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ADVANCED TECHNOLOGIES FOR TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Transdermal drug delivery systems (TDDS) represent a significant advancement in pharmacological therapies, offering a non-invasive method for drug administration that enhances patient compliance and minimizes systemic side effects. This review discusses the traditional challenges associated with drug delivery, including poor bioavailability and first-pass metabolism, and highlights innovative technologies designed to improve drug permeability and controlled release. Key advancements such as vesicular systems, microneedles, iontophoresis, and nano-formulations are explored for their roles in overcoming the stratum corneum barrier. The integration of smart patches, AI-driven optimization, and 3D printing for personalized dosages also shows promise in revolutionizing patient care. By leveraging these advanced technologies, TDDS can potentially become a cornerstone of modern medicine, offering efficient and effective alternatives to conventional drug administration methods.

Keywords: Transdermal Drug Delivery System, Drug Permeability, Smart Patches, Microneedles, Iontophoresis, Bioavailability.

1. INTRODUCTION

Appropriate drug selection and efficient drug delivery are key elements in attaining maximum treatment outcomes. The objective of any drug delivery system is to provide an effective therapeutic amount of drug to the site of action in the body at the right time with the correct drug concentration over the course of the dosage period. For decades, the oral route has been the most common mechanism of delivering medicine, and an estimated 74% of drugs are administered orally, yet they remain not as effective as projected[1].While oral delivery has the valuable advantage of being easy to give, it has significant drawbacks, including poor bioavailability due to hepatic metabolism (first pass metabolism) and a tendency to produce rapid peaks in blood levels, both low and high [2].To overcome the limitations, there was an imperative to understand and create new drug delivery systems and pathways that could increase the therapeutic efficacy and safety of drugs through more accurate placement within the body along time and space. This would minimize the dosage size and number and maximize their effectiveness through optimal dose concentration. A transdermal delivery system of medication was created to achieve these aims and improve such features.

1.1Overview of Transdermal Drug Delivery (TDD)

Transdermal drug delivery system may be termed as the topically applied drugs in self-contained, discrete dose forms of patches which upon application to the skin release the drug, via the skin portal to systemic circulation at a controlled and predetermined rate over an extended duration of time to enhance the therapeutic effectiveness and minimized side effect of drug. TDDS keeps the drug concentration within the therapeutic window for longer duration of time so that drug levels never drop below the minimum effective concentration and never rise above the maximum effective concentration.

Transdermal drug delivery systems (TDDS) are a new, non-invasive drug delivery method, in which therapeutic compounds are transported via the skin into systemic circulation. In contrast to traditional methods like oral or injectable drug delivery, TDDS offers controlled and prolonged drug release, enhancing patient compliance and decreasing systemic side effects. TDDS has been extensively utilized for long-term conditions like pain treatment, hormone therapy, and cardiovascular diseases.

Controlled drug delivery studies have increased significance in the pharmaceutical sector over the past two decades. The pharmacological activities

of a drug, i.e., effective therapeutic effect and undesirable side effect, both rely on drug concentration at the site of action, which is governed by the dosage provided and absorbed at that time. Human skin is the most convenient surface for drug delivery[3]. Every square centimeter of skin surface contains approximately 10-70 hair follicles and 200-250 sweat ducts [4]. Therefore, the potential for using uninjured skin as a portal of drug delivery to the human body has been understood since early medical times. Nevertheless, skin is a very resilient barrier to material entry, allowing only minute quantities of an object to cross over time [5] .Transdermal drug delivery (TDD) is the delivery of drugs across the skin and into systemic circulation by utilizing the increased accessibility of the skin, rather than topical drug delivery, which only reaches localized affected areas. The deeper insight into morphological, bio-physical and physicochemical structure and properties of the skin is vastly critical in order to deliver therapeutic molecules through the human skin for the systemic and desired action. Transdermal delivery offers a valuable advantage over any other injectables and oral routes by enhancing patient compliance and avoiding first pass metabolism (FPM) respectively. It allows controlled and maintained drug administration on one side and continuous drug infusion with short half-life in biologic terms so that pulsed entry into the systemic circulation and subsequent undesirable side effects are generally avoided [6][7][8]. It will be convenient, particularly prominent in those patches which can be applied just once a week. With such an easy dosing schedule, patient compliance and drug therapy adherence is facilitated. In general with all its beneficial attributes TDDS can be regarded as a possible substitute to oral as well as other forms of drug delivery.

1.1.1 Anatomy of the Skin

Skin is the body's largest organ and is divided into three broad layers: the epidermis, dermis, and hypodermis. The outermost layer is the epidermis, of which the stratum corneum serves as the initial barrier against drug penetration. The dermis beneath it consists of blood vessels, nerves, and connective tissue and has a major function in drug absorption [9] . The hypodermis or subcutaneous layer is composed of fat and connective tissue and helps with insulation and cushioning. Drugs may pass through the skin through transcellular, intercellular, or appendageal (sweat glands, hair follicles) routes. New transdermal technologies facilitate the penetration through the stratum corneum barrier for improved drug delivery [10].

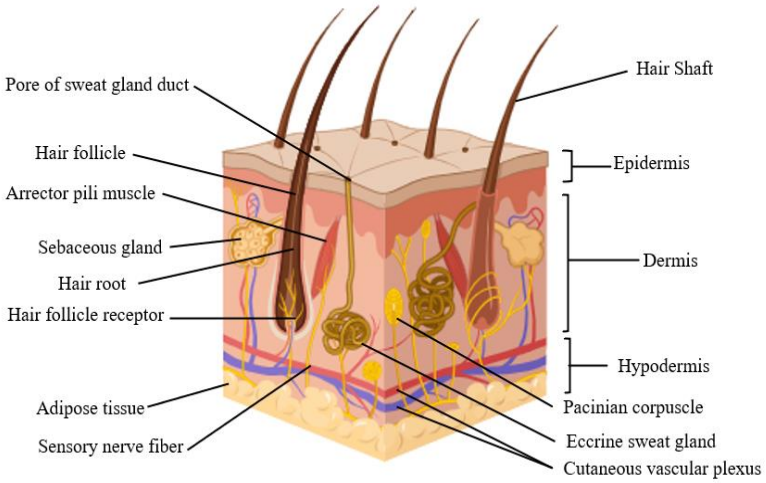


Fig. 1. Structure of Skin

1.1.2 Advantages

- Avoidance of First-Pass Metabolism: Transdermal delivery avoids the first-pass metabolism through the gastrointestinal tract, resulting in enhanced bioavailability of drugs.
- Sustained Release: TDDS ensures controlled and sustained release of medicines, producing therapeutic drug levels over a period of time.
- Minimized Side Effects: Controlled release decreases peak plasma levels, which may decrease the frequency of side effects.
- Non-Invasive: As a needle-free delivery system, TDDS is also more patient-friendly for those who dislike injections.
- Enhanced Patient Compliance: Less frequent dosing (e.g., weekly application) improves drug-taking compliance.
- Targeted Delivery: Able to deliver drugs directly into systemic circulation, thereby improving therapeutic effect for specific conditions.

