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Review Article

A Review on Transdermal Drug Delivery Systems: Transdermal Patches

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ABSTRACT

Transdermal Drug Delivery Systems (TDDS) have emerged as a pivotal facet of modern pharmacotherapy, offering a non-invasive route for systemic drug administration while enhancing patient compliance. This paper provides a comprehensive review of the historical evolution of TDDS, detailing its generational advancements and mechanisms of action. Various types of transdermal patches are explored, alongside their technical sophistication, advantages, and disadvantages. Key desirable features for effective transdermal patches are discussed, as well as potential adverse events associated with their use. The paper delves into the intricacies of skin and percutaneous absorption, highlighting the role of penetration enhancers and the multiple factors influencing transdermal permeability, including physiological and formulation characteristics. Conditions favoring and opposing the use of TDDS are examined, with a focus on drug selection, formulation strategies, and preparation methods. Evaluation techniques for assessing TDDS effectiveness are outlined, followed by an exploration of contemporary development approaches and advanced techniques aimed at enhancing TDDS performance. Finally, future directions and challenges facing the field are identified, underscoring the ongoing need for innovation in transdermal delivery technologies.

INTRODUCTION

A transdermal drug delivery system (TDDS) is a method of delivering medication through the skin for systemic effects. It typically involves the use of patches that contain a specific dose of the drug, which is absorbed into the bloodstream via the skin. This approach allows for the controlled

release of the drug over time, improving patient compliance and minimizing side effects compared to other routes of administration. Transdermal drug delivery systems (TDDS) offer an alternative to oral administration, providing sustained release of therapeutic agents and improving patient compliance.[1] TDDS is especially useful for patients unable to take oral medication, such as

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those experiencing vomiting or unconsciousness, and bypasses first-pass metabolism, reducing side effects associated with oral drugs.[2] However, TDDS efficacy depends on factors such as skin permeability, which varies among individuals, and the physicochemical properties of the drug.[3] While the market for TDDS is growing, challenges like skin irritation, variability in drug absorption, and optimizing drug delivery rates remain.[4] Adverse Despite progress, there is a gap in understanding how to enhance permeation while reducing adverse reactions. This review aims to explore the present scenario of TDDS, identify its advantages and disadvantages, and propose innovative strategies to optimize drug delivery, ensuring safety and improving clinical outcomes.

1. Skin Structure and Physiology

The human skin, the largest organ of the body, acts as a protective barrier while enabling transdermal absorption of substances. It comprises three main layers epidermis, dermis, and hypodermis. Each with distinct roles that influence skin function and drug permeability.[5]

1.1 Epidermis: A stratified squamous epithelium that varies in thickness from 0.06 mm to 0.8 mm, consisting of layers:

- **Stratum Corneum:** The outermost, dead keratinized cells, rich in lipids, provide a waterproof barrier and regulate permeability.
- **Stratum Lucidum:** Found mainly in thick skin, it offers additional protection.
- **Stratum Granulosum:** Keratinocytes undergo keratinization, enhancing skin defense.
- **Stratum Spinosum & Stratum Basale:** These layers house living cells that contribute to cellular renewal and melanin production, protecting against UV radiation. [6], [7]

1.2 Dermis: Located beneath the epidermis, the dermis contains dense connective tissue rich in collagen and elastin, and is home to blood vessels, nerves, and skin appendages like sweat glands and hair follicles, playing a critical role in thermoregulation and nutrient supply. [8]

1.3 Hypodermis (Subcutaneous Layer):

Composed of adipose and connective tissue, it insulates the body, stores energy, and provides cushioning. Larger blood vessels and nerves supply the skin with nutrients.[9], [10]

2. Skin Physiology

The skin regulates body temperature, contributes to sensory perception, and aids in vitamin D synthesis. The stratum corneum plays a crucial role as a barrier to penetration, yet drug absorption can effectively occur through two primary pathways (Figure-1):

2.1 Trans epidermal Pathway

The Trans epidermal pathway involves drug absorption through the skin's outermost layer, the stratum corneum, which acts as a complex multi-layered barrier.[11] This pathway can be further divided into two distinct routes:

- **Intra-cellular Route:** Drugs that are hydrophilic or polar solutes penetrate through corneocytes, the specialized skin cells. This route is effective for substances that can dissolve in water, allowing for their movement directly through the cellular structure.[12]
- **Inter-cellular Route:** In contrast, lipophilic or non-polar solutes navigate through the intercellular spaces between the skin cells. This route capitalizes on the continuous fatty matrix that characterizes the skin, enabling the



passage of substances that dissolve in fats. [13], [14]

utilizing tiny tunnels within the skin, facilitating the movement of specific substances. [15], [16]

2.2 Trans appendageal Pathway

The trans appendageal pathway allows drugs to pass through skin appendages, such as hair follicles and sweat glands. This route is akin to

- **Sweat Glands and Hair Follicles:** These structures provide alternative channels for drug delivery, potentially enhancing the absorption of certain compounds that may not permeate effectively through the stratum corneum. [17]

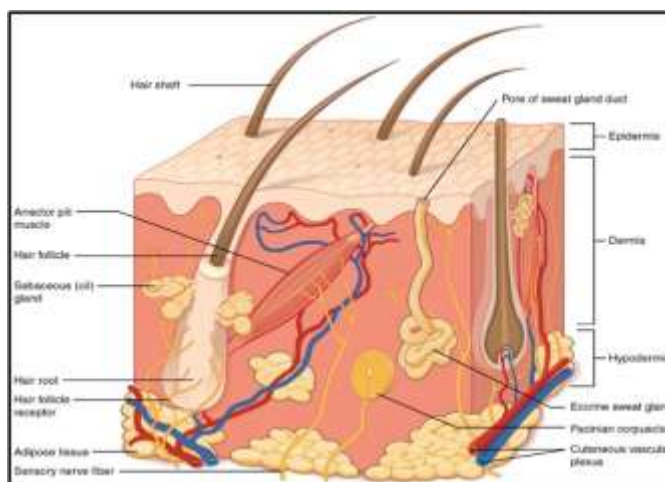


Figure 1: The Structure of human skin

3. Historical Background of Transdermal Drug Delivery Systems

The way of using the skin as a pathway for delivering medications spans thousands of years, with roots in ancient practices and evolving through modern science.

3.1 Ancient Practices

- **Egyptians (4000 BC):** Ancient Egyptians harnessed natural substances like henna and kohl for cosmetic and medicinal purposes. The Ebers Papyrus, dating back to 1500 BC, documents various remedies, including treatments for skin wounds using tiger nuts.
- **Galen's Cold Cream (circa 130-200 AD):** The Greek physician Galen formulated one of the first known creams, blending vegetable oil, beeswax, and water, to treat skin ailments.

