless, and capable of enhancing the delivery of small molecules, peptides, proteins, vaccines, and biologics through the skin barrier. This review summarizes skin anatomy relevant to MN-mediated delivery, types of microneedles, fabrication techniques, evaluation parameters, clinical applications, regulatory considerations, and recent advancements in smart and responsive systems. Conventional fabrication methods such as micromolding, photolithography, and laser ablation, along with modern approaches including 3D printing and femtosecond laser micromachining, are discussed. Current challenges involving drug loading, manufacturing scalability, formulation stability, and regulatory approval are also highlighted. Future developments in nanotechnology, biodegradable polymers, biosensors, and artificial intelligence are expected to improve the clinical translation and commercialization of MN-based systems. Overall, microneedles represent a patient-friendly and efficient platform for next-generation transdermal drug delivery and personalized medicine.

Keywords: Microneedles, Transdermal Drug Delivery, Skin Anatomy, Drug Delivery Systems, Dissolving Microneedles, 3D Printing, Biosensors

1. Introduction

Transdermal drug delivery systems (TDDS) have gained significant attention due to their ability to provide controlled and sustained drug release while avoiding first-pass metabolism and improving patient compliance. However, the outermost skin layer, the stratum corneum, acts as a major barrier that restricts the permeation of most therapeutic molecules, particularly hydrophilic drugs and macromolecules [1,2].

Microneedle (MN) technology has emerged as an innovative and minimally invasive strategy to overcome this limitation. Microneedles are micron-sized needle arrays capable of penetrating the stratum corneum without reaching deep pain receptors, thereby enabling painless drug administration [3,4]. Depending on their design and material composition, MNs can deliver drugs through solid, coated, hollow, dissolving, hydrogel-forming, porous, or smart responsive systems [5].

Recent advancements in biomaterials, microfabrication, nanotechnology, and additive manufacturing have significantly improved the efficiency, safety, and versatility of MN systems [6,7]. These systems are now being investigated for vaccine delivery, insulin administration, cancer therapy, biosensing, cosmetic applications, and regenerative medicine [8–10].

This review article provides a comprehensive overview of skin anatomy relevant to transdermal delivery, types of microneedles, fabrication methods, applications, evaluation parameters, regulatory considerations, research gaps, and future perspectives.

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2. Skin Anatomy

The skin is the largest organ of the human body and serves as the first line of defense against physical, chemical, and microbial threats. It performs several essential functions, including protection, temperature regulation, sensation, immune defense, and prevention of water loss. In transversal drug delivery, especially in micro needle-based systems, understanding skin anatomy is crucial because the skin acts as both a protective barrier and a target for therapeutic intervention.

Human skin is broadly divided into three major layers: the **epidermis**, **dermis**, and **hypodermis (subcutaneous tissue)**. Each layer has distinct structural and functional characteristics that influence drug permeation and micro needle penetration.

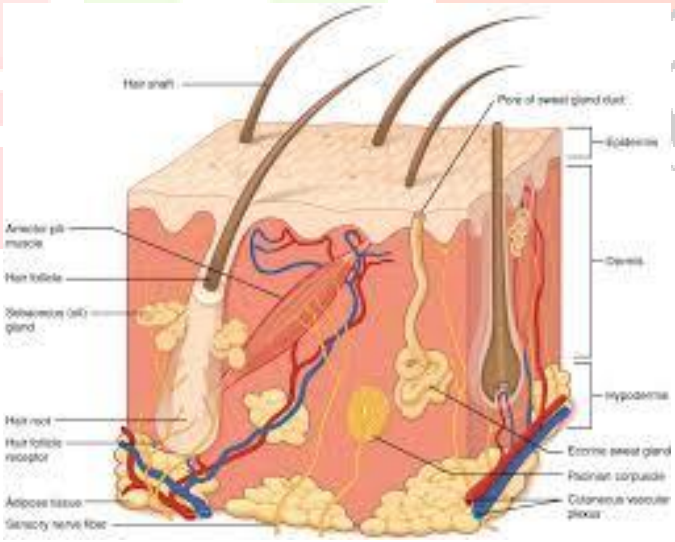

Fig No.1: Skin anatomy (19)

2.1 Epidermis

The epidermis is the outermost layer of the skin and acts as the principal protective barrier. It is composed mainly of keratinocytes arranged in multiple layers and has an average thickness of 50–150 µm depending on the body site. The epidermis is vascular, meaning it does not contain blood vessels, and nutrients are supplied through diffusion from the dermis.

