IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

An Innovative Transdermal Drug Delivery

Prof. Vikas B. Wamane, Dr. Abhishek Kumar Sen and Ayasha Nisar Patel.
Assistant Professor, Principal, Student
Department of Bachelor in Pharmacy
Pratibhatai Pawar College of Pharmacy, Wadala Mahadev, Ahmednagar
patelayasha78@gmail.com
*Corresponding author- Ayasha N.Patel

Abstract: *A review of transdermal medication delivery's current state is conducted. The benefits and limitations of systemic medication delivery through the skin are described in detail. This are the conventional drug delivery. It would also cover specific technique such as specially mentioned skin absorption delivery iontophoresis, electrophoration, sonophoresis that facilitates transdermal delivery. Currently used the patches and information about the advanced delivery technology used in biomarkers. Focused on developing transdermal therapies for neurological disorders and infectious diseases. In the future, Novel transdermal drug delivery system are projected to advance significantly through the integration of cutting edge technologies like micro needle, nanotechnology, personalized 3D printed patches*

Keywords: patches, transdermal drug delivery, skin, absorb, microneedle etc

I. INTRODUCTION

The process of delivering a medication through intact skin for systemic distribution that is, the drug entering the bloodstream to carry out its therapeutic action throughout the body is known as transdermal drug delivery, or TDD. A self contained, discrete dosage form, such a transdermal patch, which is placed to the skin and intended to distribute the medication into the systemic circulation at a predefined, controlled rate, is frequently used to do this.[1] Steer clear of first pass metabolism First pass metabolism, also known as pre systemic metabolism, is a phenomenon in which the liver (hepatic metabolism) and gastrointestinal (GI) tract enzymes dramatically lower a drug's concentration before it enters the systemic circulation following oral delivery. Benefit: TDDS avoids the gastrointestinal tract and the liver's initial metabolic phase by delivering the medication straight via the skin into the systemic circulation. As a result, medications that are heavily processed by the liver have higher bioavailability and efficacy, enabling a lower daily dose to produce the intended therapeutic effect.[2] Enhanced Adherence to Treatment The degree to which a patient appropriately complies with a doctor's recommendations is known as patient compliance. TDDS provides a number of features that improve this: Non Invasiveness: Unlike injections, the delivery is typically painless, which enhances patient acceptability and comfort. Decreased Dosing Frequency: The patient just needs to apply a patch once a day or even once a week due to the sustained release profile, which is much easier to follow than taking several tablets every day. Self Administration: Patients can easily apply and remove patches on their own without the help of a professional. Simple Termination: The therapy can be stopped right away by taking off the patch in the event of drug toxicity or adverse effects[3]

Historical context Brief of TDD patches

Galen is the "Father of Pharmacy" for introducing drug compounding ("Galenic pharmacy"). His most famous formula Is Galen's Cerate (cold cream). Medicated plasters (early transdermal patches) originated in Ancient China (2000 BC). Nicotine was used in a plaster formulation during the time of Paracelsus.[4]Transdermal drug delivery (TDD) is currently being investigated as a key alternative to traditional systemic methods like oral medication and intravenous injection. While the modern application of TDD is novel, the practice of applying substances directly to the skin for

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

therapeutic purposes has been common for thousands of years. For example, evidence shows that ancient Babylonian and Egyptian medicine (circa 3000 BC) frequently utilized localized topical treatments, including salves and patches made from plants, minerals, or animal extracts[5]

Conventional TDD Systems:-

Conventional passive transdermal patches are designed to deliver medication through the skin via diffusion and fall into two main categories:

1. Reservoir Systems (Membrane Controlled):

These are multi layered patches featuring a distinct, separate drug filled compartment (the reservoir) and a Rate Controlling Membrane (RCM). The RCM acts as a flow regulator, ensuring the patch delivers the drug at a constant, predictable rate (Zero Order Kinetics). While precise, these systems carry a risk of dose dumping if the membrane is damaged.[2]

2. Matrix Systems (Diffusion Controlled):

This simpler design integrates the drug directly into a single polymer adhesive layer. There is no separate RCM, so the release rate is controlled by the drug's properties and diffusion out of the matrix, usually resulting in a gradually decreasing release rate (First Order Kinetics). They are safer (no dose dumping risk) and easier to manufacture, making them widely adopted.[2]

Benefits of conventional TDD

Benefits	Details
Avoidance of first pass metabolism	Drug by pass by the digestive tract and liver,which prevents pre systemic breakdown,thereby increasing drug bioavailability[14]
Sustained control released	Provides stable,constant drug plasma concentrations over extended periods, minimising dose fluctuations and improving therapeutic efficacy [14]
Improved patient compliance	The non invasive and convenient nature of patches or topical application enhances patient adherence to long term regimens[2]
Easy Termination of therapy	Administration can be rapidly halted by simply removing the patch,offering a safety advantage in case of adverse reaction[14]

Table: 1, Benefits of Conventional TDD

Limitations of Conventional TDD Systems:-

The core limitations of conventional TDD systems stem from the skin barrier and the restrictive properties required for passive diffusion, effectively limiting the scope of deliverable drugs.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

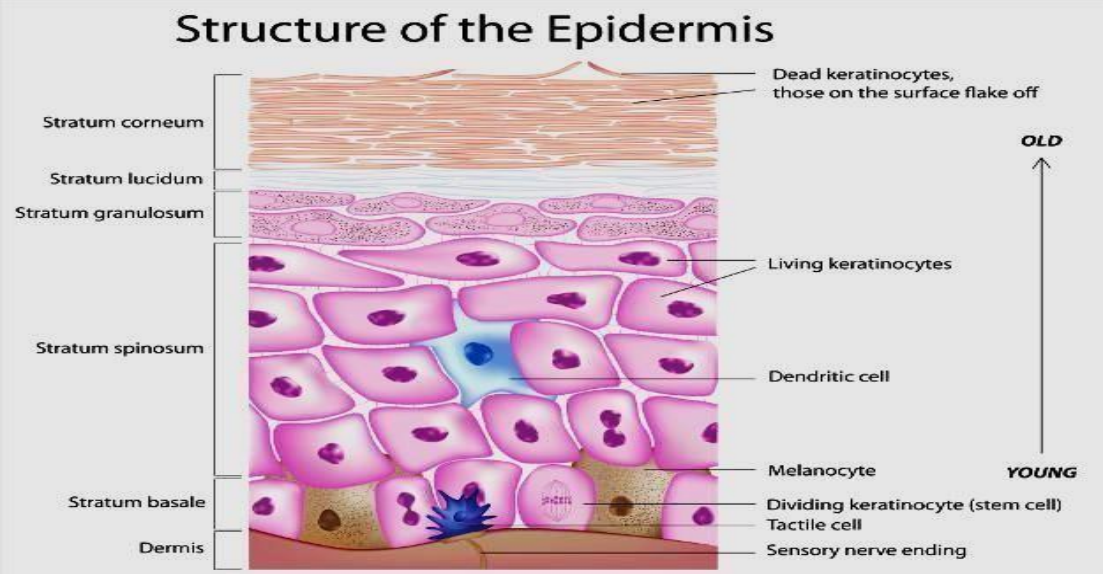

Fig.1. Structure of epidermis[6]

