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Microneedle Technology for Enhanced Transdermal Drug Delivery: A Comprehensive Review

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Abstract:

Microneedle patches represent a transformative evolution in transdermal drug delivery, offering a minimally invasive, pain-free alternative to traditional injections and improving on the limitations of conventional transdermal systems. By deploying arrays of micron-scale needles that pierce the outermost skin barrier (the stratum corneum), these devices open transient micro channels that permit efficient transport of small molecules, peptides, proteins, vaccines and other biologics directly into viable epidermal or dermal tissue. Various formats solid microneedles that pre-treat the skin, coated microneedles bearing drug on their surface, dissolving microneedles composed of drug-matrix materials, hollow microneedles that facilitate fluid flow, and hydrogel-forming microneedles that swell and enable sustained release have been developed to tailor insertion depth, drug loading and release kinetics. Their benefits include enhanced bioavailability, elimination of first-pass hepatic metabolism, improved patient compliance (especially in needle-phobic populations), and simplified administration potentially outside clinical settings. They have wide applications such as vaccine delivery, hormone therapy, pain management, localized cancer therapy particularly in melanoma & breast cancer, dermatological disorder treatment and wound healing. Nonetheless, translation to widespread clinical use remains challenged by manufacturing scalability, sterilization and storage stability, accurate dosing across skin types, regulatory approval pathways and cost-effectiveness. Future directions point toward "smart" microneedle patches integrated with sensors, responsive or triggered release, personalized dosing and combination therapies, enabling real-time monitoring of therapy alongside delivery. As such, microneedle transdermal patches stand poised to disrupt traditional delivery methods and open new frontiers in drug administration and patient-centric care.

Keywords **—** Microneedle, Stratum corneum, Needle-phobic, Drug-matrix, Sustained release, Melanoma.

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I. INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) are a category of controlled drug delivery systems designed to transport drugs through the skin at a predetermined and sustained rate. Transdermal delivery offers a significant advantage over oral and injectable methods due to its ability to prevent first pass metabolism and increase patient compliance, respectively [1].

Hypodermic needles, topical lotions, and transdermal patches are some of the common techniques utilized to deliver medications through the skin. Hypodermic needles are often less accepted due to pain and needle phobia, and topical therapies are generally poorly absorbed. On the contrary side, transdermal patches provide a practical, non-invasive and efficient way to

introduce a particular dosage of a drug into the bloodstream.

The skin serves as the primary barrier for transdermal drug delivery. In terms of structure, it is composed of three primary layers: the outermost stratum corneum, the middle epidermis, and the thickest dermis. Among these, the stratum corneum serves as a main barrier, allowing only specific molecules to efficiently pass through, usually small, lipophilic, and low molecular weight drugs [2].

To overcome above challenges, microneedle technology is introduced. Microneedle (MN) arrays are minimally invasive devices developed to bypass the stratum corneum and enhance transdermal drug delivery [3]. When microneedles are fabricated in arrays on a backing that can be applied to the skin like a bandage, the device is referred to as a microneedle. MN patches create micron sized pores in the skin, allowing efficient delivery of both small and large molecules, including hydrophilic drugs and macromolecules.

Microneedles combine the advantages of hypodermic needles and transdermal patches while overcoming their limitations.