The epidermis consists of five sub layers:

1. **Stratum cornea** – the outermost layer composed of dead, flattened keratinized cells embedded in a lipid matrix. It is the main barrier to transdermal drug delivery because it restricts the penetration of most drugs, especially hydrophilic and high molecular weight molecules.
2. **Stratum lucidum** – a thin translucent layer present mainly in thick skin such as the palms and soles.
3. **Stratum granulosum** – contains keratin granules and contributes to the formation of the skin barrier.
4. **Stratum spinosum** – provides structural integrity and contains immune cells such as Langerhans cells.
5. **Stratum basale (germinativum)** – the deepest epidermal layer where continuous cell division occurs to regenerate the skin.

Microneedles are specifically designed to penetrate the stratum corneum without reaching deeper pain receptors and blood vessels, allowing painless and minimally invasive drug delivery.

2.2 Dermis

The dermis lies beneath the epidermis and is a thick connective tissue layer rich in collagen, elastin fibers, blood vessels, lymphatics, nerves, hair follicles, and sweat glands. Its thickness ranges from 1–4 mm depending on the body region.

The dermis is divided into two regions:

- **Papillary dermis** – the superficial layer composed of loose connective tissue and capillaries.
- **Reticular dermis** – the deeper layer containing dense collagen fibers that provide strength and elasticity.

The dermis plays a major role in thermoregulation, wound healing, and nutrient supply to the epidermis. Since it contains a dense network of capillaries, drugs delivered into the dermis can rapidly enter systemic circulation. This makes the dermal region an ideal target for microneedle-mediated delivery of vaccines, insulin, peptides, and biologics.

In addition, the dermis contains sensory nerve endings responsible for touch, pressure, pain, and temperature sensations. Microneedles are generally short enough to avoid stimulating deep nerve endings, thereby reducing pain during administration.

2.3 Hypodermis (Subcutaneous Tissue)

The hypodermis is the innermost layer located beneath the dermis. It is composed mainly of adipose tissue and loose connective tissue. This layer provides insulation, cushioning, and energy storage while connecting the skin to underlying muscles and bones.

The hypodermis contains larger blood vessels and nerves and plays a role in maintaining body temperature. Conventional hypodermic injections typically deliver drugs into this layer. However, unlike traditional injections, microneedles generally do not penetrate deeply into the hypodermis, which helps avoid pain and tissue damage.

2.4 Skin as a Barrier to Drug Delivery

The skin is highly effective in preventing the entry of foreign substances. Among all skin layers, the stratum cornea is considered the primary barrier for drug permeation. Only drugs with low molecular weight, moderate lipophilicity, and adequate solubility can passively diffuse through intact skin.

This barrier function limits the effectiveness of traditional transdermal patches and topical formulations. Micro needle technology overcomes this limitation by creating microscopic pathways across the stratum corneum, allowing efficient delivery of hydrophilic drugs, macromolecules, vaccines, proteins, and nanoparticles without causing significant pain or bleeding.

2.5 Relevance of Skin Anatomy in Microneedle Technology

Knowledge of skin anatomy is essential for the successful design of microneedle systems. The length, shape, geometry, and material of microneedles are carefully optimized to penetrate the epidermis and upper dermis while avoiding deeper tissues. This ensures effective drug delivery with minimal discomfort and reduced risk of infection.

Different types of micro needles interact with the skin in unique ways:

Sr.No.	**Material Used**	**Types of Micro needles**	**Fabrication Principle**	**Characterization**
1	Coated Micro needles	Dip-coating, spray coating, inkjet printing, electrochemical deposition, layer-by-layer assembly	SEM, FTIR, XPS, UV–Vis Spectroscopy, AFM for coating uniformity, DSC for drug stability	Rapid surface drug release, potential for dual drug layers, antimicrobial or sensing coating
2	Metals (Stainless Steel, Titanium), Silicon, Polymer Composite Coatings, MOF-Based Films	Coated Microneedles	Dip-coating, spray coating, inkjet printing, electrochemical deposition, layer-by-layer assembly	SEM, FTIR, XPS, UV–Vis Spectroscopy, AFM for coating uniformity, DSC for drug stability
3	Silicon, Glass, Stainless Steel, Bioactive Glass Composites	Hollow Microneedles	Micro-drilling, MEMS lithography, 3D micro-printing, femtosecond laser ablation, LIGA process	SEM, Micro-CT for lumen verification, Pressure Flow Testing, Mechanical Compression Testing, XRD
4.	Biodegradable Polymers (PVP, PVA, CMC, Hyaluronic Acid)	Dissolving Microneedles	Solvent casting, centrifugal lithography, micromolding, 3D bioprinting	SEM, FTIR, DSC, TGA, Confocal Microscopy, XRD for polymer phase analysis
5	Cross-linked Polymers (PHEMA, PEGDA)	Hydrogel-Forming Microneedles	Photopolymerization, UV curing, mold casting, digital light processing	SEM, FTIR, Rheometry, Swelling Ratio Analysis, DSC, DMA, AFM for surface topology
6	Silicon, Alumina, Titanium,	Porous Microneedles	Sintering, phase separation, particulate leaching, gas foaming,	SEM for pore structure, BET Surface Area

	Stainless Steel, PLGA, PCL, Chitosan, Ceramic-Polymer Composites		freeze casting, electrochemical anodization, 3D micro-extrusion printing	Analysis, Micro-CT, EDS Mapping, XRD, FTIR, Compression and Fracture Force Testing
7	MOFs, Graphene Oxide, Thermo- and pH-Responsive Hydrogels	Smart / Responsive Microneedles	Hybrid 3D printing, microelectromechanical integration, stimuli-responsive polymer synthesis, digital light lithography	SEM, AFM, Electrochemical Impedance Spectroscopy (EIS), Cyclic Voltammetry (CV), Thermal Imaging

- **Solid micro needles** create micro channels for enhanced permeation.
- **Coated micro needles** release drugs directly into the epidermis or dermis.
- **Dissolving micro needles** biodegrade within the skin after drug release.
- **Hollow micro needles** inject liquid formulations into the dermal layer.
- **Hydro gel micro needles** absorb interstitial fluid and provide controlled drug release.

Thus, skin anatomy forms the foundation for understanding the mechanism, effectiveness, and safety of micro needle-based drug delivery systems.

3. Fabrication Techniques of Micro needles

Micro needle (MN) fabrication techniques have evolved significantly over the past few decades, enabling the production of precise, biocompatible, and mechanically strong micro needles for transdermal drug delivery. These fabrication methods are generally classified into conventional and modern techniques. The selection of a suitable fabrication method depends on factors such as microneedle type, material used, drug stability, mechanical strength, scalability, and cost-effectiveness.

3.1 Conventional Fabrication Techniques

Early micro needle fabrication methods were mainly adapted from micro electro mechanical systems (MEMS) and semiconductor industries. These techniques provided excellent precision and structural strength but often required expensive equipment and complex processing conditions.

3.1.1 Micromolding

Micro molding is one of the most widely used techniques for fabricating polymeric micro needles. In this process, a master mold containing micro needle cavities is first prepared, commonly using silicon or metal templates. Flexible molds made from polydimethylsiloxane (PDMS) are then cast from the master structure. Drug-loaded polymer solutions such as PVA, PVP, PLA, PEG, or CMC are poured into the mold cavities and subjected to vacuum or centrifugation to ensure complete filling. After drying or curing, the formed micro needle array is removed from the mold.

This method is especially suitable for dissolving and biodegradable micro needles because drugs can be directly incorporated into the polymer matrix. Micro molding is inexpensive, reproducible, and scalable for industrial production. However, issues such as shrinkage, incomplete cavity filling, and deformation during drying may affect needle sharpness and uniformity.

3.1.2 Photolithography and Etching

Photolithography and etching are MEMS-based techniques widely used for fabricating silicon micro needles. In this method, a silicon wafer is coated with a photosensitive material and exposed to UV light through a patterned mask. The exposed regions are then selectively etched using wet or dry etching processes to create sharp micro needle structures.

These methods provide highly precise geometries and extremely sharp tips with excellent mechanical strength. Hollow micro needles can also be fabricated using this approach. However, the process requires sophisticated clean room facilities, expensive equipment, and harsh chemicals, making large-scale production costly and limiting drug incorporation during fabrication.