- **Traditional Chinese Medicine:** Ancient Chinese practitioners also recognized the skin's potential for healing, employing herbal plasters and acupuncture to enhance therapeutic effects.[18]

3.2 19th Century Developments

- **Early Transdermal Ointments:** The 15th century saw the use of mercury-based ointments, like Unguentum hydrargyri, for syphilis. By the late 1800s, Paul Carl Beiersdorf had developed plaster formulations for skin disorders, including the notable Emplastrum belladonna. [19]

3.3 Foundations in the 20th Century

- **Accidental Intoxication Insights:** Incidents of skin poisoning, such as with phenol, highlighted the skin's permeability and

spurred interest in drug absorption through the skin.

- **First Commercial Product (1950s):** Nitrol® (2% Nitroglycerine Ointment) was the first significant transdermal product for angina, paving the way for more refined delivery methods.
- **Transderm Scop® (1979):** This was the first effective transdermal patch for scopolamine, successfully minimizing side effects compared to oral medications and proving the viability of the transdermal route for systemic delivery.
- **Expansion of Products (1980s-1990s):** Following its success, other products emerged, including Catapres TTS® for hypertension and various hormone patches like Estraderm® and Duragesic® for pain management.[20]

4. Generation of Transdermal Drug Delivery Systems [21], [22]

4.1 First Generation: Fundamental Innovations

The first generation of transdermal delivery systems has laid the groundwork for the transdermal patches currently used in clinical practice. These patches are designed as reservoirs, encased with an impermeable backing on one side and an adhesive layer on the other, which contacts the skin.[23] The ideal candidates for first-generation systems are low-molecular-weight, lipophilic compounds that demonstrate efficacy at low doses.[24] Such candidates are preferred particularly when transdermal delivery offers advantages over oral routes, such as low bioavailability, less frequent dosing, and consistent delivery profiles. Despite the initial

success and increasing public acceptance, the growth of this generation is anticipated to decline as the availability of suitable drugs diminishes (figure-2).

4.2 Second Generation: Enhanced Skin Permeability

The second generation of TDDS recognizes the need for enhanced skin permeability to broaden the range of applicable drugs. This generation employs various methods to disrupt the stratum corneum, thus facilitating drug transport.[25] Techniques such as chemical enhancers, iontophoresis, and non-cavitation ultrasound have been developed, but they often struggle to balance increased permeation with the protection of deeper tissues. For example, chemical enhancers can disrupt the stratum corneum's lipid bilayer but may lead to skin irritation. Iontophoresis employs low-voltage electrical currents to aid drug transport, while ultrasound enhances permeation but risks thermal damage to deeper tissues. Overall, the second generation has primarily advanced the delivery of small molecules, with limited success in macromolecule transport.[26]

4.3 Third Generation: Targeted Delivery and Macromolecule Penetration

The third generation represents a significant leap in transdermal technology, focusing on targeted disruption of the stratum corneum while protecting underlying tissues.[27] This generation utilizes innovative techniques such as electroporation, cavitation ultrasound, microneedles, thermal ablation, and microdermabrasion to deliver macromolecules, including therapeutic proteins and vaccines, effectively through the skin.[28] By localizing the effects to the stratum corneum, these methods allow for more aggressive strategies that enhance drug delivery without compromising safety.



Microneedles are a noteworthy advancement in this generation. These micro-structured devices can painlessly penetrate the skin, enabling the delivery of a variety of compounds, from small

molecules to proteins and vaccines. They have been shown to achieve therapeutic levels in clinical trials, demonstrating their potential for effective transdermal drug delivery.[29]

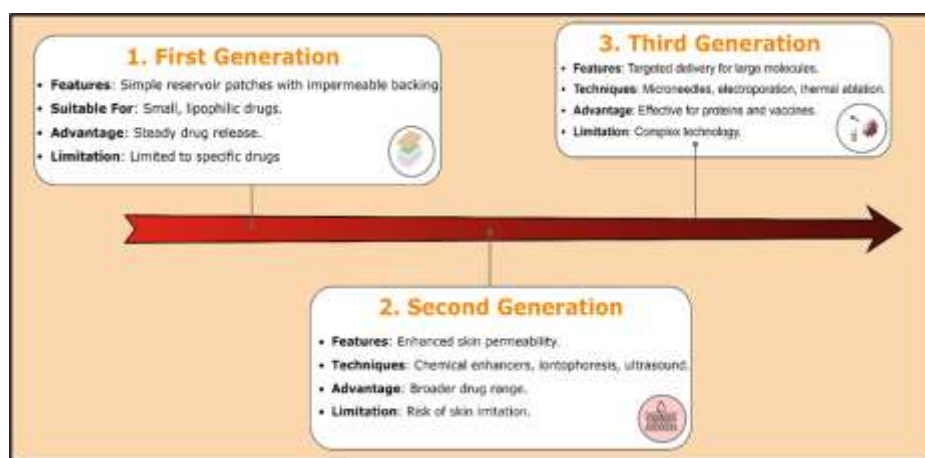


Figure 2: Generations of TDDS.

5. Transdermal Patches in the Present Scenario

Transdermal drug delivery (TDD) has seen substantial growth in recent years, becoming a key focus in non-invasive drug administration. Currently, more than 35 TDD products are available in the U.S. market, and there are around 16 distinct active ingredients that have been officially approved for use in transdermal delivery systems worldwide.[30] This rise is fueled by the demand for convenient, effective alternatives to oral and injectable drugs, offering steady, controlled drug release directly through the skin. [31]

These patches cover a range of therapeutic areas, with products for pain management, hormone therapy, cardiovascular issues, and more. Each product is tailored for specific conditions, and marketed under familiar brand names that reflect the system's purpose and benefits. As the popularity of TDD continues to grow, we can expect more innovations to address both existing and emerging therapeutic needs, demonstrating TDD's potential in modern medicine. [32], [33]

6. Mechanism of Transdermal Permeation [34], [35]

It refers to the movement of drug molecules into and within the biological environment, involving various processes of drug transport across cell membranes.

• Passive Diffusion

6.1 Fick's Law of Diffusion governs passive diffusion, where drugs move from an area of higher concentration to a lower concentration:

$$J = -D \times \frac{dC}{dx}$$

Where,

- **Flux (J):** Represents the quantity of drug that permeates through a unit area over a specific time.
- **Diffusion Coefficient (D):** Reflects how easily the drug can move through the skin.

- **Concentration Gradient** ($\frac{dC}{dx}$): The difference in drug concentration across the skin layers.