1.1.3 Disadvantages

- Skin Irritation: Long-term use of patches can lead to skin irritation or allergic responses at the site of application.
- Variable Absorption: Drug absorption is influenced by skin thickness and hydration, resulting in variable therapeutic effects.
- Dosing Limitations: TDDS is not appropriate for high-dose drugs that need large volumes or concentrations.
- Cost: The cost of developing and manufacturing TDDS can be greater than conventional dosage forms.
- Complexity: The development of effective transdermal systems demands sophisticated technology and knowledge of skin physiology.
- Drug Stability: Certain drugs may not be stable in the adhesive matrices of TDDS.

1.1.4 Limitations of Traditional Drug Delivery Systems

Although they are being used extensively, conventional drug delivery systems have many challenges:

- Oral administration: Most drugs are plagued with poor bioavailability caused by gastrointestinal degradation and hepatic metabolism (first-pass effect).
- Injectable delivery: Although effective, injections are invasive, causing pain, fear, and risk of infections, resulting in poor patient compliance.
- Topical application: Traditional topical preparations are limited in being able to penetrate the stratum corneum, the outermost skin barrier, whichrestricts drug absorption.

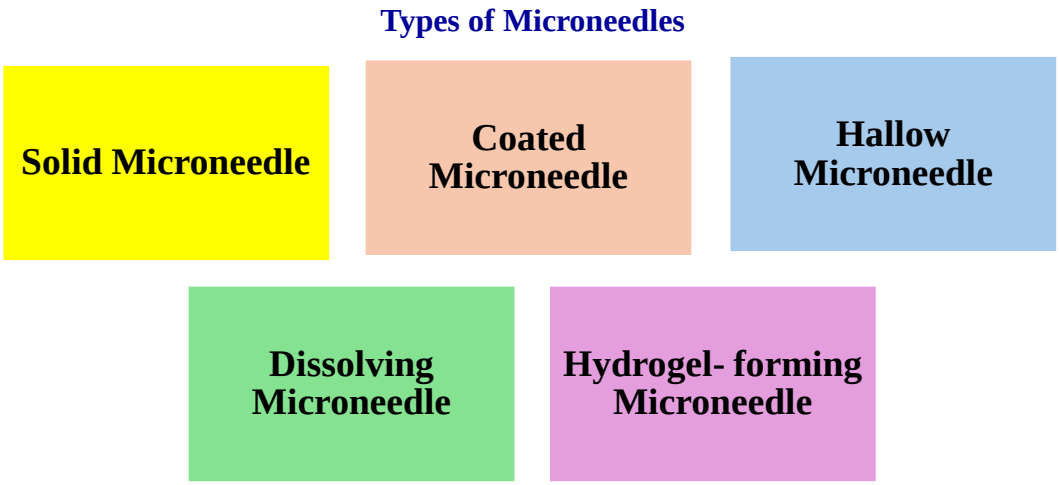
1.2 Significance of Higher Technologies in TDD

To overcome these limitations, new drug delivery technologies have been created to increase drug permeability, bioavailability, and targeted delivery. These technologies enable larger molecules, hydrophilic molecules, and biologics to penetrate the skin, creating better therapeutic effects. In addition, new-generation TDDS enhance drug stability, reduce the dosing frequency, and increase patient convenience.

2. ADVANCED TECHNOLOGIES

2.1. MICRONEEDLES

Microneedles (MNs) are small, needle-like devices that are generally smaller than 1 millimeter in size. They are designed to penetrate the outer skin layer (the stratum corneum) to allow drugs and vaccines to be delivered through the skin barrier. Microneedles contain a chamber for holding medications and a small protrusion in their design. The first microneedle was successfully developed and utilized in the 1990s [11].



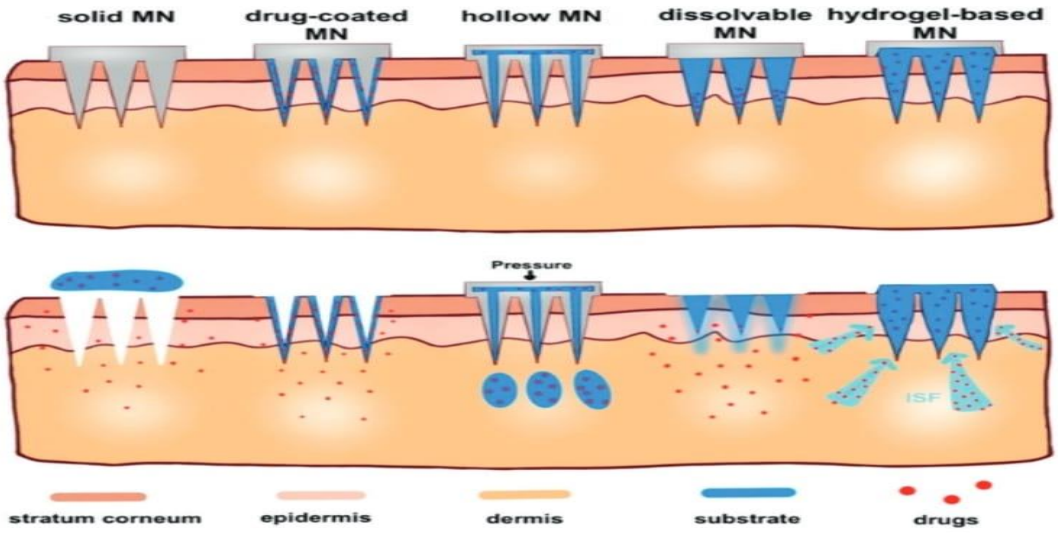


Fig. 2.Types of Microneedles

Advantages

- Minimally Invasive: Enters only the surface of the skin, causing less pain and discomfort than regular needles [17]
- Improved Drug Delivery: Allows for transdermal delivery of bigger molecules, including proteins and vaccines, that normally cannot penetrate the skin barrier efficiently [18]
- Targeted Delivery: Microneedles may be engineered for the targeted delivery of drugs to precise locations in the bone, facilitating local treatment while avoiding systemic side effects[19]
- Programmable Release Profiles: Microneedles can be designed to deliver controlled and sustained release of therapeutic agents, which can improve treatment efficacy and patient compliance[20]

