

Review on Transdermal Drug Delivery System

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Abstract—Transdermal drug delivery systems (TDDS) are innovative pharmaceutical platforms that administer drugs through the skin into systemic circulation in a controlled and sustained manner. These systems offer multiple benefits, such as bypassing first-pass metabolism, maintaining consistent plasma drug levels, enhancing bioavailability, and improving patient adherence. TDDS are particularly advantageous for medications with short half-lives, poor gastrointestinal stability, or local irritant properties. Designing transdermal patches involves selecting suitable polymers, active drugs, permeation enhancers, and excipients to achieve effective delivery and patient comfort. Various patch types, including single-layer and multi-layer drug-in-adhesive, reservoir, matrix, and vapor patches, cater to different therapeutic requirements. Strategies to enhance skin permeability, such as chemical enhancers, microneedles, iontophoresis, electroporation, thermal poration, and sonophoresis, have further broadened the scope of TDDS. Despite some limitations, including restrictions to specific drug properties and possible local irritation, ongoing advancements in formulation science, adhesive technologies, and delivery techniques continue to improve TDDS efficacy. This review provides a comprehensive overview of the development, design, mechanism, advantages, limitations, commercially available products, and future prospects of transdermal drug delivery systems, highlighting their significance in modern therapeutics.

Index Terms—Transdermal drug delivery, Controlled release systems, Permeation enhancers, Polymer-based patches.

I. INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) are advanced pharmaceutical dosage forms designed to transport medications through the skin into systemic circulation in a controlled and sustained manner [1], [4], [9]. The idea of administering drugs via the skin was introduced in the 1970s, and the first transdermal

patch received approval from the U.S. Food and Drug Administration (FDA) in 1979 for motion sickness therapy using scopolamine [3], [5]. Later, several other transdermal patches were developed, including those containing nitroglycerin, clonidine, nicotine, fentanyl, and hormonal preparations, providing a more convenient and effective alternative to oral and injectable drug delivery methods [6], [10], [11].

The transdermal route offers several therapeutic advantages, such as non-invasive administration, avoidance of first-pass metabolism, steady plasma drug levels, improved bioavailability, and better patient compliance [2], [7], [12]. It is particularly useful for drugs with short half-lives or those that irritate or degrade in the gastrointestinal tract [8], [13]. Additionally, transdermal systems allow quick termination of treatment by removing the patch, which helps minimize side effects and provides greater control over drug therapy [9], [14].

However, one of the major limitations of TDDS is the stratum corneum, the skin's outermost layer, which acts as a strong barrier and restricts drug permeation [15], [18], [21]. To overcome this challenge, advanced formulation techniques—such as penetration enhancers, microneedles, iontophoresis, and nanocarrier systems—have been explored to improve transdermal absorption and therapeutic efficiency [16], [19], [23].

With continuous research and technological innovation, TDDS have gained increasing importance in modern pharmaceuticals [17], [20], [24]. These systems not only ensure controlled and sustained drug release but also improve treatment outcomes and patient comfort [10], [22]. As research continues, transdermal patches are expected to play a vital role in the future of systemic and targeted drug delivery applications [11], [25].

Definition —A transdermal patch is a medicated adhesive device that is applied to the skin to release a specific amount of drug into systemic circulation [1], [4], [10]. It allows the medication to pass through the skin layers at a controlled rate, helping to maintain steady therapeutic levels in the body while eliminating the need for oral or injectable routes [6], [9], [12].

II. HISTORY

The idea of delivering drugs through the skin dates back to ancient civilizations, where natural materials such as oils, herbal extracts, and ointments were applied externally to heal wounds and relieve pain [13], [16]. Cultures like the Egyptians, Greeks, Chinese, and Indians made extensive use of medicated plasters, balms, and poultices, which represented the earliest attempts at topical and transdermal therapy [14], [15]. Preparations such as mustard plasters and herbal ointments demonstrated that some substances could penetrate the skin and produce systemic effects, forming the basis for modern transdermal drug delivery [17], [18].

The scientific era of transdermal systems began in the 20th century, when researchers started experimenting with methods to enhance the movement of drugs through the skin using chemical enhancers and adhesive formulations [19], [21]. The first major advancement occurred in 1979, with the approval of the scopolamine patch for motion sickness by the U.S. Food and Drug Administration (FDA) [2], [4]. This patch provided controlled drug release for up to 72 hours and marked the beginning of modern transdermal drug delivery [10], [20].

Further innovations followed soon after. In the 1970s, the nitroglycerin patch was developed for the treatment of angina, becoming one of the earliest commercially successful systems [8], [11]. The 1980s and 1990s witnessed rapid progress with the introduction of fentanyl patches for long-term pain management, nicotine patches to assist in smoking cessation, and hormonal patches for contraception and hormone replacement therapy [5], [7], [9].