6.2 Factors Influencing Diffusion:

- **Molecular Size:** Smaller molecules generally have higher permeability. Molecules larger than 500 Da often face challenges in penetrating the stratum corneum.
- **Lipophilicity:** Drugs that are lipophilic (fat-loving) tend to partition into the lipid-rich stratum corneum more effectively than hydrophilic drugs.
- **Solubility:** A drug's solubility in both the formulation and the lipid matrix of the skin is critical for effective permeation. [36], [37]

6.3 Pathways of Drug Permeation

Drug permeation can occur through distinct pathways:

A. Lipid Pathway

- **Mechanism:** Lipophilic drugs must partition into and diffuse through the lipid-rich bilayers of the stratum corneum.
- **Barrier Role:** The organized lipid structure presents a significant barrier, requiring drugs to navigate through multiple layers.[38]

B. Aqueous Pathway

- **Mechanism:** For hydrophilic drugs, permeation occurs through the aqueous channels found between keratinocytes. This pathway is less prominent but crucial for smaller, hydrophilic molecules.

- **Role of Intercellular Spaces:** Water-filled channels allow for some penetration, though they cannot accommodate larger molecules. [39]

7. Types of Transdermal Patches

7.1 Single-layer Drug-in-Adhesive:

In this configuration, the adhesive layer integrates the drug directly within it. The dual role of the adhesive is to ensure adherence to the skin and to control drug release. The rate of drug diffusion is influenced by various factors, including the skin's permeability and the adhesive's properties. This simple design is advantageous for ease of manufacturing and application (figure-3).[40]

7.2 Multi-layer Drug-in-Adhesive:

Building on the single-layer model, the multi-layer drug-in-adhesive patch includes additional layers, which may consist of membranes or extra drug-containing adhesive layers. This complexity allows for differentiated drug release profiles, enabling both rapid and sustained release phases. Such designs enhance the versatility of dosing regimens and can improve patient compliance. [41]

7.3 Reservoir System:

The reservoir patch distinguishes itself by featuring a dedicated compartment for the drug and is generally available in a liquid or gel format. A semi-permeable membrane controls the drug's release rate, facilitating zero-order kinetics, where a constant amount of drug is delivered over time. This system's ability to maintain stable serum drug levels makes it ideal for chronic conditions, with examples including Duragesic® and Estraderm®. [42]

7.4 Matrix System:



In matrix systems, the drug is evenly dispersed within a polymer matrix, allowing for controlled release. This category can be further divided into:

a) Drug-in-Adhesive System:

The adhesive layer incorporates the drug, providing both adhesion and a drug reservoir in a single formulation.

b) Matrix-Dispersion System:

The active pharmaceutical ingredient is uniformly integrated with hydrophilic or hydrophobic polymers, forming a medicated disk mounted on an impermeable backing layer. The surrounding adhesive rim ensures the patch remains secure during use.[43]

7.5 Vapour Patch:

Vapour patches are a novel innovation in transdermal delivery, designed to release essential oils for therapeutic effects, such as decongestion or sleep improvement. These patches not only adhere to the skin but also serve as a delivery mechanism for volatile compounds, making them suitable for users seeking alternative or adjunct therapies.[44]

7.6 Micro-reservoir System:

Combining elements of both reservoir and matrix systems, the micro reservoir design consists of drug particles suspended in a polymer matrix. The resulting formulation creates unreachable, microscopic drug reservoirs, allowing for controlled release while enhancing the skin's absorption capabilities. This approach provides a promising solution for delivering a wide range of therapeutic agents.[45]

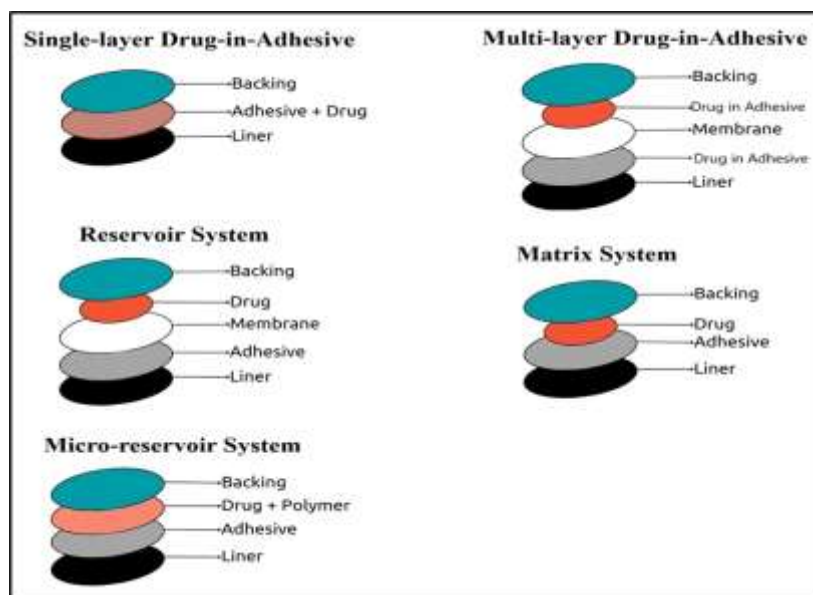


Figure 3: Types of Transdermal Patches.

8. Advantages of Transdermal Drug Delivery Systems [46], [47], [48], [49], [50], [51]

1. Avoiding First-Pass Metabolism
2. Controlled and Sustained Drug Release
3. Enhanced Patient Compliance
4. Reduced Gastrointestinal Irritation
5. Non-Invasive Administration
6. Targeted Drug Delivery
7. Stability in Plasma Drug Concentration
8. Cost-Effectiveness

9. Disadvantages of Transdermal Drug Delivery Systems [52], [53], [54], [55], [56], [57]

1. Physicochemical Requirements
2. Limited Dosage Capacity
3. Skin Compatibility Issues
4. Variability in Skin Barrier
5. Limited Therapeutic Efficacy
6. Inflammation Risks

10. Adverse Effects of Transdermal Drug Delivery Systems[58]

1. Skin Reactions:

Skin irritation is a common issue with TDDS, presenting symptoms such as redness, itching, and burning.

2. Allergic Reactions:

Allergic responses can occur due to components in the patch, including adhesives and active ingredients. Symptoms may range from localized rashes to more widespread hives, often requiring the patch to be removed.

3. Overdose Risks:

The continuous delivery of medications, particularly potent opioids like fentanyl, raises concerns about systemic overdose. Signs of overdose can include nausea, vomiting, sedation, and serious respiratory issues.

4. Variable Drug Delivery:

Drug absorption through the skin varies due to factors like skin thickness, hydration, and temperature. This variability can lead to inconsistent therapeutic.