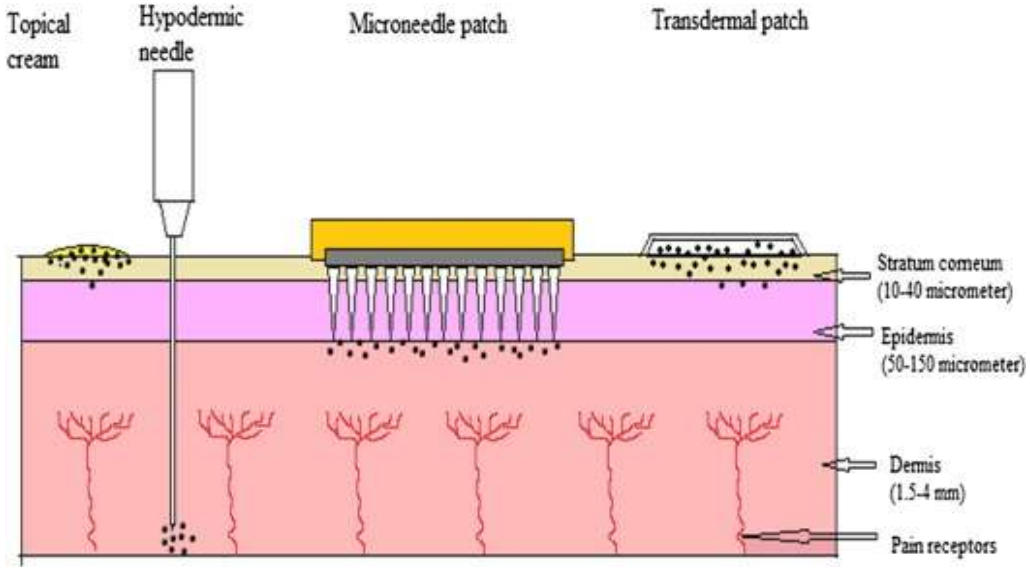


Fig. 1. Comparison of topical cream, hypodermic needle, microneedle patch and transdermal patch [2].

They are painless, easy to apply, and improve patient compliance, especially among individuals with needle phobia. As a result, MN technology has emerged as a promising platform for enhancing transdermal delivery of a wide variety of therapeutic agents [4][5].

Advantages of microneedle drug delivery technology:

1. Bypass the stratum corneum barrier
2. Enhanced drug permeation
3. Rapid onset of action
4. Possible self-administration
5. Painless drug delivery system
6. Good stability
7. Cost-effective
8. Improved patient compliance
9. Efficacy and safety comparable to approved injectable products

Historical Development and Evolution of MNs Technology:

Table No. 1: Timeline of Microneedle (MN) Technology Development

Year / Period	Milestone / Key Development	Reference
1976	The concept of microneedles for transdermal delivery was proposed (early patents, Gerstel & Place).	[6]
1990	MEMS & microfabrication advances made experimental MNs possible.	[7]
1998-1999	First experimental demonstration: Henry, McAllister, Allen & Prausnitz showed MNs increase skin permeability and are painless.	[8]
Early 2000	Hollow MNs developed for drug injection; polymer/silicon microneedles fabricated.	[9]
~2005	Dissolving/biodegradable MNs introduced (maltose, PVP, sugars).	[10]
Late 2000	Coated MNs, polymer MNs, and vaccine/DNA delivery studies expanded.	[10]
2008–2012	Rapidly dissolving polymer MNs; scalable micromolding techniques refined.	[11]
~2012	Hydrogel-forming MNs introduced for sustained release ("poke and flow").	[12]
2010	Clinical trials begin (e.g., insulin, vaccines, hollow MN devices like Micron Jet600).	[13]
Late 2010–2020	3D printing & advanced fabrication complex MN designs, smart systems.	[7]
2020–2024	Vaccine MN patches gain momentum (COVID-era), mass immunization studies expand.	[14]
2023–2025	Focus on biosensing MNs, closed loop drug delivery, regulatory & scale up challenges.	[6]

II. CLASSIFICATION OF MICRONEEDLES (MNS)

Different materials including silicon, stainless steel, sugars, and polymers have been utilized to create various types of microneedles such as solid, coated, hollow, and dissolvable forms.

Each microneedle type possesses distinct features, benefits, limitations, applications, and material compositions.

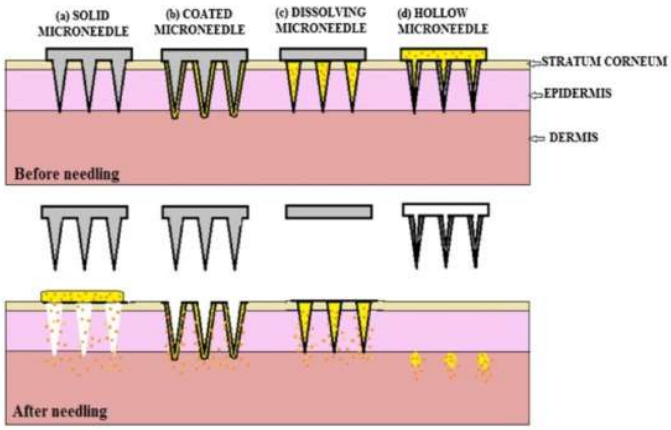


Fig. 2. Different types of microneedles (a) Solid microneedles use poke with patch approach, are used for pre-treatment of the skin; (b) Coated microneedles use a coat and poke approach, a coating of drug solution is applied on the needle surface; (c) Dissolving microneedles are made of biodegradable polymers; (d) Hollow microneedles are filled with the drug solution and deposit the drug in the dermis [2].