Types of Microneedles	Materials	Mechanism of action	Preparation Methods	Drug	Application (Disease)	Reference
Solid microneedles	Titanium,Silicon,Stain less steel and other polymer materials insoluble in water	Does not contain drugs and leaves micropores in the skin during use,The active drug components penetrate the skin through these micropores, belonging to passive transport.	Etching process, mechanical cutting.	Hyaluric Acid	Osteoarthritis	[12]
Coated microneedles	Metal or polymer materials	After insertion into the skin,the drug coating dissolves from microneedles and quickly enters the tissue for one-step administration.	Dip coating method and spraying method.	Lidocaine	Muscle Pain	[13]
Hollow microneedles	Polymer materials ,silicon, glass	The drug penetrates into the skin under pressure, acting like a microsyringe.	Lithography technology	Botulinum toxin	Muscle spasms	[14]
Dissolving microneedles	Biodegradable polymers(e.g.,maltose, carboxymethyl cellulose)	After insertion into the skin, the needle tip matrix remains in the skin while the drug, is released, requiring, only a one-step application.	Fusion method and casting method.	Methotrexate, Diclofenac	Psoriasis	[15]
Hydrogel-forming microneedles	Expandable hyperlinked polymer	By absorbing, tissue fluid and expanding, in the skin, porous microducts are formed through which drugs can be diffused into the skin microcirculation.	Vacuum method and freeze drying method.	Insulin	Diabetic wound	[16]

Table.1.Types of Microneedles

Limitations

- Restricted Drug Loading Capacity: The micrometer-scale geometry of microneedles has limited drug loading capacity, and this may be inadequate for the drug requirements in some therapies. This can be overcome by combining external drug reservoirs or optimizing microneedle geometries.
- Variability in Skin Penetration: Microneedles' efficacy may be variable with respect to skin thickness and condition, potentially causing inconsistent drug delivery among different patients or even in different regions of the same patient's skin.
- Incomplete Penetration Potential: In irregular or uneven skin surfaces, microneedles do not penetrate fully, which can limit drug delivery efficiency and therapeutic efficacy.
- Manufacturing Issues: Fabrication of microneedles involves significant engineering and quality control to guarantee uniformity and functionality, making it difficult for mass production[21][22]

2.2 IONTOPHORESIS

Iontophoresis is a method of transdermal drug delivery that facilitates the passage of charged drug molecules through the skin with the aid of a low electrical current. to propel charged molecules of medication through the skin and into deeper tissues. It is widely applied in physical therapy and sports medicine to relieve musculoskeletal inflammation and pain [23].

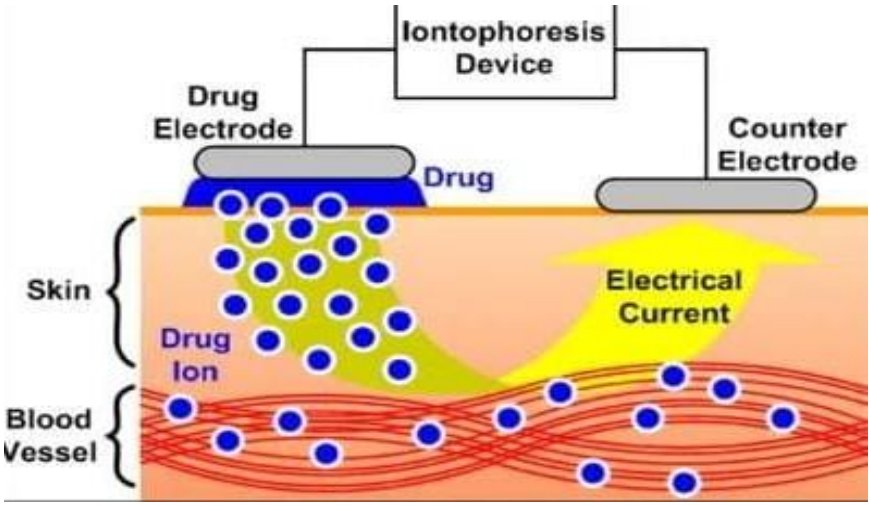


Fig. 3. Transadermal drug delivery by Iontophoresis

Mechanism of Action

Iontophoresis is based on the mechanism of electro-rejection (ER) and electro-osmosis (EO). Drug molecules charged by the electric field are driven across the skin by the electricity, which repels same charge particles (ER), while neutral or weakly charged particles are displaced by the solvent flow created by the current (EO) [24].

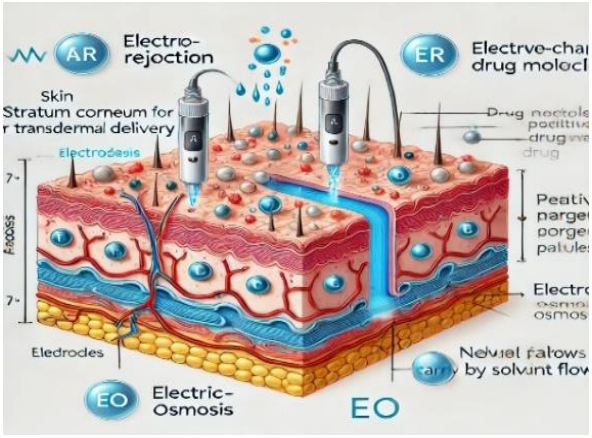


Fig. 4. Mechaism of Action

Advantages

- Improved Drug Delivery Efficiency: Iontophoresis has the ability to increase the delivery of drugs with limited skin permeability, enabling successful transdermal delivery of both ionic and non-ionic drugs.
- Controlled Release: The current of electricity may be regulated in order to govern the rate of drug delivery, giving a more accurate and controlled release profile.
- Less Biological Variability Dependence: In contrast to most conventional drug delivery systems, iontophoresis is less dependent on biological properties like the thickness of the skin and hydration, and thus, a more consistent drug delivery method [25].

Limitations

- Device Dependence: Iontophoresis needs specialized equipment and a power source, which may restrict its availability and raise costs.
- Skin Irritation: Electrical current use for extended periods could lead to skin irritation or discomfort in certain patients, requiring careful observation [26].

2.3 VESICULAR SYSTEM

Vesicular systems are sophisticated carriers aimed at improving drug delivery across the skin by breaching the barrier presented by the stratum corneum. Vesicular systems entrap drugs in bilayered or multilayered forms, enhancing drug stability, bioavailability, and controlled release.