1. Physicochemical Constraints ("TDD Sweet Spot")

Passive TDD is only viable for drugs that fit a narrow profile known as the "TDD sweet spot." The drug must be Small, generally possessing a molecular weight less than 500 Daltons (Da). Highly potent, as the low delivery rate necessitates effective dosing at only a few milligrams per day. A specific balance of lipophilicity (fat soluble, to penetrate the outer stratum corneum) and water solubility (to reach the inner viable skin layers).This narrow range fundamentally excludes the vast majority of modern pharmaceuticals, especially large molecules like peptides, proteins, and biologics.[4]

2. The Skin Barrier Challenge The stratum corneum the skin's outermost layer is an extremely effective barrier, leading to several practical issues:

Low Permeability: The barrier severely limits the maximum drug delivery rate, making TDD impractical for medications requiring high daily doses(typically less than 1 mg per day can be delivered).[4]

Variability: Drug absorption rates can fluctuate significantly based on the application site (e.g., thin vs. thick skin) and inter subject differences (variations in individual skin thickness, hydration, and blood flow), leading to unpredictable dosing.

3. Application-Site Issues

Challenges related to the patch itself further limit effectiveness:

Skin Irritation: Continuous contact with the patch, drug, or chemical enhancers often causes local adverse reactions like contact dermatitis, redness, or itching, which frequently leads to the patient stopping the treatment.

Adhesion Failure: Poor patch adhesion due to sweating or physical activity can cause detachment, resulting in incomplete or failed drug delivery.[5]

Skin Barrier The and Conventional Enhancement Techniques:-

Anatomy and Physiology of the Skin: Focusing on the Stratum Corneum The skin, or integumentary system, is the body's largest organ, serving as a dynamic interface with the environment. From the perspective of Transdermal Drug Delivery (TDD), the skin's anatomy

and physiology are dominated by its primary function:barrier protection. The skin is broadly divided into three main layers: the epidermis,the dermis,and the hypodermis(subcutaneous fat).[7]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

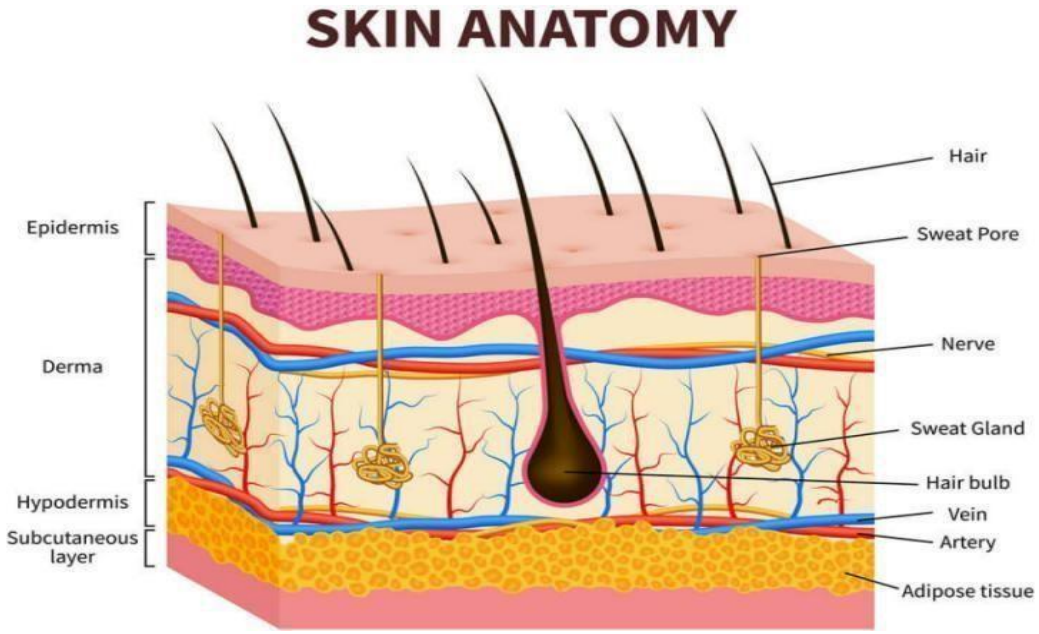

Fig.2. Anatomy of the skin[8]

1. The Epidermis and the Stratum Corneum (SC)

The epidermis is the outermost, avascular (lacking blood vessels) layer, composed primarily of keratinocytes. It is subdivided into five layers, but for TDD, the final, most superficial layer is critical: the Stratum Corneum (SC).

The Stratum Corneum: The Primary Barrier

The SC is the body's main defense against water loss, chemical penetration, and microbial invasion, making it the rate limiting barrier for almost all transdermal drug delivery[2]

Sructure: The "Brick and Mortar" Model

Bricks: The "bricks" are tightly packed, terminally differentiated cells called corneocytes.

These are dead cells composed mostly of keratin and surrounded by a tough protein envelope.[9]

Mortar: The "mortar" is the intercellular lipid matrix. This is a highly organized, complex, and semi crystalline structure composed primarily of ceramides, cholesterol, and free fatty acids [4]. This lipid domain is what gives the SC its formidable impermeability.

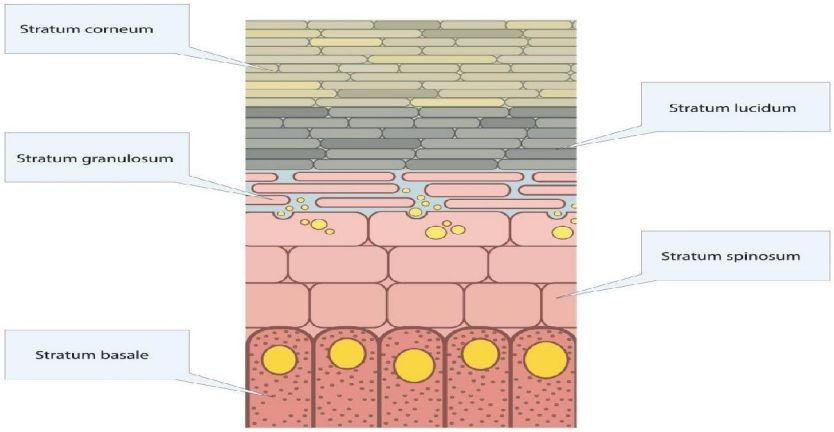

Fig.3.Physiology of epidermis structure[9]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

Physiological Effect: The high organization of the intercellular lipids dictates that drugs must be small and sufficiently lipid soluble to passively diffuse through this tortuous, oil based pathway. The resistance to penetration is immense, approximately 10^{3} to 10^{6} times higher than that of other biological membranes[5]

2. Dermis and Hypodermis (Target Layers)

Below the epidermis, the layers are highly permeable and serve as the target for systemic delivery.