3.1.3 Laser Ablation and Laser Cutting

Laser-based fabrication methods use high-energy laser beams to shape micro needles from metals, polymers, or silicon materials. In laser ablation, material is gradually removed layer by layer to create the desired micro needle geometry, while laser cutting slices needle patterns directly from thin sheets or foils.

These techniques offer flexibility, rapid prototyping, and precise control over micro needle dimensions. Laser fabrication is particularly useful for hollow micro needles and metallic arrays. However, thermal damage, surface roughness, and the need for post-processing such as polishing or etching remain major limitations.

3.1.4 Drawing Lithography

Drawing lithography involves heating a polymer above its softening temperature and mechanically pulling it into tapered micro needle shapes. This technique is simple, low-cost, and suitable for fabricating biodegradable polymer micro needles.

Although drawing lithography produces smooth and sharp structures, achieving consistent size and uniformity across large arrays is difficult. Therefore, it is more commonly used in research laboratories rather than commercial manufacturing.

3.2 Modern Micro needle Fabrication Techniques

Recent advances in material science, digital manufacturing, and nanotechnology have led to the development of modern micro needle fabrication methods. These techniques improve precision, scalability, multifunctionality, and drug-loading efficiency.

3.2.1 3D Printing (Additive Manufacturing)

3D printing has become one of the most promising modern fabrication methods for micro needles. In this technique, micro needles are fabricated layer by layer from computer-aided design (CAD) models using materials such as photopolymers, hydro gels, or biodegradable polymers.

Different 3D printing technologies, including stereo lithography (SLA), fused deposition modeling (FDM), and two-photon polymerization, are used to produce customized micro needle arrays with controlled dimensions and geometries. Drug molecules can also be incorporated directly into the printing material.

The major advantages of 3D printing include rapid prototyping, personalized designs, minimal material wastage, and flexibility in fabrication. However, limitations include slower production rates, high equipment costs, and the requirement for post-processing to ensure sterility and mechanical stability.

3.2.2 Femtosecond Laser Micromachining

Femtosecond laser technology uses ultrafast laser pulses to fabricate micro needles with extremely high precision. Because the laser pulses are very short, thermal damage to materials is minimized, resulting in smooth surfaces and ultra-sharp tips.

This method is particularly suitable for fabricating hollow micro needles and biosensor-integrated devices. Despite its excellent accuracy, femtosecond laser machining is expensive and mainly restricted to advanced research applications.

3.2.3 Hot-Melt Extrusion and Injection Molding

Hot-melt extrusion and injection molding are widely used for large-scale industrial production of microneedles. In these methods, thermoplastic polymers are melted and forced into molds to form microneedle arrays.

These techniques provide rapid production, high reproducibility, and compatibility with existing pharmaceutical manufacturing systems. They are highly suitable for mass production of dissolving and polymeric micro needles. However, exposure to high temperatures may degrade heat-sensitive drugs, proteins, and vaccines.

3.2.4 Atomization Spraying and Coating Techniques

Atomization spraying is mainly used for coating pre-fabricated micro needles with drug formulations. A fine mist of drug-polymer solution is sprayed uniformly onto the micro needle surface using ultrasonic or pneumatic systems.

This method allows accurate drug loading, rapid coating, and scalable production. Coated micro needles fabricated by this technique are widely investigated for vaccine and insulin delivery. Challenges include nozzle clogging, coating variability, and sensitivity to environmental humidity.

Material used Types of micro needles Fabrication principle Characterize action Advantage Disadvantage Application on

6. Pre-Clinical Studies

Microneedles (MNs) have emerged as a promising alternative to conventional injections for drug delivery due to their painless, minimally invasive, and patient-friendly nature. Pre-clinical and clinical studies have demonstrated their effectiveness in various therapeutic applications.

6.1 General Clinical Findings

A systematic review including randomized and controlled clinical trials reported that microneedles showed favorable safety and therapeutic outcomes. Most studies focused on dermatological applications, vaccine delivery, osteoporosis treatment, and insulin administration. Side effects were generally mild, such as slight redness or irritation, indicating good tolerability and safety.