Microneedles can be classified based on their structure and function as follows:

1. Porous MNs

These materials contain nano or microscale pores, tiny holes visible only under a microscope, that enable drug delivery or interstitial fluid (ISF) sampling through capillary action, which allows liquids to move through small spaces. They are typically made from hard inorganic materials due to their brittleness and are used in applications such as drug delivery, biosensing and ISF extraction.

2. Solid MNs

These solid tips, which contain no embedded drug, create micropores, small holes in the skin to low concentration. This design is suitable for high dose applications but requires a longer wear time to achieve effective delivery.

3. Swellable MNs

These microneedles are formed from cross-linked hydrogel polymers that swell in interstitial fluid (ISF) but do not dissolve. They create channels that facilitate drug diffusion and are useful for both drug delivery and diagnostic fluid sampling [15][16][17].

III. MICRONEEDLE FABRICATION MATERIALS

1. Silicon

Silicon was one of the first materials used for microneedle (MN) patches due to microelectronics advances in the 1990s. It allows the precise fabrication of microstructures and MEMS in different shapes and sizes. Its elastic properties, comparable to metals, support effective transdermal drug delivery. However, their production is costly and complex, with concerns over biocompatibility [18].

2. Metals

Metals such as stainless steel and titanium are widely used in microneedle (MN) patches due to their established medical applications and smooth regulatory approval. They offer good biocompatibility and excellent mechanical strength, with elastic moduli comparable to silicon (stainless steel 180 GPa, titanium alloys 110 GPa). Stainless steel was the first metal used for MNs, typically made by pressing fine needles through support materials, while titanium is also common for biological and transdermal delivery systems. Compared to silicon, metals provide higher fracture toughness and reliable mechanical properties, making them strong candidates for MN fabrication. Ceramics are used in microneedle (MN) patches through cost effective micromachining methods. Alumina (Al_2O_3) is the most common, offering high chemical stability and corrosion resistance, but it is brittle during skin insertion. Alumina MNs are suitable for “coat and poke” patches, with porosity enabling drug storage and release. Other ceramics like calcium sulfate, calcium phosphate, and hybrids such as Grocer® provide adaptable properties for MN fabrication [18].

3. Silicon glass

Glass has also been explored for microneedle (MN) patches, as it can be rapidly fabricated in various geometries for small scale laboratory use.

It is physiologically inert, allows visualization of fluid flow, and can be made at microscale dimensions. Glass MNs have mainly been used for experimental purposes, like bypassing eyes and drug injections. Although elastic due to lower modulus values, glass is fragile and has fracture properties similar to silicon. Production is mostly manual and inefficient, making glass MN's unsuitable for commercial drug delivery applications [16].

4. Carbohydrates

Carbohydrate-based microneedles (MNs) are made by molding sugars with drugs, dissolving in the skin to release cargo. Sugars like maltose, treatise, mannitol, sorbitol, and galactose have been studied. They are inexpensive and biocompatible but face drawbacks: heat treatment limits drug loading, dissolved sugars can block pores, and storage is affected by temperature and humidity. These challenges hinder their clinical and commercial use, though polysaccharides are also explored [16].

Table No.2: Carbohydrate-Based Polymers Used in MN Patches

Carbohydrates	Active Component	Function / Characteristics	Role in Patch	Reference
Hyaluronic Acid (HA)	Glycosaminoglycan	Hydrophilic, promotes healing biocompatible	Moist environment, tissue repair	[19]
Chitosan	β-(1→4) D-glucosamine	Biodegradable, mucoadhesive, antimicrobial	Adhesion, wound healing, controlled release	[20]
Starch	Amylose + Amylopectin	Biodegradable, film-forming, hydrophilic	Patch matrix, swelling, release modulator	[21]
Carboxymethyl Cellulose (CMC)	Sodium carboxymethyl cellulose	Anionic, swelling, viscosity control	Bioadhesive matrix, drug release	[22]
Hydroxypropyl Methylcellulose (HPMC)	Hydroxypropyl methylcellulose	Film-forming, hydrophilic, mucoadhesive	Matrix, controlled release	[23]