Table No. 1: List of Drugs Used in Transdermal Patches: Pharmacological Category, Formulation Type, and Clinical Applications

Sr. No.	Drug	Pharmacological Category	Formulation Type	Clinical Application
1	Nicotine	Smoking cessation agent	Matrix Patch	Smoking cessation
2	Fentanyl	Opioid analgesic	Reservoir Patch	Pain management
3	Hormones (e.g., Estradiol)	Hormone	Matrix or Reservoir Patch	Hormone replacement therapy
4	Scopolamine	Anticholinergic	Matrix Patch	Motion sickness
5	Clonidine	Alpha-2 adrenergic agonist	Matrix Patch	Hypertension treatment
6	Nitroglycerin	Nitrate vasodilator	Reservoir Patch	Angina pectoris
7	Testosterone	Androgen	Matrix Patch	Hormone replacement therapy
8	Rivastigmine	Acetylcholinesterase inhibitor	Reservoir Patch	Alzheimer's disease
9	Capsaicin	Analgesic (topical)	Matrix Patch	Pain relief (topical)
10	Lidocaine	Local anesthetic	Matrix Patch	Local anesthesia

11. Factors Influencing Transdermal Drug Delivery Systems [59], [60], [61], [62], [63], [64]

11.1 Physicochemical Factors

- **Partition Coefficient:** A higher partition coefficient (≥ 1) facilitates optimal

permeability of drugs through the skin, as the drug transitions from the formulation to the lipid-rich skin environment.

- **Skin Hydration:** Hydrated skin reduces the barrier function of the stratum corneum, enhancing drug absorption.

- **Temperature and pH:** Elevated skin temperature increases drug diffusion, while optimized pH conditions promote better drug permeability by affecting ionization.
- **Drug Concentration and Molecular Size:** A higher concentration gradient facilitates drug absorption, and smaller molecules generally permeate more easily than larger ones.

11.2 Biological Factors

- **Skin Condition and Blood Flow:** Damaged skin and variations in blood flow can significantly influence drug absorption rates.
- **Skin Metabolism:** Active metabolism in the skin can modify the drug's efficacy by activating or deactivating certain compounds.

11.3 Formulation-Related Factors

- **Release Characteristics and Penetration Enhancers:** The drug's release rate, affected by solubility and formulation composition, is critical for ensuring controlled drug delivery. Penetration enhancers, such as surfactants, can help improve absorption by altering the skin's barrier.

11.4 Environmental Factors

- **External Influences and Seasonal Changes:** Sun exposure, pollution, and seasonal changes can alter skin permeability, emphasizing the need for formulation adjustments under different environmental conditions.

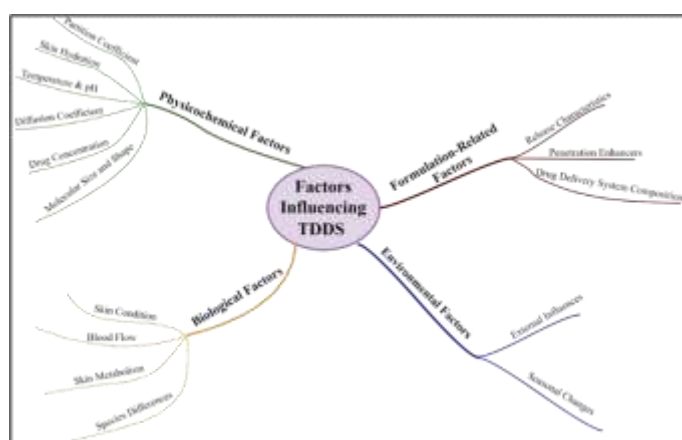


Figure 4: Factors Influencing TDDS.

12. Components of Transdermal Drug Delivery Systems

12.1 Drug

The drug used in transdermal systems is often selected for its ability to bypass first-pass metabolism and its compatibility with transdermal delivery requirements. Ideal properties include a molecular weight of less than 500 Da, an affinity for both hydrophobic and hydrophilic phases, a low melting point, and non-irritating, and non-

allergic characteristics. The drug's log partition coefficient should be between 1 and 4, with a solubility greater than 1 mg/mL within a pH range of 5.0 to 9.0.[65]

12.2 Adhesives

Pressure-sensitive adhesives (PSAs) are critical for maintaining close contact between the patch and the skin. They must be easily attachable and removable without causing irritation. The adhesive

should not interfere with drug permeation and must be compatible with other components.[66]

12.3 Membrane

The polymer matrix regulates drug release and can be prepared by dispersing the drug in a synthetic polymer. Polymers should be biocompatible, chemically compatible with the drug, and maintain consistent drug delivery throughout the shelf life. Common polymers include natural options (e.g., cellulose derivatives) and synthetic elastomers (e.g., polybutadiene). [67]

12.4 Backing Laminates

Backing films provide stability, protect the active layer, and regulate skin permeation. They must be chemically resistant and compatible with excipients to prevent leaching. Ideal materials include flexible, impermeable substances like vinyl, polyethylene, and polyester.[68]

12.5 Other Excipients

- a. **Permeation Enhancers:** They are compounds that improve the permeability of the stratum corneum, facilitating better drug delivery (e.g., DMSO).
- b. **Plasticizers:** Enhance flexibility and tensile strength, influencing drug release and permeability. (e.g., Dibutyl phthalate).
- c. **Solvents:** These are used to improve drug solubility. Examples include methanol and propylene glycol (e.g., Chloroform, and Acetone).
- d. **Surfactants:** Modify transport pathways for hydrophilic drugs, balancing penetration enhancement with irritation potential (e.g., Span 20 and Span 80). [69], [70]

12.6 Release Liner

This protective layer is removed before patch application. It must be chemically inert and allow permeation of the drug and enhancers while preventing moisture ingress.[71]

13. Penetration Enhancers in Transdermal Drug Delivery Systems

Penetration enhancers, or permeation enhancers, are substances that enhance the penetration of active compounds through the skin by temporarily altering the stratum corneum. This enhancement allows for improved delivery of topical medications into the bloodstream.[72]

13.1 Drug Penetration Mechanisms

Drug penetration through the skin involves several pathways, including:

1. **Hair Follicular Penetration**
2. **Trans corneal Penetration**
3. **Intracellular Route**
4. **Transcellular Route**

13.2 Types of Penetration Enhancers [38]

1. Chemical Enhancers

- **Fatty Acids:** (e.g., oleic acid) disrupt the lipid bilayer to enhance permeability.
- **Surfactants:** (e.g., polysorbates) reduce surface tension and aid in drug penetration.
- **Alcohols:** (e.g., ethanol) dehydrate the stratum corneum, facilitating absorption.
- **Amino Acids/Peptides:** Improve solubility and absorption of peptide-based drugs.

- **Glycols:** (e.g., propylene glycol) serve as solvents that enhance drug solubility.
 - **Iontophoresis:** It uses electric current to transfer charged medications through the skin.
 - **Sonophoresis:** Applies ultrasound to create temporary pores, increasing permeability.
 - **Thermal Methods:** Heating enhances blood flow and disrupts skin barriers.
2. **Physical Enhancers** [73]
- **Microneedles:** Create microchannels for drug delivery, effective for both small and large molecules.