The Dermis

Vascularization: The dermis is a vascularized layer, containing blood capillaries, nerve endings, and lymphatic vessels.

TDD Function: Once a drug successfully traverses the SC and the viable epidermis, it rapidly moves into the capillaries in the dermis for absorption into the systemic circulation. The dermis is therefore not a barrier but the absorption site for TDD.

The Hypodermis (Subcutaneous Layer)

Composition: Primarily consists of adipose (fat) tissue.

TDD Function: Drugs may accumulate here if they are highly lipophilic, acting as a depot before slow release into the deeper circulation.

Conventional Chemical Enhancement in TDD

Chemical Penetration Enhancers (CPEs) are compounds co formulated with drugs in conventional passive Transdermal Drug Delivery (TDD) systems to reversibly compromise the barrier function of the stratum corneum (SC), thereby increasing drug flux[4]

Mechanism of Action:-

CPEs are diverse but their mechanisms generally centre on disrupting the structural integrity of the SC, which is the rate limiting step in TDD[10]

1.**Disruption of Intercellular Lipids**: This is the most critical mechanism, focusing on the highly organized lipid matrix (ceramides,cholesterol, fatty acids) between the corneocytes.[22]

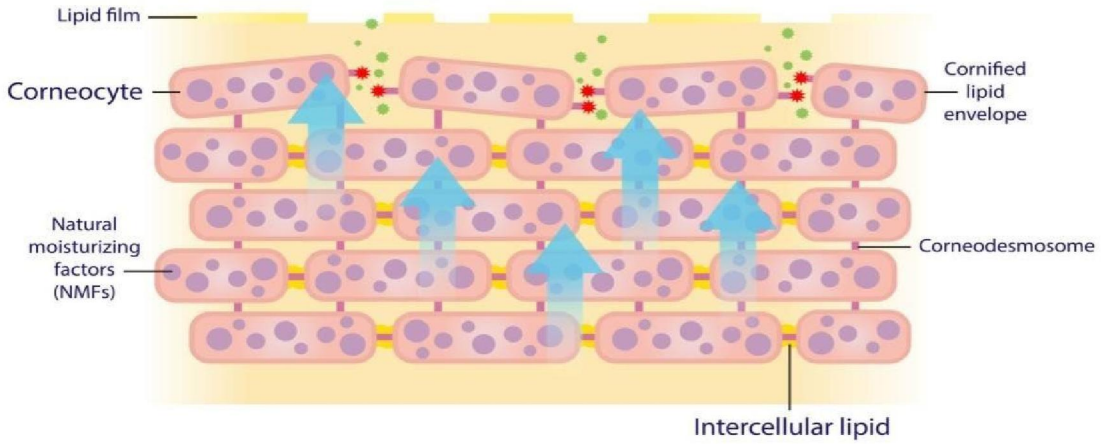

Fig. 4. The arrangement of corneocytes[11]

Mechanism: Certain surfactants and solvents (such ethanol, propylene glycol, and Azone) partition into the lipid bilayers. By "melting" the crystalline domains, this process increases the fluidity and disorder of the lipid packing structure. this makes drug diffusion easier and less convulated .

2. Interaction with Intracellular Keratin

Mechanism:

certain chemical penetration enhancers (CPEs), such as elevated concentrations of urea and potent solvents (e.g., DMSO), augment the hydration and swelling of corneocytes.[4]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

Chemical Enhancement's Limitations

The quest for "active" TDD systems has been fueled by CPEs' most serious disadvantages, which are intrinsically tied to how well they compromise the skin barrier.

1. Toxicity and Skin Irritation Problem:

Local side effects such as erythema (redness), irritation, contact dermatitis, and hypersensitivity are frequently caused by the required breakdown of the SC's barrier lipids. Trade off: There is a common efficacy toxicity trade off; more potent enhancers (e.g., Azone, oleic acid) often carry a higher risk of irreversible skin damage or toxicity, severely limiting their clinical use and leading to patient non compliance.[5]

2. Limited Effectiveness for Large Molecules Issue:

CPEs mainly improve the delivery of lipophilic small to medium sized medications that are close to the TDD "sweet spot." Since even disorderly lipid routes are too limiting for big molecules like peptides, proteins, or nucleic acids, they are typically useless for effecting therapeutic administration of these macromolecules.[2]

3. Absorption and Safety Profile Issue:

Skin penetration and systemic circulation can be achieved by effective CPEs. This raises toxicological questions about the enhancer's longterm systemic effects, particularly when patches are worn frequently or cover a lot of surface area.[12]

Conventional Physical Enhancement in TDD**:-**

Often referred to as Conventional Physical Enhancement, the following physical enhancement procedures are among the oldest and most well established “active” treatments intended to get past the stratum corneum (SC), the main skin barrier.[2,4]

Iontophoresis :-

Iontophoresis improves the transdermal distribution of ionized medication molecules by using a low level direct electric current.The movement of charged materials across a biological membrane while an electric field is present is commonly referred to as iontophoresis. A Leduc demonstrated about a century ago that this method may be used to transfer active medications across mammalian skin in vivo, thus it is by no means a novel approach.[13]

The Mechanism and Principle :-

Principle: Charged particles traveling over a gradient of electrical potential.[12]

Mechanism: A low voltage direct current is applied across the skin via two electrodes[2]

Electrorepulsion:-

The main mechanism is electrorepulsion. When a positively charged drug molecule is positioned beneath the anode, or positive electrode, it is actively rejected into the skin. On the other hand, a medication with a negative charge is repelled from the cathode.[10]

Electroosmosis:-

The movement of bulk solvent (water) caused by an electric field that can carry neutral (uncharged) drug molecules is known as electroosmosis.[4]

Electroporation:-

also called electropermeabilization, is a potent biophysical approach that uses an external
electric field to momentarily increase a cell membrane’s permeability. It is an essential technique for getting ordinarily impermeable materials into cells, such as DNA, RNA, or medications.