5. Polymer

Polymers are the core of transdermal drug delivery systems (TDDS), as they significantly influence the regulation of drug release from these devices. A polymer is a large macromolecule made up of repeating structural units linked by covalent bonds, and its distinct physicochemical characteristics make it highly valuable in pharmaceutical formulations. In TDDS, polymers are utilized to minimize dosing frequency, improve therapeutic effectiveness by targeting the site of action, and provide consistent drug delivery over a prolonged period. Based on their source, polymers are generally categorized as natural, semi-synthetic, or synthetic. Among them, natural plant-derived polymers have gained wide application in drug formulations owing to

their biodegradability, safety, and biocompatibility.

These materials are employed in diverse systems such as solid monolithic matrices, implants, films, beads, microparticles, nanoparticles, inhalable and injectable preparations, and viscous liquid dosage forms. Within such formulations, polymers fulfill multiple roles, including binders, matrix builders, drug release controllers, and coating agents. Viscosity modifiers, stabilizers, disintegrants, solubilizers, emulsifiers, suspending agents, gelling agents, and bioadhesives. For effective incorporation into TDDS, polymers must demonstrate adequate stability, compatibility with active drugs and excipients, and the capacity to provide reliable and sustained drug release while ensuring safety. Hence, polymers are indispensable elements in the design and optimization of efficient transdermal delivery systems [24].

Table No.3: Various Types of Polymers Used in MN patches

Polymer	Active Component	Function / Characteristics	Role in Patch	Reference
Polyvinylpyrrolidone (PVP)	Poly(N-vinylpyrrolidone)	Water-soluble, film-forming	Fast-dissolving films, drug carrier	[25]
Polyvinyl Alcohol (PVA)	Polyvinyl alcohol	Water-soluble, flexible, strong	Film matrix, mechanical support, modulate release	[26]
Polylactic Acid (PLA)	Lactic acid polymer	Biodegradable, strong, hydrophobic	Structural layer, sustained release	[27]
Polylactic-co-glycolic Acid (PLGA)	Lactic and glycolic acid copolymer	Biodegradable, tunable degradation	Sustained release, microspheres	[28]
Polycaprolactone (PCL)	Polycaprolactone	Flexible, slow-degrading, hydrophobic	Long-term, flexible patch support	[29]

IV. FABRICATION TECHNIQUES OF MICRONEEDLE TRANSDERMAL PATCHES:

Microneedle design starts with a clear understanding of its intended purpose. Key factors include the drug type, dosage, desired pharmacokinetics and pharmacodynamics, and target delivery site. Based on these, the optimal microneedle design and materials are selected. The manufacturing technique must fit the design and material properties. For cost-effective, scalable production, simple methods like solvent casting are often used. Solvent casting is easy to implement. If high precision, reproducibility, and structural accuracy are essential, advanced techniques are better. MEMS (Micro-Electro-Mechanical Systems) enable the fabrication of metal or silicon microneedles with high accuracy. Many fabrication methods are reported, and each has a unique advantage depending on the application and design.

1. **Laser Cutting:** Uses a focused laser to precisely slice materials with high accuracy, often for microfabrication and prototyping.

2. **Laser Ablation:** Removes very fine layers from a surface using pulsed lasers, ideal for patterning or cleaning delicate substrates.
3. **Photolithography:** Employs UV light and photoresist to create intricate micro-scale patterns on silicon wafers or polymers.
4. **Etching:** Selectively dissolves material using chemicals or plasma to define microstructures after lithography.
5. **Injection Molding:** Forms complex 3D parts by injecting molten material into a pre-shaped mold cavity.
6. **Micro-Molding:** Produces miniature, high precision plastic components with detailed features using specialized molds.
7. **Micro-Stereolithography:** Builds micro-sized 3D structures by curing resin layer-by-layer with a focused laser beam.
8. **Micro-Electrochemical System (MEMS):** Integrates electrical and mechanical elements on a chip for sensing, actuation, or signal control.
9. **Continuous Liquid Interface Production (CLIP):** Enables rapid, continuous 3D printing from liquid resin using controlled light and oxygen exposure.
10. **Two Photon Polymerization:** Utilizes simultaneous absorption of two photons to polymerize material with nanoscale precision.
11. **Automized Spraying Method:** Deposits uniform coatings or films by atomizing liquid material into fine droplets.
12. **Droplet Born Air Blowing Method:** Generates ultrafine fibers by stretching polymer droplets with high speed airflow.
13. **Pulling Pipettes:** Involves heating and pulling glass capillaries to form narrow tipped microtools for lab use.
14. **Additive Manufacturing:** Creates objects layer by layer from digital designs, reducing waste and allowing design freedom.
15. **Fused Deposition Modeling (FDM):** Extrudes heated thermoplastic filament to build 3D objects layer-by- layer.
16. **Digital Light Processing (DLP):** Cures entire resin layers simultaneously using projected light patterns for fast 3D printing.
17. **Microneedle Coating Technique:** Covers microneedles with active compounds for painless drug or vaccine delivery through skin.
18. **Dip Coating Technique:** Submerges a substrate into a coating liquid and withdraws it to form Page 1 of 2 thin, even films.
19. **Gas Jet Drying Method:** Rapidly removes solvents from coatings or droplets using a focused stream of gas.