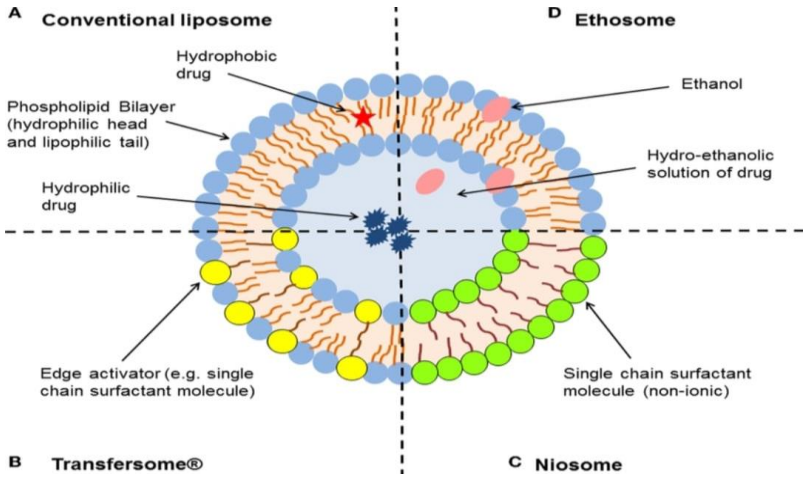


Fig. 5. Structures of various somes

Ethosomes

Ethosomes consist of vesicles that contain phospholipids, large levels of ethanol (20–45%), and water[27] .The mode of action includes destruction of the SC's lipid organization, disruption of intercellular lipids leading to cell death, and interference with the phase transition temperature of the SC[28].Some ethosomes are attached to the SC, while others pass through the intercellular space, releasing the drug on penetration[29].They have better drug entrapment compared to conventional liposomes and very good stability owing to ethanol's preservative action[30] . Safety issues do arise, though, since some patients may develop an allergic reaction to ethanol or other constituents of ethosomes. Ethosomes are used in the treatment of diseases like cerebral infarction[31], gout[32], melanoma[33] and myocardial ischemia[34].

Transferosomes

Transferosomes or shape-shifting liposomes are vesicles that contain phospholipids and edge activators (EAs) and improve flexibility and deformability of the membrane[35]. Penetration of transferosomes is facilitated by flexibility of the membrane, hydrophilicity, and integrity of vesicles, while permeability gradients propel vesicles into lower strata of skin[36][37]. They modify the composition of intercellular lipids in the SC to increase permeation of drug[38] . Transferosomes are very deformable, highly permeable in the skin, and transdermally effectively deliver drugs, which renders them useful for preclinical and clinical studies[39] . Yet they induce irritation to the skin as a result of EAs and impure phospholipids and are chemically unstable due to their sensitivity to oxidative degradation and external factors[40][41][42]. Transferosomes are employed as transdermal drug delivery systems (TDDSs) in the treatment of tumors, inflammation, and dermatosis[43][44][45].

Liposomes

Liposomes are phospholipid and cholesterol-containing spherical vesicles that can encapsulate hydrophilic and lipophilic drugs[46][47]. Their amphiphilic structure makes them good carriers for molecules of varying polarities[48]. Liposomes interact with SC lipids, breaking the lipid layer and increasing transdermal drug delivery[49][50].Their sticking to SC lipids facilitates mixing with the SC lipid layer, facilitating localized drug release[51].These vesicles are biocompatible, biodegradable, and suitable for topical and transdermal drug delivery[52].However, their penetration into deep skin layers and systemic circulation is restricted, and they are prone to degradation, including aggregation, flocculation, fusion, agglomeration, change in size, and loss of drug[53]. Liposomes are employed in the treatment of tumors, rheumatoid arthritis, fungal infections, and other diseases[54][55].

Niosomes

Niosomes are spontaneously assembled vesicles composed of nonionic surfactants, cholesterol, and other amphiphilic compounds[56][5] . Niosomes increase permeability, solubility, and bioavailability, suppress p-glycoprotein, and decrease hemolysis and cell surface irritation[58][59] The vesicles give greater skin penetration, enhanced bioavailability and stability of drugs, prolonged release of drugs, lower toxicity, and strong surface binding[60][61].Sterilization, however, poses problems since elevated temperatures can destabilize the vesicle structure, although preparation under sterile conditions will help to circumvent this problem[62].Niosomes have applications in the treatment of diabetes[63], Alzheimer's disease[64], wound healing[65], actinic keratosis[66], and other diseases.

2.4 SONOPHORESIS (ULTRASOUND ENHANCED DELIVERY)

Sonophoresis employs low-frequency ultrasound waves to enhance the permeability of the skin so

that drugs penetrate deeper into tissues. It is a non-invasive process and offers a targeted method for delivering therapeutic agents directly to the site of injury or inflammation[67] .

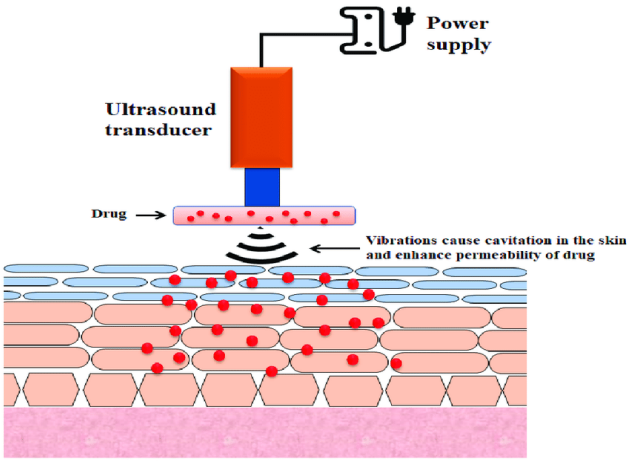


Fig. 6. Schematic of the fundamental design of ultrasound enhanced delivery device.

Mechanism of action

Cavitation is the major mechanism in sonophoresis, which is the formation, growth, and implosive collapse of bubbles in the interstitial fluid of the skin under the influence of ultrasound. This action breaks down the skin barrier, allowing for drug transport across the stratum corneum.Thermal effects are also important, as there is the generation of localized heat caused by ultrasound that increases drug diffusion through increased molecular kinetic energy and decreased skin viscosity. Localized heat tends to alter the structure of the skin temporarily, making it more permeable. Also, mechanical disruption happens when vibrations in the form of ultrasound waves result in breaking the lipid bilayers of the stratum corneum and temporarily opening pores for drug diffusion. The synergy between these mechanisms creates a tortuous route for drug molecules, facilitating their diffusion, particularly for hydrophilic and larger molecules. The incorporation of ultrasound contrast agents (UCAs) also enhances cavitation activity, increasing permeability of the skin without damaging it, and sonophoresis is a promising method for transdermal drug delivery[68] .