Principle:- The fundamental principle of electroporation relies on the effect of a pulsed electric field on the cell’s lipid bilayer membrane. The membrane acts like an electrical capacitor.[16,17]

Induced Transmembrane Potential (Delta V_m): Applying a short, high voltage electric pulse induces a significant potential difference across the membrane, which is highest at the poles of the cell facing the electrodes[17,18]

Critical Threshold: When this induced potential reaches a critical breakdown voltage (typically 0.5 V to 1.5 V), it overcomes the electrostatic and mechanical stability of the lipid bilayer, leading to localized membrane disruption[17,21]

Mechanism: Transient Aqueous Pores

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

The application of short, high voltage pulses (microseconds to milliseconds) causes a physical rearrangement of the lipid molecules, resulting in the formation of transient, hydrophilic pores[18]

Water Dipole Alignment: The high electric field causes water molecules to align and penetrate the hydrophobic core of the lipid bilayer, initially forming hydrophobic defects[20]

Pore Transformation: If the electric field is maintained, lipid molecules reorient their hydrophilic heads toward the interior of the defect, stabilizing it and transforming it into a hydrophilic (aqueous) pore[17]

Molecular Transport: Molecules in the surrounding medium are then driven into the cell through these pores, often assisted by electrophoresis (movement of charged molecules in the electric field) and electroosmotic flow[19]

Resealing: After the pulse ceases, the membrane potential decays. If the parameters are optimized (Reversible Electroporation RE), the lipid bilayer spontaneously returns to its stable state, and the pores reseal quickly, maintaining cell viability.[17]If the field is too strong, the damage is permanent (Irreversible Electroporation IRE).[18]

Utility (Applications)

Electroporation has a wide range of applications, from basic research to medicinal treatments.[19]

Application	Specific utility
Molecular Biology Transfection	Transfection/Transformation: Introducing plasmid DNA, siRNA, or mRNA into various cells for genetic modification and protein production.[16]
Oncology (RE)	Electrochemotherapy (ECT): Enhancing the uptake of non permeant chemotherapeutic drugs (e.g., Bleomycin) into solid tumor cells.[21]
Oncology (IRE) Irreversible	Irreversible Electroporation (IRE): Using high-intensity pulses to cause non thermal ablation (destruction) of soft tissue tumors.[18]
Vaccinology	Gene Electrotransfer (GET) / DNA Vaccination: Enhancing the delivery and expression of DNA based vaccines (gene therapy) in vivo.[19]

Table:2 Application of Electroporation

Sonophoresis (Phonophoresis)

Sonophoresis (also known as Phonophoresis) is a non invasive, active physical enhancement technique used in advanced transdermal drug delivery (TDD). It utilizes ultrasound energy to temporarily and reversibly increase the permeability of the skin barrier, primarily the stratum corneum (SC), to facilitate the transport of therapeutic agents[23]

Sonophoresis increases skin permeability by using frequencies between 20 kHz and 16 MHz and intensities up to 14 W/cm2 (spatial average pulse average intensity, or ISAPA).[24]

Principle

The principle relies on the interaction of acoustic energy with the skin and the drug vehicle, resulting in physical effects that modify the SC structure. Low frequency ultrasound{20 kHz} to {1 MHz}) is typically used as it is significantly more effective than high frequency ultrasound[24]

Key Mechanism:

Acoustic Cavitation: The dominant mechanism for enhancing drug transport is acoustic cavitation (the formation and violent collapse of microscopic bubbles)[2,23]

Bubble Dynamics: Ultrasound waves generate cycles of high pressure (compression) and low pressure (rarefaction) within the fluid medium (coupling gel, interstitial fluid)[25]

Violent Collapse: Tiny gas nuclei enlarge during the low pressure cycle. These bubbles collapse violently and asymmetrically during the ensuing high pressure cycle.[23]

Mechanical Disruption: Shock waves, high velocity microjets, and shear strains are among the strong, highly localized forces produced by this collapse.[25],These forces create temporary aqueous channels or drug transport paths by mechanically disrupting the densely packed SC lipid bilayers and loosening the corneocytes.[2, 25]

Sonophoresis's limitations

Sonophoresis has practical and therapeutic limits even though it is effective in enhancing skin permeability for macromolecules:

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

Systemic medication Delivery Variability: Because cavitation effects and acoustic coupling are inherently variable, it can be difficult to achieve constant and predictable systemic medication levels .[23,15] It is therefore more suited for regional or local applications.

Thermal Control: To avoid localized overheating and possible thermal damage or discomfort to the tissue, the accompanying thermal effect needs to be carefully controlled.[24]

Equipment Dependency: Compared to straightforward patches or lotions, the employment of specialist ultrasonic equipment and coupling agents can be cumbersome and less convenient.[25]

Efficacy vs. Size: Although the mechanism works well, it is typically less successful for the larger macromolecules (such as large proteins or gene vectors) than methods like electroporation or sophisticated microneedles.[2]

Advanced Transdermal Delivery Technologies (Innovative TDD)

Microneedle

The Big Innovation: Microneedle Technology (MNs) Microneedle arrays are patches or devices with many tiny projections that are intended to pierce the skin's outer layers. These projections are usually {25-1500} (micrometer)in length and {10-100}(micrometer) in base width.The capacity of MNs to specifically target the epidermis while avoiding the dermal pain receptors is what makes them successful.[27]

Mi-croneedles were essentially divided into three types:

(1) hollow polymer microneedles for liquid distribution into the skin

(2) solid microneedles used for skin preparation or solid drug coated microneedles

(3) porous microneedles impregnated with molecular particles generated in various sizes.[26,29]

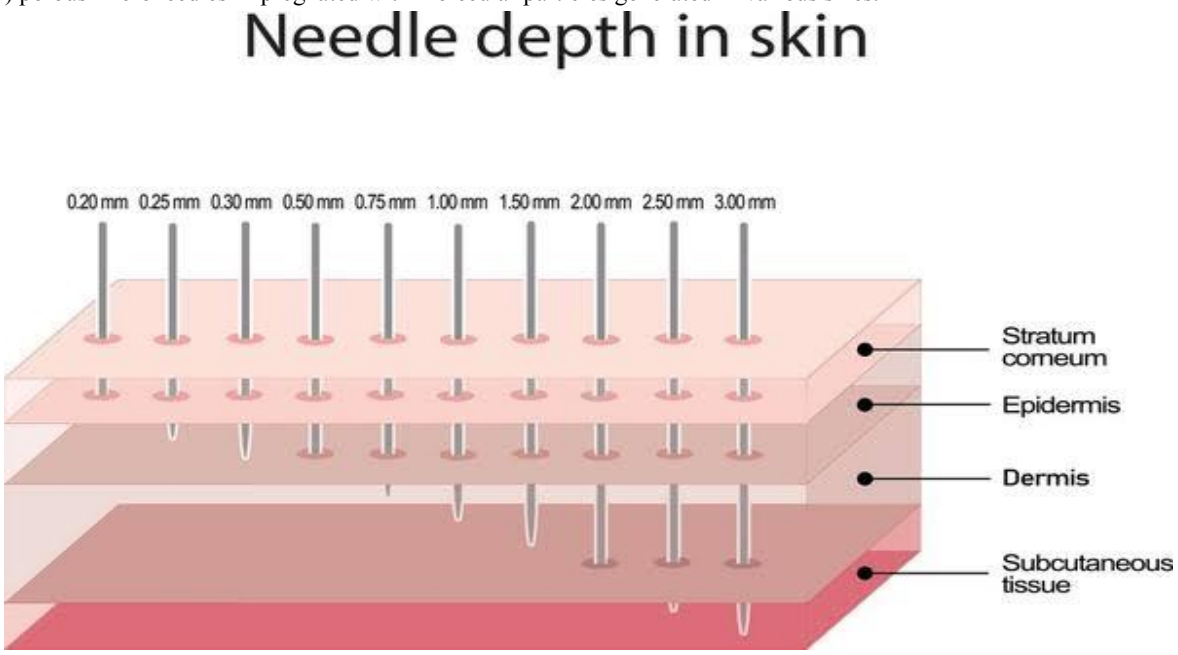

Fig.5. Needle depth in skin[28]