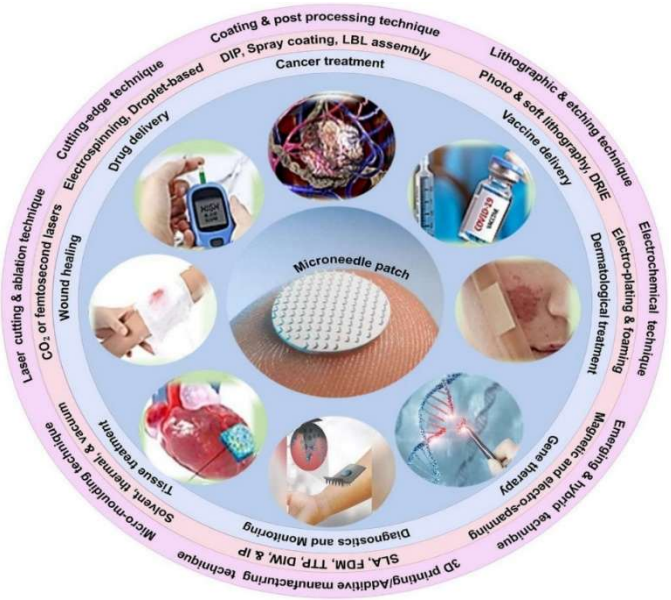
20. **Piezoelectric Inkjet Printing:** Uses piezoelectric pressure pulses to eject tiny material droplets for precise deposition or patterning [30].

Fig. 3. An illustration of different techniques of micro-needles patches preparation and their applications [30].

V. APPLICATION OF MICRONEEDLE TRANSDERMAL PATCHES:

1. Drug Delivery Using Microneedles

- First used in 1998 with solid silicon MNs.
  Types & Applications:
  Dissolvable MNs: Delivered human growth hormone and caffeine (for obesity treatment).
  Coated MNs: Delivered salmon calcitonin.
  Solid MNs: Delivered ovalbumen,



calcein, BSA, and insulin.
Enhanced Transdermal Delivery:
Ibuprofen, ketoprofen, paracetamol.
Other drugs delivered: Ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine, and glycerol.

- Tissue Penetration: Proven effective even in difficult tissues like the brain and chicken muscle.

2. Vaccine Delivery Using Microneedles

- Dissolvable MNs: Preferred for vaccine delivery due to safety, scalability, and no sharps waste.
- Effective against malaria, diphtheria, influenza, hepatitis B, HIV, and polio. Coated MNs: Used for the BCG vaccine in pigs.
  DNA vaccines (e.g., Hepatitis C, influenza antigens) are effective in mice.
- Hollow MNs: Delivered anthrax vaccine in rabbits and plague vaccine in mice. Clinical trials for influenza vaccines showed responses similar to intramuscular injection.

3. Cosmetic Applications

- Skin Treatments: Hyaluronic acid-based dissolvable MNs delivered ascorbic acid and retinyl retinoate.
- Hair Growth: Effective in treating alopecia areata.
  Facial Hair Control: Eflornithine delivery improved via solid MNs.
- Scar Treatment: Effective on acne scars, facial scars, and burn scars.
- Market Potential: Growing demand for MN patches and rollers in dermatology.
- Other Uses: Wrinkles, acne, ageing skin, and lesions.