Advantages

- Sonophoresis is a needleless, non-invasive drug delivery process, obviating pain and minimizing discomfort.
- Allows direct delivery of anti-inflammatory medication to areas of inflammation.
- Facilitates enhanced therapeutic outcomes through improved permeability of skin.
- Facilitates efficient delivery of hydrophilic and large molecules.
- Reduces systemic side effects and enhances patient compliance owing to ease of administration.

Limitations

- Drug Selection: All drugs cannot be used for sonophoresis; the drug should penetrate the skin barrier.
- Skin Integrity: Compromised or diseased skin can change the safety and efficacy of the procedure.
- Equipment Dependence: Is dependent on specialized ultrasound equipment and skilled manpower, making it inaccessible and more expensive.
- Ultrasound exposure can result in skin discomfort or irritation.

Drugs Frequently Employed

a. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- E.g., Diclofenac, Ibuprofen, Ketoprofen.
- Decrease pain and inflammation.

b. Corticosteroids

- E.g., Hydrocortisone, Dexamethasone.
- Affect inflammation in serious conditions.

c. Other Agents

Muscle relaxants or local anesthetics such as lidocaine can also be employed.

2.5 ELECTROPORATION

Electroporation is a physical improvement method involving the application of brief, high-voltage electrical pulses to form temporary pores in the cell membranes of biological tissues. It is a very useful method in the context of transdermal drug delivery since it can allow penetration of small and large molecules through the skin[69][70] .

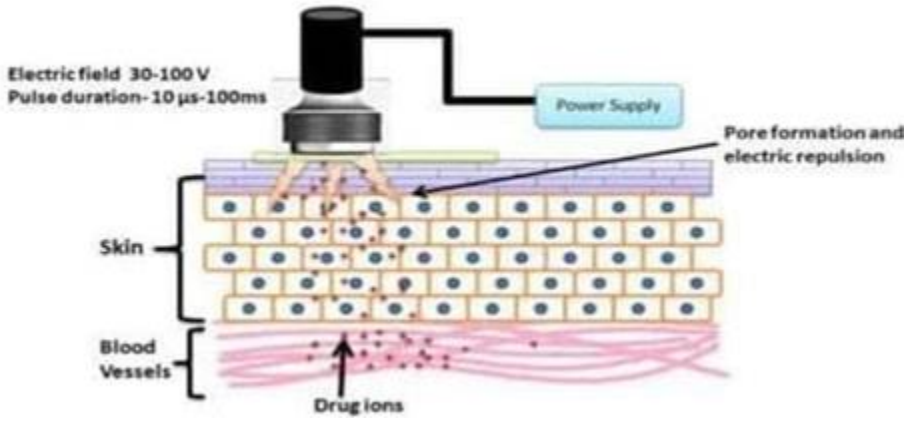


Fig. 7.Illustrates the process of electroporation

Mechanism of action

- Pulse Application: Electroporation is the delivery of a succession of brief pulses of electricity onto the skin that briefly disturbs the lipid bilayer of cell membranes in the stratum corneum.
- Pore Formation: The electric pulses result in the creation of hydrophilic pores that generate temporary routes for the drug molecules to move through the skin barrier.
- Reversibility: The pores that are induced tend to be reversible, and the skin can regain its barrier function once the electrical treatment has stopped[71] .

Advantages

- Increased Permeability:
- Strongly increases the transdermal absorption of a wide range of drugs, such as macromolecules and charged molecules.Adjustable Parameters: Electroporation parameters (intensity, duration, frequency) may be adjusted to regulate the rate and degree of drug permeation.
- Low Damage: Produces less damage to the skin than other techniques, which makes it a safer method for drug delivery.
- Wide Applicability: Suitable for a range of drugs, such as hydrophilic, lipophilic, and charged molecules, which would otherwise have low skin permeation properties [72].

Limitations

- Transient Effects: Pore formation is transient; increased permeability lasts for a few hours only before the barrier of the skin recovers.
- Collateral Cell Damage: Can produce temporary disruption and localized tissue damage through cell death.
- Patient Discomfort: High-voltage pulses can cause discomfort, pain, or muscle contractions during the procedure.
- Equipment Complexity: Needs specialized equipment and trained staff, hence less accessible than simpler procedures.
- Variable Efficacy: Effectiveness is different in every individual and relies on drug properties

and skin features, resulting in variable outcomes,

- Limited Sustained Release: Short-lived pores limit sustained drug release, frequently requiring repeated treatment[73][74][75].

Applications

- Gene Therapy: Electroporation improves plasmid DNA delivery in muscle, supporting anti-inflammatory cytokine gene therapy.
- Targeted Drug Delivery: Merges methotrexate with electroporation for safer treatment of rheumatoid arthritis
- Cell Therapy: Enables gene delivery in muscle tissue for regenerative medicine
- Immune Modulation: Alters immune responses through plasmid DNA delivery for autoimmune diseases.
- DNA Vaccines: Facilitates intramuscular gene delivery for treatment of autoimmune diseases[76][77][78][79].

2.6 PRODRUG

Prodrugs are pharmacological agents which are initially less active or inactive. They have to undergo metabolic conversion in the body to exhibit pharmacological activity. This usually happens through enzyme-catalyzed reactions[80] .

Mechanism of Action

- Chemical Modification: Prodrugs are prepared by modifying an active drug chemically so that some desirable properties, i.e., solubility and stability, can be enhanced.
- Administration: The prodrug is given through different routes (oral, transdermal, etc.). For instance, prodrugs can be prepared for application in transdermal drug delivery systems (TDDS) to facilitate skin penetration and absorption.
- Metabolism: Upon entry into the body, the prodrug is metabolically converted:
- Enzymatic Hydrolysis: Enzymes (e.g., esterases or other metabolic enzymes) catalyze the process, cleaving the prodrug to its active state.
- Release of Active Drug: Due to this conversion, the active drug gets released, which can then exercise its therapeutic actions[81][82] .

Advantages

- Enhanced Solubility:Prodrates increase the solubility of low-solubility drugs, thereby boosting their bioavailability when administered.
- Greater Stability: They tend to be more chemically stable than the active drug, minimizing degradation on storage and shelf life.
- Targeted Delivery: Prodrives can facilitate targeted delivery to targeted tissues and organs to avoid systemic exposure and decrease potential side effects.
- Increased Absorption: Changes in their characteristics may enhance their ability to pass through biological barriers (e.g., skin, gastrointestinal tract), which is relevant to transdermal delivery[83][84] .