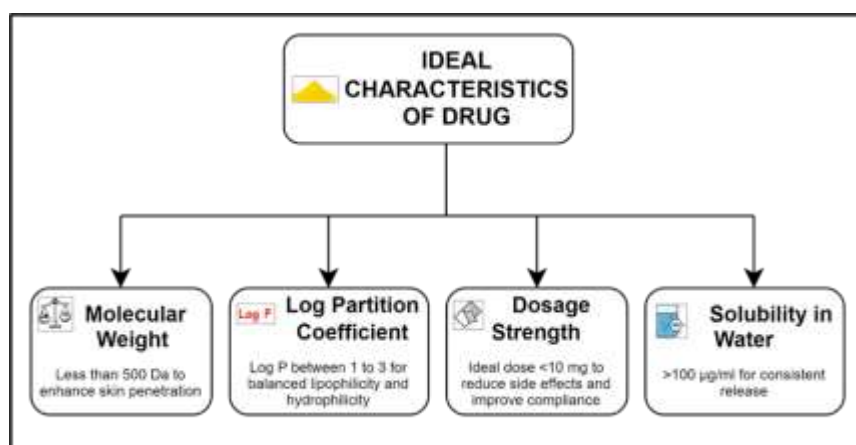


Figure 5: Ideal Characteristics of Drug

Table No. 2: Ideal Properties of Drug

Parameter	Properties
Dose	Less than 20 mg/day
Molecular weight	Less than 1000 Dalton
Melting point	Less than 200°C
Half-life	Less than 10 hours
Shelf life	Up to 2 years
Partition coefficient	1 to 4
Aqueous solubility	Greater than 1mg/mL
pH of the aqueous saturated solution	5-9
Skin permeability coefficient	Greater than $0.5 \times 10^{-3} \text{ cm/h}$
Skin reaction	Non-irritating and non-sensitizing
Oral bioavailability	Low

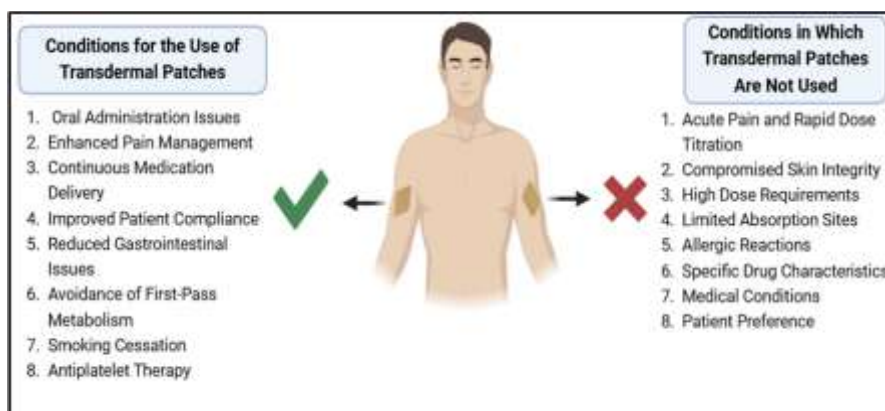


Figure 6: Clinical Conditions Supporting and Limiting Transdermal Patch Utilization

14. Methods for Preparation of Transdermal Drug Delivery Systems

14.1 Asymmetric TPX Membrane Method

This method involves fabricating a prototype patch using a heat-sealable polyester film (type 1009, 3M) with a 1 cm diameter concave as the backing membrane. A drug sample is dispensed into this concave, covered with a TPX poly (4-methyl-1-pentene) asymmetric membrane, and sealed using an adhesive. The TPX membrane is prepared through a dry/wet inversion process, where TPX is dissolved in a solvent mixture at 60°C, followed by casting on a glass plate and coagulating in a bath maintained at 25°C.[78]

14.2 Circular Teflon Mold Method

In this approach, polymer solutions in various ratios are dissolved in an organic solvent. A calculated amount of drug is dissolved in half of the solvent, while enhancers are dissolved in the other half. Di-N-butyl phthalate is added as a plasticizer to the drug-polymer solution. The combined mixture is stirred for 12 hours and then poured into a circular Teflon mold. These molds are placed on a leveled surface and covered with an inverted funnel to control solvent vaporization in a laminar flow hood at an air speed of 0.5 m/s. After allowing the solvent to evaporate for 24 hours, the dried films are stored in a desiccator containing silica gel for an additional 24 hours to eliminate aging effects. [79]

14.3 Mercury Substrate Method

In this method, the drug is dissolved in a polymer solution that includes a plasticizer. This mixture is stirred for 10-15 minutes to achieve a homogeneous dispersion, which is then poured onto a levelled mercury surface. An inverted

funnel is used to control solvent evaporation, allowing for efficient film formation.[80]

14.4 IPM Membranes Method

The drug is dispersed in a mixture of water and propylene glycol containing Carbomer 940 polymer and stirred for 12 hours using a magnetic stirrer. The dispersion is neutralized with triethanolamine to enhance viscosity. A buffer with a pH of 7.4 can be used to achieve a gel-like consistency, particularly when drug solubility in aqueous solutions is poor. This gel is subsequently incorporated into the IPM membrane.[81]

14.5 EVAC Membranes Method

To create a transdermal therapeutic system, a 1% Carbopol reservoir gel, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) membranes serve as rate control membranes. For drugs insoluble in water, propylene glycol is used to prepare the gel. The drug is dissolved in propylene glycol, mixed with Carbopol resin, and neutralized with a 5% w/w sodium hydroxide solution. The drug in gel form is then placed on a backing layer and covered with a rate-controlling membrane, with edges sealed by heat to form a leak-proof device. [82]

14.6 Aluminum Backed Adhesive Film Method

This method is particularly suitable for drugs with a loading dose greater than 10 mg, as it helps avoid unstable matrices. Chloroform is the solvent of choice, dissolving both the drug and adhesive. The drug is combined with the adhesive material in chloroform, and a custom-made aluminum former is lined with aluminum foil and sealed with cork blocks.

14.7 Preparation of TDDS Using Proliposomes



Proliposomes are prepared via the carrier method using a film deposition technique. An optimized ratio of drug and lecithin (0.1:2.0) is employed. Mannitol powder (5 mg) is placed in a round-bottom flask, heated to 60-70°C, and dried under vacuum for 30 minutes. The drug and lecithin are dissolved in an organic solvent mixture. Aliquots of this solution are introduced into the flask, and following complete drying, the proliposomes are lyophilized, stored in a desiccator, and sieved through a 100-mesh screen. [83]

14.8 Free Film Method

This method involves casting a free film of cellulose acetate on a mercury surface. A 2% w/w polymer solution is prepared using chloroform, with plasticizers incorporated at 40% w/w of the polymer weight. The polymer solution is poured into a glass ring on the mercury surface, and the solvent evaporation is controlled by an inverted funnel. After complete evaporation, the dry film is separated and stored in a desiccator between sheets of wax paper. [84]

14.9 Simple Method of Preparing Transdermal Patches

The preparation of TDDS is modified from earlier reported methods using a solvent casting approach. A polymer (e.g., PVP/HPMC) is mixed with a minimum quantity of solvent, followed by the addition of other polymers (e.g., PVA) and thorough stirring. A plasticizer is incorporated, and the drug is added with continuous agitation. The resultant films are cast onto a glass mold and dried in an oven at 40°C. After drying, the films are carefully removed, wrapped in butter paper, and stored in a cool, light-protected environment.