Types of Microneedles (MNs)

Solid MNs: Mainly used to create microchannels and pretreat the skin. The treated area is subsequently covered with a medication formulation (such as a patch or cream) to diffuse through the channels[30]

Hollow MNs: They work similarly to microscopic hypodermic needles. Similar to an injection but with exact depth control, they are used to infuse liquid medicine formulations straight into the epidermis or upper dermis[31]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

Mechanism of Microneedles

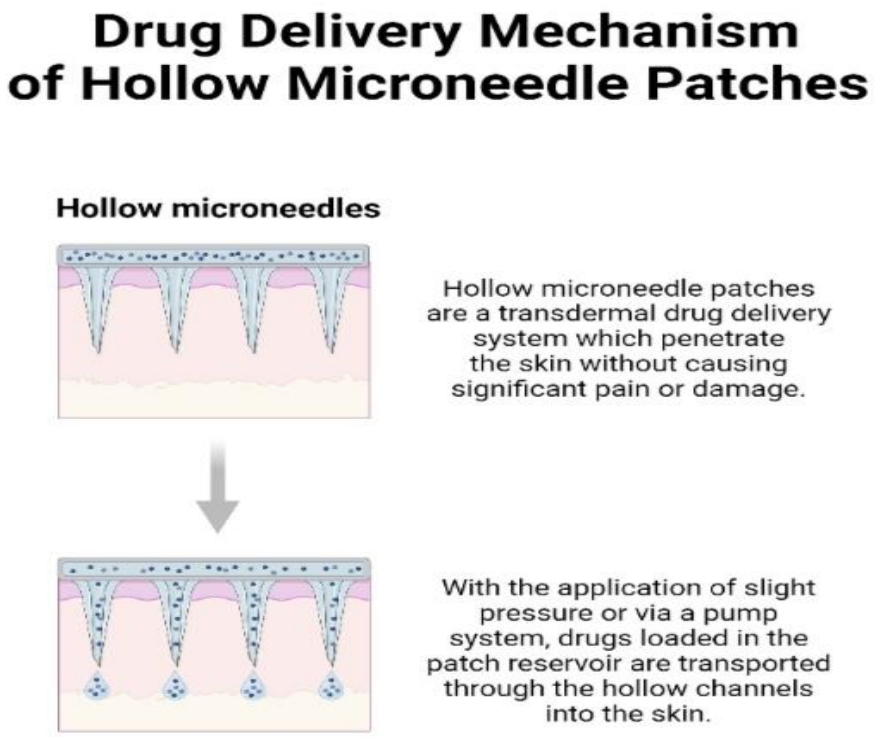

Fig. 6. Drug Delivery Mechanism of Hollow Microneedle Patches[42]

Coated MNs: A solid, inert needle typically made of metal or ceramic is coated with the medication. The covering quickly dissolves or releases into the skin[32]

Dissolving (or Degradable) MNs: The needles are fabricated entirely from a drug loaded, water soluble polymer (e.g., hyaluronic acid). Upon insertion, the needles dissolve completely within minutes or hours, releasing the encapsulated drug into the interstitial fluid .[33]This is a highly favored type for single dose applications.

Hydrogel Forming MNs: The needles swell upon contact with interstitial fluid, forming a hydrogel matrix in situ. This hydrogel then serves as a reservoir for sustained, long term drug release[34]

Mechanism: Bypassing the Stratum Corneum Without Hitting Dermal Nerves

1.The success of MNs lies in their ability to precisely target the epidermis while avoiding the pain receptors located in the dermis[35]

2.Pain Avoidance: The needle length is a critical design parameter that should be maintained short (preferably less than 200 µm for many applications) in order to stop short of the dermal nerve endings .[36] This depth control makes the MN administration almost painless, which significantly improves patient compliance[37]

3.Microchannel Creation: Through the SC, penetration produces transitory aqueous microchannels or holes that greatly increase the skin's permeability for big molecules by several orders of magnitude[38]

Applications

Because MNs can deliver large, complicated, and high molecular weight medicines , they are extending the reach of TDD to domains that were previously dominated by injections.[39]

Vaccinations(Microneedle Patches): Protein and nucleic acid based vaccinations (DNA/RNA) can be administered very successfully using MN patches. Targeting the medicine to the immune cell rich epidermis and upper dermis can

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

induce a superior immunological response compared to intramuscular injection, frequently needing a fraction of the usual dose[40]

Biologics (Peptides and Proteins): MNs provide an alternative to frequent subcutaneous injections for chronic disorders by enabling the painless transdermal administration of large therapeutic biologics such as insulin, human growth hormone, and monoclonal antibodies[41]

Chronic Disease Management

Used for the regulated administration of medications for long term ailments, including osteoporosis therapies, parathyroid hormone, and specialty small molecules with low oral bioavailability [24]

Nanotechnology in TDD

Nano carriers, generally defined as vehicles ranging from 10 to 1000 nm, enhance TDD by increasing drug stability, improving SC penetration, and enabling targeted release[43]

Nanoparticles and Liposomes:

Nanoparticles and Liposomes These are the most common types of Nano carriers used for drug encapsulation in TDD[15]

Carrier	Description and mechanism	Utility TDD
Nanoparticles (NPs)	Solid colloidal systems (e.g., polymeric, lipid, or inorganic) where the drug is dissolved, entrapped, or adsorbed. Their small size facilitates penetration through skin appendages (hair follicles) or minor SC defects[15]	Enhanced Penetration: Protect drugs from degradation and enhance permeability via follicular or intercellular routes. Targeted Delivery: Can be surface modified for selective targeting within the skin[15,43]
Liposomes	Spherical vesicles composed of one or more phospholipid bilayers encapsulating an aqueous core. Conventional liposomes face challenges due to their rigid structure[43]	Drug Encapsulation: Suitable for encapsulating both hydrophilic and lipophilic drugs . Their utility is primarily as the precursor to more advanced, deformable vesicles [15]

Table: 3 Types of Nano carriers

Cutting-Edge Techniques:

Thermal Ablation/Poration

Thermal ablation or thermal poration uses localized, controlled heat to rapidly and precisely disrupt the SC barrier, creating transient microchannels for drug transport[15,44]