6.2 Microneedles in Diabetes Management

Microneedles are being widely explored for insulin delivery in diabetes mellitus. Unlike conventional insulin injections, MNs provide painless transdermal administration with improved patient compliance. Studies indicate that MN-based insulin delivery systems can effectively control blood glucose levels while reducing discomfort associated with repeated injections.

6.3 Cell-Based Therapies

Microneedle patches have shown potential in delivering therapeutic cells for tissue regeneration, cancer therapy, immune monitoring, and targeted treatment. Their minimally invasive nature improves localized delivery and enhances therapeutic effectiveness while reducing tissue damage.

6.4 Cancer Therapy Applications

Microneedles are increasingly used for localized cancer treatment. Drug-loaded biodegradable MN patches can deliver chemotherapeutic agents directly to tumors, reducing systemic toxicity and improving drug retention at the target site. MNs have also been investigated for cancer immunotherapy and controlled release of immune checkpoint inhibitors.

7. Evaluation Parameters of Microneedles

Evaluation of microneedles is essential to ensure their effectiveness, safety, and quality. Important parameters include mechanical strength, insertion efficiency, drug permeation, dissolution behavior, biocompatibility, and manufacturing consistency.

7.1 Mechanical Strength

Mechanical strength determines the ability of microneedles to penetrate skin without bending or breaking. Testing is usually performed using texture analyzers or universal testing machines. Optimized microneedles typically show fracture forces greater than 0.1 N per needle.

7.2 Insertion Efficiency

Insertion efficiency measures how effectively microneedles penetrate the stratum corneum and reach viable skin layers. Optical microscopy, OCT imaging, and dye staining methods are commonly used. Efficient MN systems generally achieve 80–90% penetration efficiency.

7.3 Drug Permeation Studies

Drug permeation studies evaluate the amount of drug delivered across the skin using Franz diffusion cells. These studies help determine drug flux, cumulative permeation, and bioavailability. MN systems often show significantly improved drug permeation compared to conventional topical delivery.

7.4 Dissolution Rate

For dissolving microneedles, dissolution rate indicates how rapidly the polymer matrix dissolves after insertion. Most dissolving MNs completely dissolve within 5–15 minutes, ensuring rapid drug release.

7.5 Safety and Biocompatibility

Biocompatibility studies assess cytotoxicity, skin irritation, and tissue compatibility using cell culture and animal skin models. Polymeric microneedles generally show high cell viability and minimal irritation.

7.6 Manufacturing Uniformity

Uniformity studies ensure consistency in needle dimensions, tip sharpness, and drug loading across batches. SEM and optical profilometry are commonly used for dimensional analysis.

8. Acceptability of Microneedles

Microneedles have gained high acceptance among patients and healthcare professionals because they are painless, easy to use, and suitable for self-administration. They reduce needle fear, improve patient compliance, and minimize the need for trained healthcare workers.

Children and adults generally prefer MN patches over traditional injections. Healthcare providers also support microneedles because they reduce needlestick injuries, biomedical waste, and administration costs. Biodegradable microneedles further contribute to environmentally sustainable healthcare.

9. Regulatory and Safety Considerations

Regulatory approval and safety assessment are essential for successful clinical use of microneedles.

9.1 Regulatory Considerations

United States (FDA)

Microneedles are regulated as medical devices or drug-device combinations depending on their application. Preclinical testing, clinical trials, and compliance with FDA quality regulations are required.

European Union (EMA)

In Europe, microneedles must comply with Medical Device Regulation (MDR 2017/745), including CE marking, biocompatibility testing, and post-market surveillance.

Other Regions

Countries such as Japan, China, and India regulate microneedles through their national medical device authorities, focusing on safety, sterility, and effectiveness.

9.2 Safety Considerations

Important safety factors include:

- Use of biocompatible and non-toxic materials
- Proper sterilization to prevent infection
- Controlled needle length to avoid pain and bleeding
- Minimization of skin irritation and allergic reactions
- Safe disposal of non-biodegradable microneedles

Studies have shown that MNs cause significantly less pain and tissue damage compared to conventional hypodermic needles.

10. Regulatory Considerations for Microneedles in India

In India, microneedles are regulated under the **Drugs and Cosmetics Act, 1940** and **Medical Devices Rules, 2017** by the Central Drugs Standard Control Organization.

10.1 Classification

Microneedles are generally classified as Class C or Class D medical devices depending on their intended use and risk level.