15. Evaluation Methods for Transdermal Drug Delivery Systems

15.1 Physical Appearance:

Each patch undergoes visual inspection for color, clarity, transparency, flexibility, and surface smoothness, all crucial for product uniformity and quality assurance. [85]

15.2 Interaction Studies:

To ensure excipient compatibility with the drug, analytical methods like thermal analysis, Fourier-transform infrared (FT-IR) spectroscopy, UV spectroscopy, and chromatography are employed. These help detect possible physical or chemical interactions, thus preserving the drug's stability and bioavailability. [86]

15.3 Thickness Measurement:

Measured at multiple points using a micrometer, uniform patch thickness ensures consistent drug release and dosage. [87]

15.4 Folding Endurance

A strip of the patch is repeatedly folded up to 300 times until it breaks, measuring its flexibility a key property for body movement adaptability. [88]

15.5 Weight Uniformity:

After drying, patches are weighed to confirm uniform drug distribution. Variability should remain within acceptable limits, ensuring dose consistency. [89]

15.6 Moisture Content and Uptake:

Moisture content and absorption are evaluated by exposing patches to controlled humidity levels. Moisture content is determined by placing patches in a desiccator, while uptake is assessed by re-weighing patches exposed to high humidity. [90]



%Moisture Content

$$= \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

15.7 Water Vapor Permeation (WVP) Test:

Patches are sealed over vials containing calcium chloride and kept at 63% relative humidity. Weight changes after 72 hours assess the patch's permeability to moisture, essential for product stability.[91]

$$WVP = \frac{\Delta W}{A \cdot t}$$

Where,

- ΔW = Weight change (g)
- A = Surface area of the patch (cm²)
- t = Time (hours)

15.8 Drug Content Analysis:

To ensure accurate drug loading, patches are dissolved in solvents (e.g., methanol or phosphate buffer) and analyzed via UV or HPLC techniques.[92]

15.9 Polariscopic Examination:

Polariscopic microscopy determines whether the drug remains crystalline or transforms to an amorphous form in the patch, impacting stability and release profile.[93]

15.10 Flatness Test:

Flatness is assessed by measuring strips from different patch areas. Zero constriction indicates uniform flatness, a quality essential for even adhesion to the skin. [94]

15.11 Tensile Strength:

This test, often performed with a universal testing machine, measures the force required to break the

patch, indicating its durability and mechanical strength. [95]

15.12 Adhesion and Tack Tests

a. Shear Adhesion Test:

Measures the time a patch holds under a specific weight on a smooth surface, indicating adhesive strength.

b. Peel Adhesion Test:

The force to remove a patch from a steel surface at a 180-degree angle, testing adhesive durability.

c. Rolling Ball Tack Test:

Measures the distance a steel ball travels on the adhesive surface, indicating quick adhesion.

d. Thumb Tack and Quick Stick Tests:

These tests measure the ease of separating a thumb or probe from the adhesive, providing tack values crucial for user application.

e. Probe Tack Test:

A probe contacts the adhesive surface; the force to separate the probe is recorded as tack, reflecting quick adherence. [96]

15.13 In Vitro Release Study:

Using a USP dissolution apparatus, patches are tested in a buffer at body temperature, and drug release is measured over 24 hours. This ensures controlled and sustained drug delivery.

15.14 Stability Studies:

Patches are stored at high temperatures and humidity according to ICH guidelines, with periodic assessments over six months to verify long-term stability. [97]



15.15 In Vitro Permeation Studies

In vitro permeation studies evaluate drug release and absorption through the skin, providing an initial indication of the formulation's in vivo behavior.[98], [99]

a. Diffusion Cells:

Typically employing Franz or flow-through diffusion cells, these studies simulate the permeation environment with a donor compartment (holding the patch) and a receptor compartment (buffer solution) with constant stirring to ensure uniform drug distribution.

b. Skin Samples:

Skin from animals (e.g., rats or pigs) or synthetic membranes with properties mimicking human skin are commonly used, with the epidermal side facing the patch to simulate skin application.

c. Controlled Conditions:

The system is maintained at 32°C to replicate human skin temperature, with samples collected periodically from the receptor compartment over 24 hours for analysis.

d. Analysis

Samples are analyzed via UV spectrophotometry or HPLC to determine cumulative drug release, permeation rate, and permeability coefficient. Flux is calculated from the steady-state slope of drug permeation versus time.[100]

In vivo studies assess the TDDS's actual performance within a living system, considering absorption, metabolism, and excretion.

a. Animal Models:

Before human trials, animal models (e.g., hairless mice, rats, or rabbits) provide initial pharmacokinetic and pharmacodynamic data. The TDDS is applied to the skin, and blood or tissue samples are collected at intervals to study bioavailability and absorption rates.[101]

b. Human Studies:

In clinical trials, patches are applied to human subjects, measuring pharmacokinetics, safety, and efficacy. Plasma drug levels indicate how efficiently the drug enters systemic circulation, with side effects and compliance closely monitored.

c. Pharmacokinetic and Pharmacodynamic Data:

Human studies provide unique insights into individual variations in drug absorption and metabolism. These results inform therapeutic effectiveness, dosing, and action duration.

d. Clinical Implications:

Clinical trials validate that the TDDS can achieve therapeutic drug levels with minimized side effects, often using crossover studies to compare the transdermal route's advantages over alternative administration forms.[102]

15.16 In Vivo Studies

Table No. 3: Evaluation Methods with United States Pharmacopeia (USP) Limits for Patches.