Principle and Mechanism

Heat Application: A brief pulse of intense thermal energy (often generated by radiofrequency, laser, or focused resistive heating) is applied to a tiny area of the skin (typically 50-1000 µm in diameter)[44]

Ablation/Poration: The intense, localized heat instantly vaporizes the water in the SC and viable epidermis. This vaporization process creates microscopic, dry pores by removing the barrier at those targeted sites[44]

Transport: Drugs are subsequently applied to the ablated site, where they diffuse rapidly through the microchannels into the highly permeable dermis[15]

Painless Delivery: The heat pulse is highly controlled to limit penetration depth, ensuring that the dermal nerves are avoided, thus maintaining a painless delivery route[44]

Utility

Thermal poration is valuable for delivering large, temperature sensitive molecules (like peptides and proteins) and for vaccines, as the heat is extremely localized and short lived[44]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

Jet Injectors (Needle-Free Injection)

Jet injectors are non conventional devices designed to deliver liquid drug formulations across the skin without using a traditional hypodermic needle[15,44]

Principle and Mechanism

Pressure Generation: A mechanical (spring) or gas powered mechanism rapidly pressurizes the liquid drug formulation[15,44]

Micro Jet Formation: The high pressure forces the liquid through a tiny nozzle at an extremely high velocity (often >100 µm), creating an ultra fine, high speed liquid micro jet[15]

Skin Penetration: This micro jet acts as a "liquid needle" that pierces the SC and epidermis, delivering the drug to the underlying tissue layers (dermis or muscle)[44]

Controllable Depth: Drug penetration depth can be precisely controlled by adjusting the driving pressure, nozzle diameter, and volume of the liquid [15]

Utility

Jet injectors offer a needle free, painless alternative to conventional injections, significantly improving patient compliance. They are widely studied for the systemic delivery of: Vaccines (e.g., flu vaccines),High volume, rapid uptake drugs (e.g., insulin) [15,44]

Focus on Therapeutic Areas and Integration

Novel Transdermal Therapies

Neurological Disorders:

Delivering drugs to the central nervous system (CNS) is inherently challenging due to the restrictive blood brain barrier (BBB) and the need for stable, chronic dosing. TDD overcomes these by providing sustained, non-invasive delivery[15]

Parkinson's Disease (PD): PD requires stable plasma concentrations of drugs like dopamine agonists (e.g., rotigotine) to minimize the debilitating "on-off" motor fluctuations associated with oral dosing . The TDD patch provides continuous transdermal infusion, bypassing the frequent peaks and troughs, thereby stabilizing drug levels[45]

Alzheimer's Disease (AD): AD management requires sustained delivery of agents like cholinesterase inhibitors (e.g., rivastigmine). TDD provides a simple, non invasive route that improves patient compliance and reduces administration burden for caregivers compared to repeated oral dosing[46]

Challenges Overcome: TDD avoids the high hepatic (first-pass) metabolism that degrades many CNS acting drugs and provides precise control over drug concentration over extended periods[18]

Oncological Applications

TDD is being explored to reduce the systemic toxicity associated with conventional chemotherapy and to enhance the targeting of powerful immunotherapy agents[45]

Chemotherapy Delivery: TDD can deliver chemotherapeutic drugs (e.g., 5-fluorouracil, doxorubicin) either systemically (for sustained release) or, more importantly, locally for skin or superficial cancers. Localized delivery minimizes systemic exposure and severe side effects[46]

Immuno Oncology: Advanced TDD techniques, notably Electroporation and Microneedle (MN) arrays, are being developed for the delivery of cancer vaccines and immunomodulators .[47] These methods can specifically target the drug to the immune cell rich epidermal and dermal layers (containing Antigen Presenting Cells like dendritic cells), potentially eliciting a stronger and more focused anti-cancer immune response than traditional injections.[46,45] Infectious Diseases and VTDD is considered a crucial platform for vaccination, offering a path toward self-administration and improved logistical management[2]

Vaccine Delivery (MN Patches): Microneedle (MN) patches are the most advanced TDD application for vaccines (e.g., influenza, measles, COVID-19)[15,47]

Mechanism Advantage: MNs deliver the antigen directly to the highly concentrated immune cell populations in the epidermis/upper dermis[47] This targeted delivery often results in a superior immune response while requiring only a smaller antigen dose compared to traditional intramuscular injection[48]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

Logistical Advantages: MN patches are simple, virtually painless, eliminate the risk of needle stick injuries, and can be engineered to be thermostable (stable at room temperature), overcoming the "cold chain" challenge for global vaccination campaigns[15,46]

Integration with Biosensors and Biomarkers

This integration moves TDD from passive, scheduled dosing to active, personalized medicine, optimizing therapeutic outcomes and minimizing side effects.The convergence of advanced Transdermal Drug Delivery (TDD) systems with biosensors and biomarkers represents a crucial future direction, leading to the development of sophisticated "sense and treat" and feedback controlled patches[49].

"Sense and Treat" Patches

"Sense and treat" patches are closed loop systems that combine two functions: continuous monitoring of a physiological parameter (the biomarker) and controlled delivery of a drug (the treatment)

Glucose Monitoring Integration: The most prominent application is in diabetes management. The system continuously monitors glucose levels (the biomarker) via minimally invasive sensors (e.g., integrated microneedle electrodes or subcutaneous probes)[49]

Insulin/Glucagon Delivery: If the glucose level exceeds or falls below a set threshold, the patch automatically initiates or adjusts the release of insulin or glucagon (the treatment).

Mechanism: These systems often utilize hydrogel forming microneedle array or iontophoresis where the delivery mechanism is coupled to the sensor output[48]

Feedback-Controlled Systems

Feedback controlled systems ensure that drug release is dynamic and customized based on real time biological data, mimicking the body's natural regulatory processes.

Automated Drug Release: These systems employ a closed loop algorithm that takes the realtime biomarker concentration as the input and calculates the required drug release rate as the output.

Biomarker Targets: Beyond glucose, targets include {pH} (for infection monitoring), lactate (for exercise/trauma), and inflammatory markers (cytokines).[48,49]

Smart Patches: The patch components typically include a sensing module (biosensor), a processing module (microcontroller/algorithm), and an actuation module (delivery mechanism like a temperature sensitive hydrogel or an electric pulse generator).