4. Disease Diagnosis & Management

a. Diabetes:
Type 1: Glucose-responsive MNs regulate blood sugar using artificial vesicles.
Type 2: Alginate based pH-responsive MNs offer sustained release.

b. Cancer:
MNs allow controlled and precise delivery of tumor vaccines and siRNA.

Examples: MNs delivering E6/E7 DNA with RALA peptide slowed tumor growth.

c. Obesity:
Caffeine loaded dissolvable MNs promoted weight loss in obese mice by improving thermogenesis via BAT.

d. Alzheimer's Disease

Huperzine A (Hup A): Delivered through DMNPs, improving bioavailability and controlled release.

e. Migraine
Dihydroergotamine mesylate (DHE): MN based delivery offers painless, fast-acting relief with higher bioavailability than injections or nasal sprays [16][31].

VI. EVALUATION OF MICRONEEDLE PATCHES:

The evaluation of microneedle patches is a rigorous process that involves both in vitro (laboratory) and in vivo (on-body) testing to ensure their efficacy, safety, and performance. The parameters can be broadly categorized as follows:

1. Physical and Mechanical Characterization

These parameters are evaluated to ensure the patches are robust enough to withstand manufacturing, handling, and application without breaking or deforming.

a. Needle Geometry and Morphology

- Length, width, and tip radius: These dimensions are critical for ensuring the needles can penetrate the stratum corneum (the outermost layer of the skin) without causing pain by reaching deep into the dermis, where nerve endings are located.
- Aspect Ratio (length/width): A higher aspect ratio is often associated with easier skin penetration and less pain, but it can also reduce mechanical strength.
- Needle-to-needle Spacing: The distance between needles affects the insertion force and the distribution of the drug in the skin [32].

b. Mechanical Strength:

- Puncture Force: The minimum force required for the needles to successfully penetrate the skin. This is a crucial parameter for effective drug delivery [33].
- Fracture Force/Brittleness: The force at which the microneedles break. This is tested to ensure they don't fracture upon application and leave broken pieces in the skin.
- Tensile Strength and Percent Elongation: These parameters measure the patch's ability to resist breaking under tension and its flexibility, which is important for user comfort and application [34].

c. Drug Loading and Uniformity:

- Drug Content: The amount of drug loaded onto each microneedle or throughout the entire patch is measured to ensure accurate dosing.
- Content Uniformity: This verifies that the drug is evenly distributed across all microneedles in the array, preventing dose variation [35].

2. In Vitro Performance

These tests are performed in a controlled laboratory setting to predict the patch's behaviour in the human body.

a. Skin Penetration (In Vitro):

- Puncture Efficiency: This is a key test to confirm that the microneedles can create channels in the skin. It's often performed

on surrogate materials like Parafilm or on excised animal or human cadaver skin. The number of holes created and their depth are measured.

- Dye or Fluorescent Probe Test: A dye or fluorescent marker is loaded onto the microneedles and applied to a skin sample. The skin is then examined under a microscope to visualize the channels created by the needles.

b. Dissolution/Swelling Studies:

- Dissolving Microneedles: The rate at which the needles dissolve in simulated interstitial fluid is measured to predict how quickly the drug will be released in the body.
- Hydrogel-forming Microneedles: These patches are tested for their ability to swell and absorb interstitial fluid, which is crucial for their function in collecting biomarkers or releasing drugs [36].

c. Drug Release/Permeation:

- In Vitro Drug Release: The rate and total amount of drug released from the patch over time are measured using a Franz diffusion cell, which simulates drug transport through the skin.
- Bioavailability: This is a measure of the fraction of the administered drug that reaches the systemic circulation, often compared to a standard drug administration method [37].

3. In Vivo Evaluation (Clinical)

These are tests performed on living subjects (animals and humans) to confirm the safety and effectiveness of the patch in a real world setting.

a. Safety and Biocompatibility:

- Pain and Irritation: Subjects are monitored for skin redness (erythema), swelling, and pain sensation immediately after patch removal and over a period of time.

b. Skin Resealing Time:

- This is a crucial safety parameter, often measured using Transepidermal Water Loss (TEWL). It confirms that the microchannels created by the patch close quickly to prevent the entry of pathogens [38].

c. Efficacy and Pharmacokinetics/Pharmacodynamics:

- Drug Delivery Efficacy: The actual amount of drug delivered into the skin and blood circulation is measured to confirm that the patch is delivering a therapeutic dose.
- Pharmacokinetics (PK): This involves measuring the concentration of the drug in the blood over time to determine its absorption, distribution, metabolism, and excretion.
- Pharmacodynamics (PD): This measures the biological or physiological effects of the drug to confirm that it is producing the desired therapeutic outcome [39].

d. Patient Compliance:

- User friendliness: The ease of application, comfort, and patient acceptability are evaluated through user surveys and interviews. This is a significant factor for commercial success, as microneedle patches are designed to be user friendly [40].