10.2 Approval Process

Manufacturers must obtain licenses, comply with ISO 13485 standards, and provide technical and clinical data. Drug-device combination products require approval from CDSCO and the Drug Controller General of India (DCGI).

10.3 Manufacturing and Import

Imported and locally manufactured MNs must follow Good Manufacturing Practices (GMP), labeling requirements, and safety regulations.

10.4 Post-Market Surveillance

Manufacturers are required to report adverse events through the Materiovigilance Programme of India (MvPI) to ensure continuous monitoring of product safety.

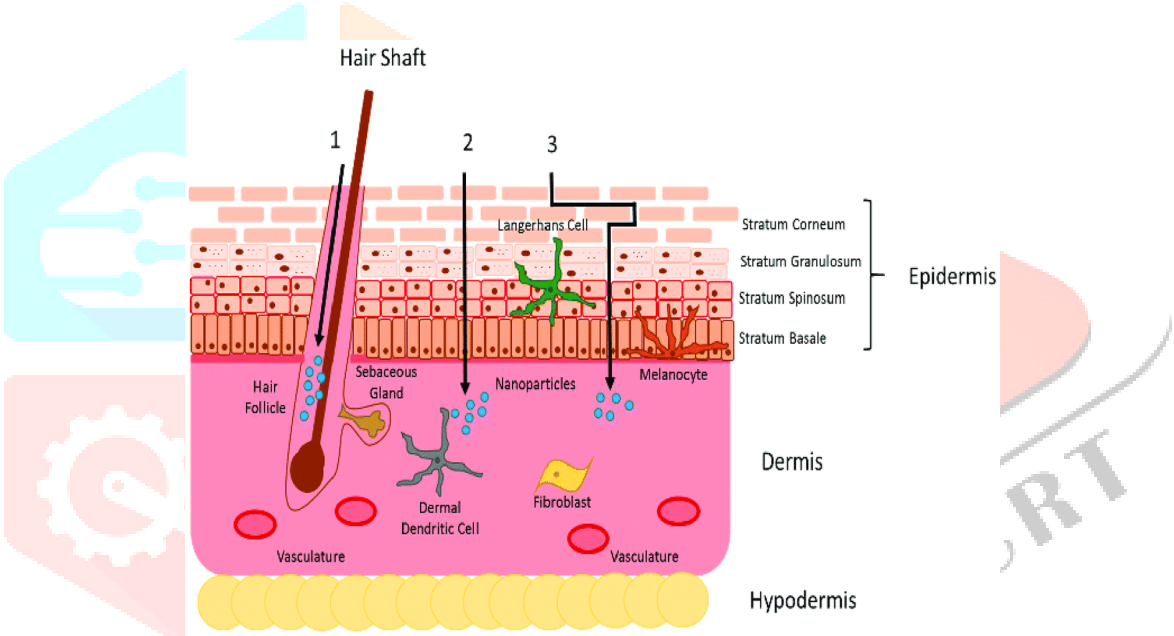

Fig.2 Overview of Transdermal Drug Delivery Systems:

11. Comparison of Transdermal Drug Delivery Approaches

Transdermal drug delivery systems include topical creams, hypodermic needles, microneedle patches, and transdermal patches, each differing in penetration depth, drug delivery mechanism, and therapeutic application.

Topical creams are conventional formulations applied directly onto the skin surface for localized treatment of skin disorders, inflammation, and cosmetic conditions. They are non-invasive and easy to use but provide limited systemic absorption due to the barrier function of the stratum corneum.

Hypodermic needles deliver drugs directly into dermal or subcutaneous tissues, ensuring rapid systemic absorption and accurate dosing. Although highly effective for vaccines, insulin, and biologics, they are invasive, painful, and associated with needle phobia and infection risks.

Microneedle patches represent a minimally invasive alternative that creates temporary microchannels across the stratum corneum without stimulating pain receptors. They enable efficient delivery of small molecules, vaccines, peptides, and biologics while improving patient compliance and reducing needlestick injuries. However, challenges such as limited drug loading and manufacturing complexity still exist.

Transdermal patches deliver drugs through passive diffusion across intact skin, providing sustained and controlled drug release. They are painless and convenient for chronic therapy but are mainly limited to lipophilic, low-molecular-weight drugs.