Sr. No.	Evaluation Method	United States Pharmacopeia Limits
1.	Physical Appearance	Clear, no discolouration; flexible, smooth
2.	Interaction Studies	No detectable interaction impacting drug bioavailability
3.	Thickness Measurement	±10% variation in thickness
4.	Folding Endurance	Minimum 100 folds, ideal 300



5.	Weight Uniformity	$\pm 5\%$ weight variation
6.	Moisture Content and Uptake	Moisture content $\leq 5\%$, uptake $\leq 10\%$
7.	Water Vapor Permeation (WVP) Test	WVP ≤ 0.05 g/24 hrs./cm ² at 63% RH
8.	Drug Content Analysis	90-110% of labelled drug content
9.	Polariscopic Examination	No crystalline content if amorphous form is intended
10.	Flatness Test	Maximum variation ≤ 1 mm
11.	Tensile Strength	Tensile strength ≥ 5 N/cm ²
12.	Adhesion and Tack Tests	
	a) Shear Adhesion Test	≥ 50 g/cm ²
	b) Peel Adhesion Test	≥ 100 g/cm ² at 180° angle
	c) Rolling Ball Tack Test	< 2 cm
	d) Thumb Tack Test	Easy separation of tack
	e) Probe Tack Test	Reflects quick adherence
13.	In Vitro Release Study	$\geq 80\%$ release within 24 hours
14.	Stability Studies	$\leq 5\%$ degradation at 40°C, 75% RH after 6 months
15.	In Vitro Permeation Studies	$\geq 50\%$ drug release within 24 hours
16.	In Vivo Studies	$\geq 80\%$ bioavailability within 24 hours

16. Different Transdermal Drug Delivery Technologies

Transdermal drug delivery systems (TDDS) have gained prominence due to their ability to facilitate effective medication administration while minimizing invasive procedures. Several innovative technologies have emerged, each with unique mechanisms and applications.

16.1 Thermal Ablation

Thermal ablation, also known as thermophoresis, utilizes targeted heat to disrupt the stratum corneum, thereby creating microchannels that enhance drug permeability. Achieving temperatures above 100 °C is crucial for vaporizing keratin and altering the skin's structure.[103] This technique can be executed using various thermal energy sources, such as lasers and radiofrequency devices. By carefully adjusting parameters like wavelength and exposure duration, practitioners can control the depth and extent of skin ablation, significantly improving drug delivery efficiency.[104], [105]

16.2 Microneedles

Microneedle technology represents a groundbreaking method in transdermal delivery, employing micron-sized needles to penetrate the skin's outer layer. These needles, typically measuring 25 to 2000 μm in height, allow for the direct administration of medications into the dermal capillaries, thus enhancing absorption while reducing pain. The success of this approach hinges on optimizing the geometry of microneedles to ensure they reach the target without contacting nerve endings. They are generally arranged in arrays to maximize skin contact and drug delivery.[106], [107], [108]

16.3 Jet Injectors

Needle-free jet injectors propel liquid formulations through narrow nozzles, ranging from 50 to 360 μm in diameter.[109] This method eliminates concerns associated with needle disposal and injury, although risks of cross-contamination from the nozzle remain. Solid jet injectors utilize compressed gas to deliver powdered medications, creating Micro perforation in the skin that facilitate drug absorption. Key factors influencing drug distribution include particle size and impact



velocity, which are critical for achieving effective delivery of specific therapeutics.[51], [110]

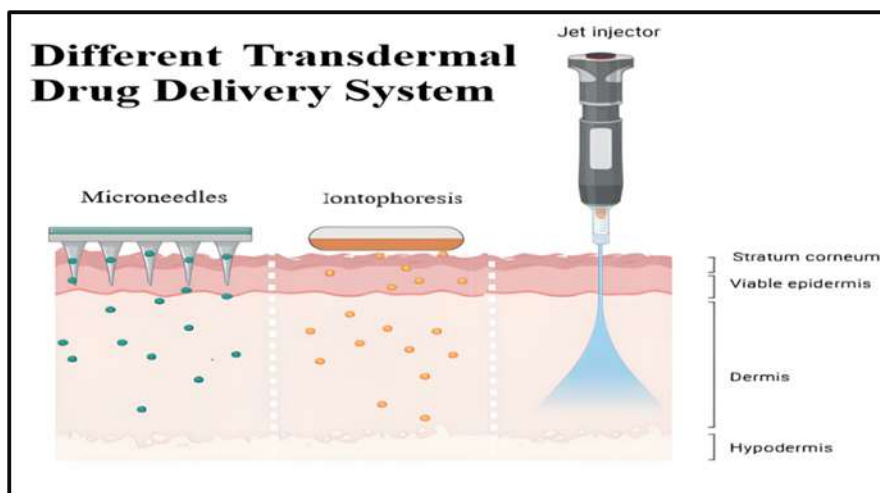


Figure 7: Different Transdermal Drug Delivery System

17. Advances in Transdermal Drug Delivery Systems

Recent innovations in transdermal patch technology are transforming how medications are delivered, enhancing both patient comfort and treatment efficacy. Here are some notable advancements in this field:

17.1 Protein Delivery Systems:

New patches are now capable of delivering protein-based therapies effectively. This is particularly important since proteins are often too large to penetrate the skin easily.[111] By improving the technology behind these patches, researchers are making it possible to treat various conditions with protein drugs that were previously difficult to administer.[112]

17.2 Pain-Free Diabetes Monitoring:

Transdermal patches are being developed for continuous glucose monitoring, offering a pain-free alternative for those managing diabetes.[113] These patches allow for real-time data collection without the need for finger pricks, making diabetes

management more comfortable and less invasive. [114], [115]

17.3 Hormonal Therapy for Women:

A groundbreaking testosterone transdermal patch has been created for young women experiencing spontaneous premature ovarian failure.[116] This non-invasive approach provides a reliable method for hormone replacement therapy, helping to improve the quality of life while minimizing potential side effects often associated with oral medications. [117]

17.4 Overactive Bladder Management:

Transdermal patches containing Oxybutynin are now being used to treat overactive bladder (OAB). [118] These patches deliver a consistent dose of medication, which simplifies the treatment regimen and helps improve adherence by reducing the frequency of doses needed throughout the day. [119], [120]

18. Patents Granted on Transdermal Drug Delivery System

Numerous patents have been granted to utility. The table below presents a selection of researchers in the field of Transdermal Drug significant patents.

Delivery Systems (TDDS) due to their clinical

Sr. No.	Patent Number	Title	Inventor	Key Innovation	Year	Reference
1.	US3598122A	Bandage for administering drugs	Alejandro Zaffaroni	First transdermal patch system with a drug reservoir and semi-permeable membrane for controlled delivery	1971	[121]
2.	US-4668232-A	Transdermal drug patches	Ginter Cordes, Michael Wolff	Pioneering work on drug patches, including adhesives and drug formulations for enhanced drug delivery.	1987	[122]
3.	US4839174A	Novel transdermal nicotine patch	Richard W. Baker, Frank Kochinke, Carl Huang	Transdermal nicotine patch for smoking cessation therapy.	1989	[123]
4.	US 5008110A	Storage-Stable Transdermal Patch	Arnold G. Benecke, Daniel J. Kinne, Andrew J. Wnuk	Development of a storage-stable transdermal patch, addressing stability issues and ensuring consistent drug delivery.	1991	[124]
5.	US-5232702-A	Silicone pressure sensitive adhesive compositons for transdermal drug delivery devices and related medical devices	William R. Pfister, Jeniffer M. Wilson	Innovative silicone-based adhesives designed for use in transdermal patches and medical devices.	1993	[125]
6.	US5262165A	Transdermal Nitroglycerin patch with penetration enhancers	Sharad K. Govil, Edward M. Rudnic, Dale G. Sterner	Transdermal patch for nitroglycerin, using penetration enhancers for improved drug absorption	1993	[126]
7.	US-5290561-A	Single layer transdermal drug administration system	Bahram Farhadieh, Rajeev D. Gokhale	Simplified single-layer patch design for efficient drug delivery and reduced production complexity.	1994	[127]
8.	US-5486362-A	Controlled, sustained release delivery system for treating drug dependency	Judith P. Kitchell, Indu A. Muni, Yvonne N. Boyer	Sustained-release system for drug dependency treatment with controlled release mechanisms.	1996	[128]
9.	US-5703101-A	Agonist-antagonist combination to reduce the use of nicotine and other drugs	Jed E. Rose, Edward D. Levin	Innovative combination of agonists and antagonists for drug	1997	[129]