Precision Dosing:

This level of control eliminates the need for patient estimation or fixed dosing schedules, significantly reducing the risk of overdosing or under dosing and improving efficacy for drugs with a narrow therapeutic window.[49]

Future Directions and Challenges

Future research and clinical translation in Transdermal Drug Delivery(TDD) are focus on overcoming scale up and regulatory hurdles while leveraging advanced manufacturing techniques like 3D printing to achieve personalized medicine.[48]

Personalized Medicine and 3D Printed Patches

3D printing (Additive Manufacturing) offers an unparalleled ability to rapidly prototype and manufacture TDD systems with high precision, moving TDD towards truly personalized medicine.[50]

Concept	Role of 3D Printing
Customizing Patch Geometry	Allows for the creation of intricate microneedle (MN) arrays with tailored shapes, lengths, and tip sharpness optimized for different skin sites (e.g., thinner skin on the wrist vs. thicker skin on the back)[51]
Drug Dose and Release Kinetics Enables	Micro-dosing and the fabrication of patches with complex internal architectures (e.g., multi layered or reservoir in matrix designs) to achieve precise zero order (constant) or pulsatile release kinetics tailored to the drug's therapeutic window[52]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

Personalized TDD	The ultimate goal is to tailor patches based on individual skin properties (thickness, hydration, age) and therapeutic needs (specific dose and timing). 3D printing makes "on demand" manufacturing feasible for specific patient populations or even single[50]
"Polypills" and Combination Devices	The ultimate goal is to tailor patches based on individual skin properties (thickness, hydration, age) and therapeutic needs (specific dose and timing). 3D printing makes "on demand" manufacturing feasible for specific patient populations or even single patients[53]
Materials Innovation	Allows the use of novel materials (e.g., biocompatible, dissolving polymers) that are difficult to process via traditional methods, enhancing both efficacy and patient safety/comfort.[48]

Table: 4 Personalized Medicine and 3 D Printing patches.

Key Challenges and Regulatory Hurdles

For advanced TDD systems to move from bench to bedside, significant challenges in manufacturing, cost, and regulation must be addressed[49]

Manufacturing and Economic Challenges

Manufacturing Scalability: Scaling up the production of sophisticated micro scale devices, like microneedle arrays or 3D printed patches, from laboratory prototypes to commercial, millions per year production remains difficult, especially while maintaining the required precision and quality control[54]

Cost of Goods (CoG): The specialized equipment and materials needed for advanced fabrication (e.g., lithography, photopolymerization for 3D printing) can result in a high cost per unit, making them less economically competitive than traditional patches or simple injections[50]

Reproducibility and Stability: Ensuring that complex structures (like microchannels or dissolving matrices) maintain their integrity, sterility, and performance over the required shelf life and across different manufacturing batches is critical[49]

Regulatory Hurdles and Safety

Regulatory Approval for Complex Combinations

Integrated TDD systems (e.g., "sense and treat" patches) are classified as Drug Device Combination Products . These products face a complex and often lengthy approval pathway, requiring simultaneous evidence of drug safety/efficacy and device functionality/safety (hardware, software, and delivery mechanism)[55]

Long-Term Skin Safety

While new techniques (MNs, electroporation) are often painless, long term safety data is required, especially regarding the repeated creation of micro channels or the use of novel materials . Regulatory bodies require assurance that micro channels close quickly and that the risk of infection or chronic irritation remains negligible[56]

Dose Control and Accuracy: Demonstrating that active systems (e.g., iontophoresis, feedback control) can deliver the drug dose with the same or better accuracy and consistency than conventional methods is essential for clinical acceptance.[57]

II. CONCLUSION

The future of TDD is bright, driven by technologies that allow precise manipulation of the skin barrier (Electroporation, Sonophoresis, Microneedles) and personalized manufacturing (3D Printing). Success hinges on overcoming regulatory inertia and achieving scalable, cost effective manufacturing processes to bring these sophisticated smart patches from the bench to routine clinical practice.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, March 2026
Impact Factor: 8.2

REFERENCES

1.Ahlam Zaid Alkilani, Maeliosa T.C McCrudden, Ryan F.Donnelly, Transdermal Drug Delivery:Innovative Pharmaceutical Development Based on Disruption of the Barrier Properties of the stratum corneum.Pharmaceutics(2015),7(2):438-470.

2.Mark R. Prausnitz, Robert Langer, Transdermal drug delivery Nat Biotechnol.(2008) November; 26(11): 1261–1268.

3.K Purushotham, K Anie vijetha, A review on transdermal drug delivery systemGSC Biological and Pharmaceutical Sciences, 2023, 22(02), 245–255.

4.Michael N Pastor, Yogeshvar N Kalia, Michael Horstmann et.al, Transdermal patches:History, development and pharmacology, British journal of Pharmacology(2015)172:2179-2209.

5. Naveen Joshi ,Sina Azizi Machekposhti , Roger J. Narayan Evolution of Transdermal Drug Delivery Devices and Novel Microneedle Technologies: A Historical Perspective and Review (2023)3,(6):100225.

6.https://share.google/images/RpvuwY0oinia4F8R Assest on 5 november 2025.

7.Zahra LotfollahiThe anatomy, physiology and function of all skin layers and the impact of ageing on the skin, wound practice and research,(2024) 32.(1).6-10

8.https://share.google/AKxTCTki8iRHHMPWC Assest on 5 november 2025.

9. https://share.google/images/sXjw320Flxz3AxBe4 Assest on 5 november 2025.

10.Adrian C. Williams, Brian W. Barry,Penetration enhancers, In Pharmaceutics (pp. 53-73). Springer, Berlin, Heidelberg.

11.https://share.google/images/qSOHOEmSpX6CJJnzM

12.B.W.Barry, Novel mechanism and devices to enable successful transdermal drug delivery, European Journal of Pharmaceutics Sciences (2001) 14, 101-114.

13.M. Begon, Delgado-Charro, Richard H. Guy, Transdermal drug delivery,Second edition, Iontophoresis: Applications in Drug Delivery and Noninvasive Monitoring, Marcel Dekker.

14.Denet, A. R., Preat, V.,Versali, P. Skin electroporation for transdermal and topical delivery. Advanced Drug Delivery Reviews, (2004)56(5), 659-674.

15.Phatale, V.,vaiphei,k.k.,jha,S,et al,Overcoming skin barriers through advanced transdermal drug delivery approaches, Journal of Controlled Release, (2022)351, 361-380.

16.Neumann,E.,Schaefer-Ridder,Wang,E,et al,Gene transfer into mouse lyoma cells by electroporation in high electric fields. The EMBO Journal, (1982)1(7), 841–845.

17.Weaver, J. C., & Chizmadzhev, Y. A. Theory of electroporation: a review. Bioelectrochemistry and Bioenergetics, (1996)41(2),135–160.

18.Davalos, R. V., Mir, L. M., & Rubinsky, B.Tissue ablation with irreversible electroporation. Annals of Biomedical Engineering, (2005)33(11), 1618–1626.

19.Somiari, S.,Glasspool,j.,Elizabeth et al. Theory and in vivo application of electroporative gene delivery. Molecular Therapy, (2000)2(3), 178–187.

20.Somasundaram, H. S.,and deshpande,A.P,Mechanics of water pore formation in lipid membrane under electric field. Acta Mechanica Sinica, (2017)33(2), 263-272.

21.Gehl, J., & Mir, L. M. . Electroporation-Based Therapies in Cancer: A Comprehensive Review. Cancers, (2024)16(2),329.