VII. MARKETED FORMULATIONS:

Table No. 4: Various microneedle marketed formulations for different diseases/diseased conditions

Brand Name	Drug/Active Ingredient	Polymer Used	Manufacturer	Category	Duration	References
ZitSticka KILLA Kit	Salicylic Acid, Niacinamide, Oligopeptide-76	Sodium Hyaluronate (a dissolving polymer)	ZITSTICKA INC.	Cosmetic/Skincare	6+ hours (overnight recommended)	[41]
Peace Out Skincare Acne Healing Dots	Salicylic Acid, Retinyl Acetate	Hydrocolloid polymer (for the patch) with dissolving microneedles (often hyaluronic acid-based)	Peace Out Skincare	Cosmetic/Skincare	6+ hours (overnight recommended)	[42]
Acropass Trouble Cure	Salicylic Acid, Hyaluronic Acid	Hyaluronic Acid (a dissolving polymer)	RAPHAS CO., LTD.	Cosmetic/Skincare	2 hours minimum (overnight for best results)	[43]
Vaxxas HD-MAP	Vaccine antigen (e.g., Influenza vaccine)	Solid materials (e.g., polycarbonate or silicon) coated with the vaccine	Vaxxas Pty Ltd.	Therapeutic/Medical	A few minutes (patch is removed)	[44]
V-Go Disposable Insulin Delivery Device	U-100 rapid acting insulin	Soft cannula made of a polymer (e.g., Teflon)	Mannkind Corporation	Therapeutic/Medical	24 hours (a wearable, single use device)	[45]

VIII. CHALLENGES AND LIMITATIONS:

The transdermal drug delivery method comes with its own set of challenges and design hurdles. A significant issue is the sluggish absorption of

compounds through the skin. Due to the skin's very low permeability, large molecules struggle to penetrate properly. The most challenging issues stem from contradictory requirements.

The contradiction here involves:

1. The skin should prevent harmful or foreign substances from entering from the outside. To fulfill this role, its outer structure is designed to function like a closed valve, particularly against high molecular weight molecules.
2. The skin needs to allow the purposeful passage of medications from the outside so that patients can receive effective treatment. Many of these medications are high molecular weight compounds [46].

1] Safety considerations

Safety is a crucial aspect in developing transdermal drug delivery systems (TDDS). While TDDS reduce systemic side effects, they may still cause local reactions such as skin thinning, cytotoxicity, and phototoxicity. Nanostructured lipid carriers (NLCs) are considered safe but may include surfactants that cause irritation. Microneedles create small skin lesions, yet their penetration can enable bacterial entry and inflammation. Ethanol, though widely used for its efficiency, may irritate at high concentrations. Higher drug doses often increase adverse effects rather than improve efficacy. Though TDDS minimize local issues, transdermally absorbed drugs may still produce systemic effects, making dosage and frequency control vital, especially on damaged skin. Despite advancements in penetration-enhancing devices, no standardized technique ensures complete reliability. Therefore, strict regulatory oversight and quality evaluation are needed to ensure TDDS safety [47].

2] Challenges in large scale manufacturing

Scaling up TDDS production from laboratory to industry faces major hurdles, including high costs and complex processes. Industrial environments demand strict control of parameters like temperature, humidity, aseptic conditions, and contamination prevention, or product safety may be compromised. Batch-to-batch consistency is critical to ensure uniform pharmacological effects. Compared to oral or injectable systems, TDDS are structurally complex and harder to manufacture. For example, large-scale microneedle patch production remains difficult due to intricate designs that increase costs and complicate quality control. Moreover, TDDS are sensitive to environmental factors such as light, heat, and humidity, which may accelerate drug degradation. Careful regulation during production, packaging, and storage is therefore essential, while future strategies must focus on overcoming these obstacles to enable cost-effective and reliable large scale TDDS manufacturing [47].