				addiction and smoking cessation therapy.		
10.	US-5721257-A	Method and therapeutic system for smoking cessation	Richard W. Baker, Giancarlo Santus, Susan Vintilla-Friedman	Advanced system focusing on effective smoking cessation strategies.	1998	[130]
11.	US5869090A	Transdermal delivery of dehydroepiandrosterone	Jerry Rosenbaum	Development of a TDDS for dehydroepiandrosterone (DHEA), a hormone with potential therapeutic uses.	1999	[131]
12.	US-5948433-A	Transdermal patch	Scott Allison Burton, Shahnaz Tata	Transdermal patch design with improved adhesive and drug stabilization properties.	1999	[132]
13.	US-7642232-B2	Compositions and methods for the prevention and control of insulin-induced hypoglycemia	Daniel T. Green, Robert R. Henry	Systems to prevent hypoglycemia caused by insulin treatment through innovative transdermal delivery.	2010	[133]
14.	US8197844-B2	Active electrode for transdermal medicament administration	Jamal S. Yanaki	Active electrode design enhancing the precision of transdermal drug delivery.	2012	[134]
15.	US-8641689-B2	Transdermal porator and patch system and method for using same	Bernadette Messier, Zoran Novakovic, Jeremiah Peter O'Leary	Integration of porators with patches to improve the efficiency of drug absorption.	2014	[135]
16.	US-9056061-B2	Transdermal nicotine salt delivery system	Robert M. Gale, Jay Audett, Rama V. Padmanabhan	Advanced nicotine salt delivery system improving stability and absorption.	2015	[136]
17.	US-10556106-B2	System and method for biphasic transdermal iontophoretic delivery of therapeutic agents for the control of addictive cravings	Mir A. Imran, Talat Imran, Mir Hashim	Innovative biphasic iontophoretic delivery system for addressing addictive cravings.	2020	[137]
18.	US-11129975-B2	Transdermal delivery of high viscosity bioactive agents	Russell F. Ross	Method for transdermal administration of bioactive agents with high viscosity.	2021	[138]
19.	CA-2955247-C	Abuse deterrent opiod/opiod-antagonist transdermal patch	Audra Lynn Stinchcomb, Dana Carmel	Abuse-deterrent patch combining opioids and antagonists to prevent	2023	[139]

			Hammell, Stan Lee Banks, Josh ELDRIDGE, Miroslaw Jerzy Golinski	misuse and ensure controlled release.		
20.	US11648214-B2	Systems and methods for long term transdermal administration	Eun Soo Lee, Amit K. Jain, Parminder Singh	Systems enabling sustained and long-term drug administration through transdermal patches	2023	[140]
21.	US11911522-B2	Process for the continuous manufacture of a polyisobutylene based transdermal patch	Russell Adam Baird, Brad L. Barnett, Russell D. Beste	Continuous production process for polyisobutylene-based transdermal systems ensuring scalability.	2024	[141]
22.	US-11938160-B2	Pharmaceutical composition and method of manufacturing	Gary J. Speier	Improved composition and manufacturing methods for advanced transdermal patches.	2024	[142]

19. Future Innovations in Transdermal Drug Delivery Technologies

The future of transdermal drug delivery systems (TDDS) is promising, with advancements aimed at overcoming traditional challenges like low drug solubility and skin permeability.[143] New formulation techniques, such as liposomes and microemulsions, are improving the delivery of poorly soluble drugs. Innovations in patch design are expected to boost the popularity of transdermal analgesics, while technologies that leverage mechanical energy, like iontophoresis, electroporation, sonophoresis, and thermal energy, are enhancing drug delivery by modifying the skin barrier or boosting drug molecule energy.[144]

The TDDS market is growing rapidly, projected to reach \$2 billion, with a 25% annual growth rate. Microneedle technology, such as the NanoPatch®, is showing promise for single-dose vaccine delivery.[145] Advances like thermal poration, jet injectors, and micro-infusion systems are further improving drug delivery efficiency. Companies

like Trans Pharma and Altea Therapeutics are developing products to enhance patient compliance, focusing on sustained-release formulations and innovative vaccination methods. [146]

20. Challenges

Transdermal drug delivery systems (TDDS) face numerous challenges that can impact their effectiveness and acceptance by patients. A primary concern is the skin's natural barrier function, particularly the stratum corneum, which restricts the absorption of larger molecules and hydrophilic drugs.[147] This limitation narrows the scope of medications suitable for transdermal application, often leaving out vital treatments. Moreover, variations in skin properties among individuals such as thickness, temperature, and hydration can lead to unpredictable absorption rates, complicating dosing and therapeutic outcomes.[148]



Formulation stability is another pressing issue; many active ingredients can degrade due to environmental factors like light and humidity, leading to a potential loss of efficacy over time. [149] Additionally, patient compliance can suffer due to skin irritation or allergic reactions from adhesives or drug compounds, making it difficult to ensure consistent usage.[150] The regulatory environment further complicates the landscape, as manufacturers must navigate rigorous approval processes that require comprehensive safety and efficacy data. These multifaceted challenges underscore the need for ongoing research and innovation to improve the design and functionality of TDDS, ultimately enhancing patient outcomes and acceptance.[151], [152], [153], [154]

21. CONCLUSION

Transdermal drug delivery systems are one of the significant advances in modern medicine, being a patient-friendly and efficient alternative to the traditional drug delivery methods. The review discusses the evolution, mechanisms, types, and applications of TDDS with advantages and limitations. This also includes complex issues on skin permeability, formulation strategies, and advanced technologies, which might make TDDS a possible revolution in pharmacotherapy. Despite these challenges, which include adverse effects, continuous innovation and research may be able to overcome them. TDDS represents the best example of science and technology fusion into the creation of more efficient and convenient drug delivery.

ABBREVIATIONS

1. TDDS: Transdermal Drug Delivery Systems.
2. USP: United States Pharmacopeia

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