22.Lane, M. E, Skin penetration enhancers. International Journal of Pharmaceutics, (2013)447(1-2), 12-23.

23.Mitragotri, S., & Kost, J. Low-Frequency Sonophoresis: Application to the Transdermal Delivery of Macromolecules and Hydrophilic Drugs. Pharmaceutical Research,(2000) 17(11), 1351–1356.

24.Kotb, E., & Ma, M. Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum.pharmaceutics,(2015)7(4),437-463.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

25.Sabrina N. Campelo, Po-Hsun Huang, Cullen R.Buie, et al. Recent Advancements in Electroporation Technologies: From Bench to Clinic, Annual Review of Biomedical Engineering,(2023)25,77-100.
26.Junwei Li, Mingtao Zeng, Hu Shan, Microneedle Patches as Drug and Vaccine Delivery PlatformCurrent Medicinal Chemistry, (2017), 24, 2413-2422.
27.Yeu-Chun Kim, Jung-Hwan Park, and Mark R. Prausnitz,Microneedles for drug and vaccine delivery,Adv Drug Deliv Rev. (2012)64(14): 1547–1568.
28.https://share.google/images/qvbSkuHpKBjS7Fl4v Assest on 6 november 2025.
29.Kim, Y.C., Park, J.H.,Prausnitz, M.R. Microneedles for drug and vaccine delivery. Adv. Drug Deliv. Rev., 2012, 64(14), 1547-1568.
30.McAllister DV, Wang PM, Davis SP, et al.Microfabricated needles for transdermal delivery of macromolecules and nanoparticles:Fabrication methods and transport studies. Proc Natl Acad Sci U S A. (2003) 100,13755–13760.
31.Muhammad Bilal, Shahid Mehmood, Ali Raza,et.al, Microneedles in Smart Drug Delivery.Advances in Wound Care,(2019)1122.
32.Jain AK, Lee CH, Gill HS. 5-Aminolevulinic acid coated microneedles for photodynamic therapy of skin tumors. Journal of Controlled Release. (2016)239,72-81.
33.Chen CH, Shyu VBH, Chen CT. Dissolving microneedle patches for transdermal insulin delivery in diabetic mice: potential for clinical applications. Materials, (2018)11(9),1625.
34.Waghule T, Singhvi G, Dubey SK, et al. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomedicine & Pharmacotherapy. 2019;109,1249-1258.
35.G. Honari, H. Maibach, Chapter 1 – skin structure and function, in: H. Maibach, G. Honari (Eds.), Applied Dermatotoxicology, Academic Press, Boston, 2014, pp. 1–10.
36. A. Herman, A.P. Herman, Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review, Journal of pharmacy and pharmacology.(2015) 67(4),473–485.
37.Prausnitz, MR.; Gill, HS.; Park, JH. Modified Release Drug Delivery. In: Rathbone, MJ.; Hadgraft, J.; Roberts, MS.; Lane, ME., editors. New York: Informa Healthcare; 2008.
38.Gill HS, Prausnitz MR. Coated microneedles for transdermal delivery. J Control Release (2007)117,227–237.
39.Anselmo, A.C.; Mitragotri, S. An Overview of Clinical and Commercial Impact of Drug Delivery Systems. J. Control. Release (2014), 190, 15–28.
40.Donnelly, R.F.; Singh, T.R.R.; Morrow, D.I.; Woolfson, A.D. Microneedle-Mediated Transdermal and Intradermal Drug Delivery; Wiley: Hoboken, NJ, USA, 2012.
41.M. Sharma, Chapter 18 – transdermal and intravenous nano drug delivery systems: present and future, in: S.S. Mohapatra, et al. (Eds.), Applications of Targeted Nano Drugs and Delivery Systems, Elsevier, 2019, pp. 499–550.
42.https://share.google/VeVBEGuSj5t1cVzt4 Assest on 7 november 2025.
43.Sabrina N. Campelo,Po-Hsun Huang,Cullen R.Buie,Recent Advancements in Electroporation T echnologies:From Bench to Clinic Annual Review of Biomedical Engineering(2023) 25,77–100
44.Karande, P., & Mitragotri, S.Advanced physical methods for enhancing transdermal drug delivery: Recent progress and current challenges. Advanced Drug Delivery Reviews,(2008) 60(11), 1311–1334.
45.Jeffrey D. Rudie,Andreas M. Rauschecker,R. Nick Bryan,et.al.Emerging Applications of Artificial Intelligence in Neuro-Oncology, Radiology.(2019),290(3),607–618.
46.Gholami, F.,Alimohammadi,A.,Ghasemi,M., et al. Recent Advancements in Electroporation Technologies: From Bench to Clinic. Pharmaceutics,(2022) 14(12), 2673.
47.Martanto, W.,Davis,S.L.,Nazanin A et al. Transdermal delivery of insulin using microneedles in vivo. Pharmaceutical Research, (2004)21(6), 947–952.
48.Ma, Y., et al. Microneedle-based smart patch for advanced transdermal drug delivery. Advanced Drug Delivery Reviews,(2024)205, 115202.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, March 2026 Impact Factor: 8.2

49.Syed Waqas Ali Shah, Xingxing Li, Hao Yuan, et.al,Innovative transdermal drug delivery systems:Benefits, challenges, and emerging application ,BMEMat.

50.Xiao Zhu, Hongjian Lia, Lianfang Huang,et.al,3D printing promotes the development of drugs, Biomedicine & Pharmacotherapy 131 (2020) 110644.

51. Rutuja N. Meshram and Dimitrios A. Lamprou, Mould-Free Microneedles in a Single Step: 3D Printing with Photopolymer Resins for Transdermal Delivery, Pharmaceutics (2025), 17,1498.

52.Sophia N. Economidoua, Dimitrios A. Lamproua, Dennis Douroumisb,3D printing applications for transdermal drug delivery,International Journal of Pharmaceutics,(2018).

53.David Bird Nuggehalli M. Ravindra,Transdermal drug delivery and patches An overview Med Devices Sens. (2020)

54.PooyanMakvandi,AzizMaleki,MajidShabani,et.al,Bioinspiredmicroneedlepatches:Biomimetic designs, fabrication, and biomedical applications, (2022)Matter 5,390–429.

55.Kotha Arun Kumar, Penjuri Subhash Chandra Bose,Tummala Screedhar ,et al,Strategic approaches for selecting regulatory pathways in drug-device combination products: A comprehensive review,Journal of Applied Pharmaceutical Science October (2025)15(10), pp 003-021,

56.Helen L Quinn,Eneko Larrañeta,Ryan F Donnelly,Dissolving microneedles: safety considerations and future perspectives,Ther.(2016)7(5), 283–285.

57.Carl M. Schoellhammera, Daniel Blankschtein, and Robert Langer,Skin Permeabilization for Transdermal Drug Delivery: Recent Advances and Future Prospects,Expert Opin Drug Deliv. 2014 March ; 11(3): 393–407.