3] Limitations in assessing bioequivalence of TDDS

Bioequivalence testing for transdermal drug delivery systems (TDDS) is difficult due to the lack of standardized regulatory guidelines from the FDA and EMA and variations in skin physiology between animals and humans. Current methods include clinical endpoint studies, regarded as the gold standard but are costly, time consuming, and ethically challenging. Pharmacodynamic studies, such as the FDA approved vasoconstriction assay, are mainly limited to corticosteroids. Alternative methods include in vivo pharmacokinetics to detect systemic absorption, tape stripping for stratum corneum drug levels (abandoned in 2002), and microdialysis, which suffers from probe placement variability and is unsuitable for slow penetrating drugs. Since no universal gold standard exists, the choice of method should depend on the drug's physicochemical properties and its site of action [47].

IX. FUTURE ASPECTS OF MICRONEEDLE TRANSDERMAL PATCHES:

1) Expansion to biologics, mRNA and complex payloads

Microneedles are moving beyond small molecules into the delivery **of** proteins, peptides, vaccines, and nucleic acids

(including mRNA/LNPs). Advances in formulation and polymer/LNP embedding are enabling thermostable, efficacious microdoses in patches, opening possibilities for painless, self administered vaccines and gene based therapies [48].

2) **Vaccination at scale driven by thermostability & self-administration**
Thermostable microneedle vaccine patches and "printing" approaches reduce or remove cold chain constraints and enable mass immunization with minimal training. This is a major near term translational opportunity for global public health deployment [48].

3) **Accessibility for low-resource & emergency use**
Thermostable, easy to store MN patches with simple applicators are especially promising for low resource settings, outbreak response, and rapid deployment where syringes/cold chain are barriers [48].

4) **Integrated therapeutics & sensing (theranostics & closed-loop systems)**
Convergence of MNs with biosensing (electrochemical/aptamer sensors, ISF sampling) promises patches that both deliver drugs and monitor biomarkers in real time, enabling personalized dosing and closed-loop therapies (e.g., diabetes, anticoagulation, therapeutic drug monitoring) [49].

5) **Smart, stimuli responsive and multi-stage release**
Future MNs will increasingly use stimuli-responsive materials (pH, enzyme, temperature, electrical) and layered/coreshell designs to achieve programmable, pulsatile or long-acting release profiles tailored to therapy [50].

6) **Advanced materials & better bio-compatible formulations**
New photopolymer resins, biodegradable/dissolvable polymers, hydrogels and composite formulations improve mechanical strength, drug loading and safe in skin dissolution, helping balance insertion performance and safe biodegradation [51].

7) **New clinical niches expanding into dermatology, metabolic disease & oncology**
Expect to see growth in dermatologic therapies (cosmetic and medical), hormone/metabolic delivery (insulin, GLP-1s), and localised oncology applications (intratumoral microdelivery), leveraging both local and systemic effects [52].

8) **User centric design & adherence**
Future designs will emphasize painless application, intuitive applicators, clear dose indicators and tailored patches for special populations (children, elderly) to drive acceptance and adherence [53].

X. CONCLUSION:

In today's world, where patients seek painless and convenient treatment options, microneedle transdermal patches have emerged as a smart and patient friendly way to deliver medicines through the skin. These tiny, minimally invasive devices gently pierce the skin's outer layer without causing pain, allowing efficient and controlled delivery of various therapeutic agents such as small molecules, peptides, proteins, and even vaccines. The versatility of microneedle systems lies in their different designs: solid, coated, dissolving, and hydrogel-based, each developed to meet specific therapeutic needs. This innovative technology improves patient comfort and compliance while offering the possibility of self administration and large-scale vaccination programs. It also minimizes the need for healthcare professionals, reduces needle-stick injuries, and lessens biohazard waste. Studies continue to highlight their effectiveness, safety, and enhanced bioavailability compared to traditional delivery routes. Nonetheless, certain challenges like large-scale production, formulation stability, and regulatory approval

still need to be addressed before full clinical adoption.

Overall, microneedle transdermal patches represent a significant step forward in modern therapeutics. Their ability to deliver drugs painlessly, efficiently, and conveniently makes them a promising alternative to oral and injectable methods. With ongoing research and innovation, microneedle technology is poised to transform drug delivery systems, making treatments more comfortable, accessible, and effective for patients worldwide.

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