Limitations

- Conversion Variability: Metabolic conversion rates can differ significantly from person to person because of genetic, age-related, or other reasons, resulting in unpredictable therapeutic effects.
- Potential Toxicity: Fast conversion of prodrugs into active forms may lead to toxic effects, making dosing and monitoring difficult.
- Bioavailability Problems: Not all prodrugs are metabolized well in the body, which might lower their potency, especially among patients with erratic enzymatic function[85].

Prodrug	Types	Active Form	Mechanism	Advantages
Nabumetone	NSAID (Prodrug)	6-MNA (6-Methoxy-2-naphthylacetic acid)	Converted in the liver to 6-MNA, inhibiting COX-2 > COX-1,	Less GI toxicity, long half-life, lower ulcer risk

			reducing inflammation	
Sulindac	NSAID (Prodrug)	Sulindac sulfide	Converted in the liver to sulindac sulfide, inhibiting COX-1 and COX-2	Reduced GI side effects, anti-inflammatory & analgesic effects
Aspirin (Acetylsalicylic Acid)	NSAID (Prodrug)	Salicylic acid	Hydrolyzed to salicylic acid, inhibiting COX enzymes, reducing prostaglandin synthesis	Well-established anti-inflammatory effects, cardioprotective at low doses
Prednisone	Corticosteroid (Prodrug)	Prednisolone	Converted in the liver to prednisolone, binding to glucocorticoid receptors to suppress inflammation	Reduced systemic side effects, used in RA & lupus
Cortisone Corticosteroid (Prodrug)	Corticosteroid (Prodrug)	Hydrocortisone	Converted in the liver to hydrocortisone, suppressing immune response & inflammation	Used in autoimmune disorders, less potent than prednisone but effective
Leflunomide	DMARD (Prodrug)	Teriflunomide	Metabolized into teriflunomide, inhibiting dihydroorotate dehydrogenase, reducing immune cell proliferation	Effective in RA, long half-life allowing less frequent dosing
Sulfasalazine	DMARD (Prodrug)	5-Aminosalicylic Acid (5-ASA) &Sulfa pyridine	Broken down in the colon to active components, modulating immune response & reducing	Used in RA & ankylosing spondylitis, anti-inflammatory & immunosuppressive effects.

			inflammation	

Table. 2.Examples of Prodrug[86,87]

3. RECENT REPORTED CASESTUDYFOR TRANSDERMALDRUGDELIVERYSYSTEM

Recent developments in transdermal drug delivery systems (TDDS) have resulted in cutting-edge technologies to enhance drug permeability, patient compliance, and controlled release. Some of the latest technologies and recent case studies illustrating their applications are as follows:

3.1 MICRONEEDLE

Case study.1

Introduction: Alopecia areata (AA) is a prevalent autoimmune disorder causing non-scarring loss of hair, most common in children. Its pathogenesis is mediated by T cells and environmental conditions, complicating its treatment, particularly for resistant patients to standard therapies.

Objective: This research seeks to assess the efficacy of microneedling and compound betamethasone in the treatment of extensive alopecia areata in a child patient, monitoring hair regrowth and general safety following a 6-month course of treatment.

Aspects	Details
Case Presentation	3-year-old female with progressive hair loss for 2 months after stress; previous treatments ineffective. leading to almost complete hair loss in multiple areas.
Method	Treated with microneedling + compound betamethasone for 6 months, applying lidocaine prior to sessions.
Results	Almost complete hair regrowth after 6 months; no adverse reactions reported.
Discussion	Highlights microneedling's potential to enhance drug efficacy in severe alopecia areata in children. The successful outcome suggests that microneedling may improve drug penetration and efficacy, potentially leading to enhanced regeneration of hair follicles.
Conclusion	Supports microneedling + betamethasone as an effective treatment for severe alopecia areata; further research needed.

Table. 3.Case study on Alopecia areata[88][89]

Case study.2

Introduction: Radiofrequency (RF) microneedling is a minimally invasive method of skin tightening and cellulite reduction, more commonly used in body contouring.

Objective: This case study assesses the efficacy of RF microneedling in enhancing thigh skin laxity as a result of severe weight loss, making it a non-surgical option to consider.

Aspects	Details
Case Presentation	A 39-year-old woman (Fitzpatrick Skin Type II) presenting with skin laxity and cellulite on thighs following weight loss of 47.7 kg.
Method	Two treatments with subcutaneousRF microneedling (PROFOUND™) on bilateral thighs, measured with Hexsel and Dal'Forno Scale; total score was 14.
Result	Five-point decrease in cellulite score (14 to 9) following treatment; depth of depressions and skin laxity were improved. Patient was satisfied.
Discussion	RF microneedlingis an innocuous, noninvasive procedure. It can cause collagen contraction and neocollagenesis but has not achieved surgical effectiveness levels.
Conclusion	RF microneedling is a good option with low side effects to treat skin laxity and cellulite; more studies required.

Table. 4.Case study on RF for thigh skin laxity and cellulite reduction[90][91]

3.2 IONTOPHORESIS

Case study.1

Introduction: Insulin-like growth factor 1 (IGF-1) is a vital protein for growth and development, indicated for treating growth failure in pediatric patients. Its typical administration via subcutaneous injections poses compliance challenges due to discomfort and infection risks. This study focuses on the stability of IGF-1 during transdermal delivery, particularly its degradation by skin enzymes.

Objective: The study aims to assess IGF-1 stability in porcine and human skin and evaluate whether protease inhibitors can enhance its stability during transdermal delivery through iontophoresis, addressing issues related to enzymatic degradation and improving therapeutic efficacy.

Aspects	Details
Methodology	**Sample Preparation**: IGF-1 was cloned, expressed, and purified in-house. Porcine skin samples (250 μm and 750 μm) obtained from a local abattoir; human skin collected immediately after surgery. Stability testing involved placing IGF-1 solution in contact with skin samples and analyzing for concentration after 8 hours using an ELISA kit.
	IGF-1 concentration decreased significantly (to 23.63 ± 2.48% and 21.58 ± 2.62% for 250 μm and 750 μm thick porcine dermis, respectively).Pre-heating skin at 60 °C for 2 min improved stability.PMSF alone did not enhance stability, but a protease inhibitor cocktail prevented degradation. Recovery with cocktail: 103.87 ± 9.15% (porcine) and 99.31 ± 9.98% (human).

Conclusion	Incorporating protease inhibitor cocktails in formulations can enhance the stability and effectiveness of IGF-1 during iontophoresis and transdermal delivery, improving treatment for dermatological conditions.[92,93,94]

Table. 5.Case study onstability of Insulin-like growth factor 1(IGF-1)[92][93][94]

Case study.2

Introduction: Pressure sores, or decubitus ulcers, affect about 9% of hospitalized patients and up to 25% of nursing home residents, especially within the first two weeks of hospitalization. The risk is higher in patients with neurological impairments, with a lifetime risk of approximately 85%. Due to rising antibiotic resistance, alternative antibiotic delivery methods are needed. This case study evaluates the effectiveness of gentamicin sulphate iontophoresis in managing decubitus ulcers.