Overall, micro needles and transdermal patches offer advanced, patient-friendly approaches for controlled and efficient drug delivery

12. Research Gaps and Major Challenges

Despite significant advancements, several challenges limit the large-scale clinical application of micro needle technology.

One major research gap is the incomplete understanding of drug release and skin absorption mechanisms, especially for proteins, peptides, and large biomolecules. Variations in skin type and physiology can affect drug bioavailability and therapeutic outcomes.

Stability and storage remain important concerns because many drug-loaded microneedles are sensitive to temperature and humidity, reducing shelf life and potency. Manufacturing and scalability also present challenges, including maintaining consistent needle geometry, drug loading, and mechanical strength during large-scale production.

Safety issues such as skin irritation, incomplete needle dissolution, infection risk, and accidental breakage have also been reported in some studies. In addition, limited drug-loading capacity and formulation instability restrict the delivery of high-dose medications.

Economic factors further affect widespread adoption, particularly in low-resource settings where advanced fabrication and sterilization methods increase production costs.

Future developments in 3D printing, nanotechnology, biodegradable materials, biosensors, and AI-based design are expected to improve microneedle performance, scalability, and personalization. These advancements may accelerate the clinical translation of smart microneedle systems for personalized medicine and controlled drug delivery.

13. Future scope:

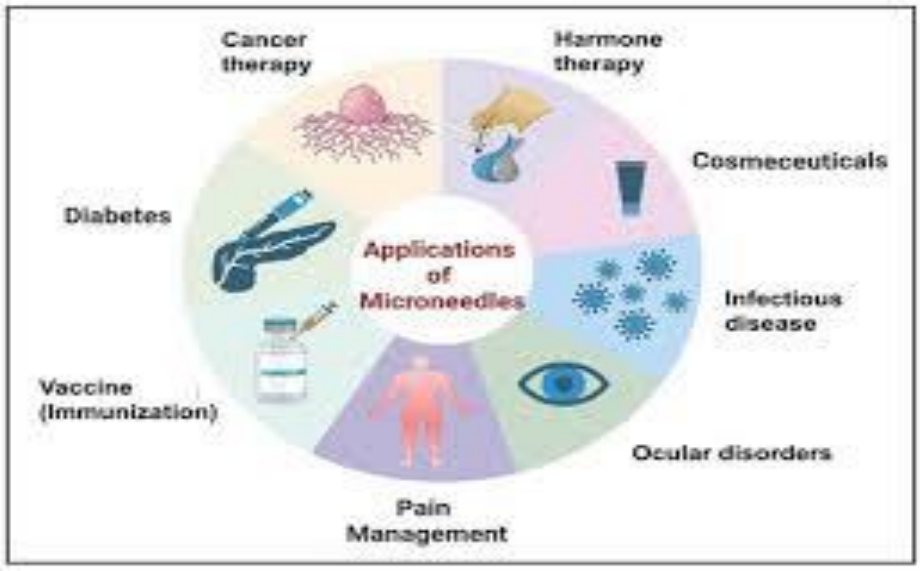

Fig No.3: Future scope of micro needles

14. Conclusion: Fig No.3: Future scope of microneedles Microneedle (MN) technology has rapidly evolved into one of the most promising tools in modern drug delivery and diagnostics. By combining the precision of injections with the comfort of transdermal systems, microneedles offer a minimally invasive and patient-friendly route for effective therapy. Their ability to cross the outer skin barrier without pain or damage has opened new possibilities for vaccines, biologics, peptides, and even cell-based treatments. Recent advances in fabrication—such as 3D printing, biopolymer casting, and smart material integration—have greatly improved control over microneedle design, drug release, and mechanical strength. Preclinical and early clinical investigations have shown encouraging outcomes, confirming both the safety and efficiency of this approach. In addition, microneedles are being developed for novel applications such as biosensing, wound repair, and controlled regenerative therapy, showing how flexible and adaptable this platform can be. 21 In the coming years, progress in biomaterials, nanotechnology, and micro engineering will likely enhance the commercial and clinical translation of microneedle-based systems. Future research should focus on large-scale, cost-effective production, quality assurance, and long-term clinical validation. As healthcare continues to move toward personalized, sustainable, and patient-centred care, microneedles are expected to become an integral part of next-generation medical practice— delivering therapy with precision, safety, and comfort.

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