Objective: To assess the efficacy of gentamicin sulphate iontophoresis in reducing wound surface area and bacterial growth in a patient with a decubitus ulcer, while enhancing healing through combined topical treatment and traditional wound dressing.

Aspects	Details
Participant	27-year-old male, diagnosed with mild head injury from a motor vehicle accident, developed pressure sore on the left gluteal region.
Wound Characteristics	Stage 2 pressure sore, initial surface area: 9.20 cm^2, increased to 14.80 cm^2 after 4 weeks before treatment began.
Treatment Protocol	Gentamycin sulphate iontophoresis for 15 minutes, three times a week for five weeks; along with traditional saline-wet-to-moist wound dressing.
Treatment Method	Iontophoresis used an Interrupted Direct Current (IDC) at 2.72 mA intensity; 1.7 mg gentamicin sulphate per gram of ointment applied on active electrode.
Goals of Treatment	Reduce wound surface area, manage bacterial growth.
Bacterial Findings	Initially cultured Staphylococcus aureus, Klebsiella species, and Proteus vulgaris. Staphylococcus aureus and Klebsiella sensitive to gentamicin.
Outcome	After 5 weeks, wound surface area reduced by 65.7% (initially 14.81 cm^2 to 5.10 cm^2), resolution of purulent exudates, and nearly complete epithelial cell formation.
Conclusion	Gentamycin sulphate iontophoresis as an effective adjunct treatment for decubitus ulcer healing.

Table. 6. Case study on decubitus ulcers[95][96]

Characteristics	1st week	2nd week	%decrease
Surface Area(cm^2)	14.81	5.10	65.7
Type of exudates	Purulent	No exudate	-

Appearance	Moderately clean	Clean	-
Edge	Well-defined	Indistinct	-
Bacterial growth	Very heavy growth	Scanty growth	-

Table. 7 Decubitus ulcer Characteristics Over Time[95][96]

3.3 VESICULAR SYSTEM

Liposomes

Introduction: Managing relapsed ovarian cancer becomes increasingly challenging with each line of chemotherapy, as effectiveness of platinum-based therapies diminishes. This case study focuses on the combination of Trabectedin and pegylated liposomal doxorubicin (PLD) as a third-line treatment for platinum-sensitive relapsed ovarian cancer.

Objective

The objective is to demonstrate the complexities of treatment selection in such cases and to highlight the safety and efficacy of the Trabectedin + PLD regimen in improving patient outcomes and potentially restoring platinum sensitivity.

Aspects	Details
Case Presentation	48-year-old woman with stage IVa high-grade serous ovarian cancer; previous treatment included carboplatin and paclitaxel, followed by maintenance therapy with bevacizumab. After a 21-month progression-free interval, the disease progressed.
Method	Treated with nine cycles of Trabectedin + PLD due to limited platinum sensitivity (PFI 9 months).
Results	No evidence of disease after treatment; CA-125 decreased; ECOG performance status improved to 0.
Discussion	Trabectedin + PLD was effective and may restore platinum sensitivity while maintaining a good safety profile.
Conclusion	Trabectedin + PLD is a viable option for platinum-sensitive relapsed ovarian cancer, improving quality of life and treatment response.[97,98]

Table. 8. Case study onplatinum-sensitive relapsed ovarian cancer [97][98]

Case study.2

Introduction: Cryptococcus neoformans CNS infections are severe and often fatal in HIV-infected patients, despite existing antifungal therapies. Current guidelines favor liposomal amphotericin B, but treatment outcomes are frequently inadequate.

Objective: This report aims to present two cases demonstrating the successful use of posaconazole as salvage therapy combined with standard treatments, highlighting its effectiveness and potential for long-term maintenance in preventing recurrent infections.

Aspects	Details
Case presentation	A 45-year-old HIV-1 infected male with severe headaches and a CD4 count of 4 cells/ml presented with positive cryptococcal antigen.
Method	Initial treatment with liposomal amphotericin B (5 mg/kg/day) failed after 30 days due to lack of improvement and severe side effects. Therapy was changed to include posaconazole (800 mg/day) and reduced flucytosine (100 mg/kg/day).
Results	After 100 days of therapy, the patient showed significant improvement, with negative cryptococcal antigen and normal cerebrospinal fluid (CSF). He remained recurrence-free after 8 months on maintenance therapy with posaconazole (400 mg bid).
Discussion	The case illustrates challenges in managing refractory cryptococcal meningitis in HIV patients, highlighting the synergy of posaconazole with other antifungal therapies.
Conclusion	Posaconazole serves as an effective salvage and maintenance therapy for cryptococcal meningitis, warranting further exploration of combination treatment strategies.[99,100].

Table.9. Case study on Cryptococcus neoformans CNS infections[99][100]

3.4 ULTRASOUND (SONOPHORESIS)

Case study.1

Introduction: Thyroid tuberculosis (TT) is a rare form of tuberculosis affecting the thyroid gland, often leading to misdiagnosis due to its non-specific clinical and imaging features. Due to its low incidence, TT is frequently overlooked, complicating timely diagnosis and treatment.

Objectives:

This study aims to present a case of TT where diagnosis was confirmed through ultrasound-guided core-needle biopsy and to highlight the role of ultrasound in monitoring the disease's progression and treatment response.

Aspects	Details
Case Presentation	45-year-old male with a painless swelling in the left neck, gradually increasing over two weeks, weight loss, no past TB history
Method	Ultrasound revealed a hypoechoic mass; US-guided core-needle biopsy performed after non-diagnostic FNA. Follow-up US

	monitored treatment.
Results	Initial mass size was 34x27x24 mm, grew to 65x35x38 mm. CNB showed granulomatous inflammation; treated with antituberculosis medication, reducing size to 16x10x12 mm.
Discussion	TT is rare, often misdiagnosed. US is vital for accurate diagnosis and monitoring, preventing unnecessary surgeries.
Conclusion	Ultrasound plays a critical role in the diagnosis and management of thyroid tuberculosis. Dynamic ultrasound monitoring is key in managing thyroid tuberculosis and assessing treatment response.

Table. 10. Case study on Thyroid tuberculosis[101][102]

Case study.2

Introduction: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, with prevalence rates reported between 1.55% and 14.4%. Diagnosed primarily through electrophysiological studies and increasingly through ultrasound imaging, CTS is often treated with minimally invasive carpal tunnel release in cases not responding to conservative management. This surgical approach boasts advantages such as earlier recovery, yet concerns about incomplete decompression persist.

Objective:

The objective of this case study is to introduce a novel application of dynamic ultrasound imaging to evaluate the adequacy of median nerve decompression after minimally invasive carpal tunnel release and to demonstrate the technique's effectiveness in enhancing surgical outcomes.

Aspects	Detail
Case Presentation	Two patients with carpal tunnel syndrome: 39-year-old female (numbness for 4 years) and 56-year-old female (numbness for 3 years); both had prior treatment failures.
Method	Minimally invasive carpal tunnel release with intraoperative dynamic ultrasound to evaluate median nerve decompression.
Results	Patient 1: Boston symptom severity scale improved from 32 to 11, VAS from 7 to <3. Patient 2: Scale improved from 28 to 21, VAS from 6 to 2.
Discussion	Dynamic ultrasound confirms complete decompression, addressing a major concern in surgery. It helps prevent incomplete releases and vascular injuries.
Conclusion.	Dynamic ultrasound effectively assesses carpal tunnel decompression and warrants further prospective studies to enhance surgical

	outcomes.

Table. 11. Case study onCarpal tunnel syndrome (CTS) [103]

3.5 ELECTROPORATION

Case study.1

Introduction: Irreversible Electroporation(IRE) offers advantages over traditional thermal ablation methods, especially in areas near vital structures, as it does not depend on heat. However, the delivery of electrical pulses carries a risk of inducing cardiac arrhythmias, particularly when treating lesions close to the heart.

Objective: The objective of this case study is to assess the safety of IRE when applied to metastatic liver lesions located near the heart and to highlight the importance of cardiac synchronization during the procedure to minimize the risk of arrhythmias.

Aspects	Details
Participants	48-year-old man with metastatic liver lesions after rectal adenocarcinoma resection; prior chemotherapy halted due to adverse events; referred for IRE treatment.
Method	Ultrasound-guided IRE using NanoKnife; general anesthesia with neuromuscular blockade; ECG synchronization (AccuSync 72) to deliver pulses safely
Result	Episode of ventricular extrasystoles occurred due to synchronization device failure, with pulses delivered during the vulnerable T wave.
Discussion	Highlights risks of IRE near the heart; emphasizes distance of 1.7 cm to prevent arrhythmias; raises concerns about reliability of synchronization devices
Conclusion	Caution recommended for IRE near the heart due to synchronization failure risk; avoid procedures if the heart is within the reversibly permeabilized area.[104’105]

Table. 12. Case study onIrreversible Electroporation (IRE) [104][105]

Case study.2

Introduction: Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels. Insulin therapy is a common treatment approach, but it can cause hypoglycemia, weight gain, and other side effects. Electroporation-mediated transdermal insulin delivery has emerged as a promising alternative.

Objective: The study aimed to explore how exercise influences insulin resistance in Type 2 Diabetes Mellitus (T2DM)by examining the role of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and its interaction with microRNA-382-3p and resistin to inform therapeutic strategies.

Aspects	Details
Case Presentation	A 45-year-old male patient with type 2 diabetes mellitus presented with poorly controlled glucose levels despite insulin therapy. He was administered electroporation-mediated transdermal insulin delivery using a custom-made device.
Method	The patient underwent electroporation-mediated transdermal insulin delivery for 30 minutes, twice a day, for 7 days. Insulin doses were adjusted based on glucose levels.
Results	The patient showed significant improvement in glucose control, with a reduction in HbA1c levels from 9.5% to 7.2%. Insulin doses were reduced by 30%. No adverse effects were reported.
Discussion	This case report demonstrates the potential of electroporation-mediated transdermal insulin delivery in improving glucose control and reducing insulin doses. Further studies are needed to confirm these findings.
Conclusion	Electroporation-mediated transdermal insulin delivery may be a promising treatment option for diabetic patients. Larger studies are needed to establish its safety and efficacy.[106,107].

Table. 13. Case study onDiabetes mellitus[106][107]

4. Challenges and Future Prospects

Advanced TDDS technologies, including nanotechnology, 3D printing, and artificial intelligence, face significant challenges despite their potential to revolutionize drug delivery. The primary hurdle is overcoming the skin barrier, particularly the stratum corneum, which limits drug penetration. While nanoparticles, microneedles, and penetration enhancers have been developed, ensuring efficient drug transport without causing skin irritation or systemic toxicity remains a concern. Additionally, formulation stability and large-scale manufacturing pose difficulties, as complex carriers like liposomes and polymeric nanoparticles require precise conditions to maintain efficacy. Regulatory hurdles further complicate adoption, with stringent safety evaluations needed for novel materials. Patient compliance, influenced by factors such as patch adhesion, irritation, and dose consistency, is another critical factor. The high cost of these advanced technologies, along with challenges in integrating AI-driven optimization into existing TDDS, also limits widespread implementation.

Despite these challenges, the future of TDDS is promising, with nanotechnology playing a crucial role in enhancing drug bioavailability and controlled release. Polymeric nanoparticles and lipid-based carriers are expected to improve penetration and therapeutic efficacy while minimizing side effects. 3D printing offers the potential for personalized transdermal patches with precise drug dosages, allowing on-demand

production at healthcare facilities. AI and machine learning will further optimize TDDS by predicting ideal formulation compositions and enhancing patient adherence. The evolution of microneedles, particularly dissolvable and biodegradable variants, opens new possibilities for painless transdermal delivery, including for biologics and vaccines. Additionally, smart patches integrated with biosensors could enable real-time monitoring and on-demand drug release, paving the way for more efficient and patient-centered drug delivery solutions. As research continues to refine these technologies, TDDS is set to become a key pillar in precision medicine, offering safer and more effective alternatives to traditional drug administration methods.

5. CONCLUSION

Transdermal Drug Delivery Systems (TDDS) offer a non-invasive and controlled method of administering drugs through the skin, providing advantages such as improved bioavailability, reduced side effects, and enhanced patient compliance. This review outlines advanced technologies including microneedles, iontophoresis, vesicular carriers (like ethosomes, transferosomes, liposomes, and niosomes), sonophoresis, electroporation, and prodrugs that have significantly improved the effectiveness of transdermal delivery. These technologies enhance drug penetration, stability, and targeted delivery, though they each come with certain limitations such as cost, formulation complexity, and device dependency. Despite challenges like skin barrier resistance and regulatory issues, the integration of nanotechnology, artificial intelligence, and 3D printing holds great promise for the future. These innovations are expected to drive the development of personalized, efficient, and smart transdermal therapies, positioning TDDS as a vital component of next-generation drug delivery systems.

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