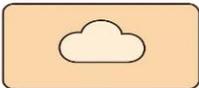
Over time, the concept of transdermal therapy evolved from simple topical applications into an advanced pharmaceutical technology that provides

controlled, sustained, and patient-friendly drug delivery [1], [3], [12]. Continuous improvements in patch design, materials, and permeation techniques have made TDDS a reliable and effective route for systemic medication in modern therapeutics [22], [23], [25].

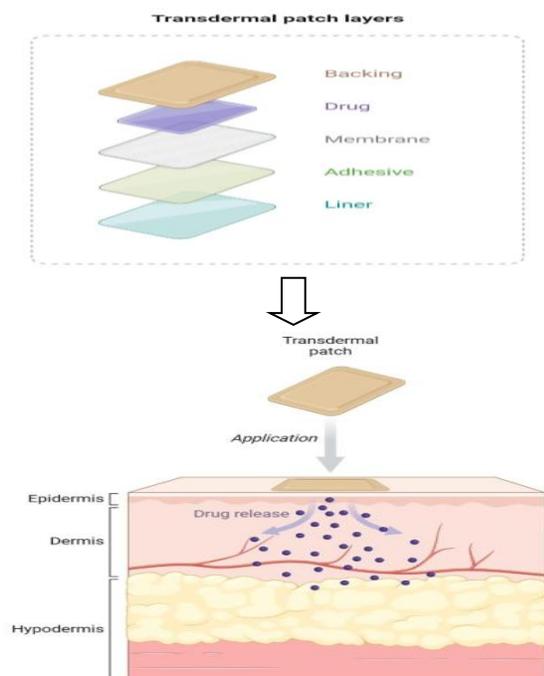
III. TYPES OF TRANSDERMAL PATCHES

Table I: Different Types of Transdermal Patches

Type of Patch	Description
<p>Single-layer Drug-in-Adhesive</p>  <p>1. SINGLE-LAYER DRUG-IN-ADHESIVE Drug incorporated directly into adhesive layer</p>	<p>The drug is blended directly into the adhesive, which both sticks the patch to the skin and regulates drug release. It includes a backing layer and a protective liner. Simple design, thin, comfortable for patients. [11, 13]</p>
<p>Multi-layer Drug-in-Adhesive</p>  <p>2. MULTI-LAYER DRUG-IN-ADHESIVE Several adhesive layers containing the drug</p>	<p>Contains two or more drug-containing adhesive layers, sometimes separated by a membrane. Provides better control over release rates. Extended-release action, flexibility in drug loading. [12, 14, 16]</p>
<p>Reservoir System</p>  <p>3. RESERVOIR SYSTEM Drug in a separate reservoir</p>	<p>The drug is stored in a gel or liquid compartment separated from the adhesive by a rate-controlling membrane. Delivers drugs at a constant rate; used for nitroglycerin, clonidine, and fentanyl patches. [1, 6, 10, 15]</p>
<p>Matrix System</p>  <p>4. MATRIX SYSTEM Drug embedded in a polymer matrix</p>	<p>The active ingredient is dispersed within a semi-solid polymer matrix in direct contact with the skin. Adhesive surrounds the matrix to hold the patch. Common for hormone and nicotine patches; steady diffusion-based release. [1, 6, 10, 15]</p>

<p>Vapour Patch</p>  <p>5. VAPOUR PATCH Releases essential oils as vapours</p>	<p>Designed to release volatile compounds such as essential oils rather than drugs. Works via inhalation of vapours. Used for sleep and Relaxation. [19, 20, 23]</p>
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IV. MECHANISM OF ACTION



Transdermal patches deliver medications through the skin into systemic circulation in a controlled and sustained manner. Once applied, the patch adheres to the skin, and the drug diffuses from its reservoir or adhesive layer across the stratum corneum and underlying tissues [1], [5], [8], [26].

This process avoids gastrointestinal degradation and first-pass hepatic metabolism, ensuring improved bioavailability and consistent plasma drug levels [2], [7], [9], [27]. The drug molecules move primarily by passive diffusion, driven by the concentration gradient between the patch and the skin surface [3], [5], [13].

Modern transdermal systems incorporate permeation enhancers and microneedle-assisted delivery to improve skin absorption for drugs with limited permeability [14], [23], [26], [28]. Some patches also utilize electroporation and iontophoresis, applying

mild electrical currents to enhance the diffusion rate without damaging the skin barrier [20], [26], [29].

Overall, this mechanism provides steady-state therapeutic levels for extended periods, reduces dosing frequency, and minimizes fluctuations in drug concentration [4], [12], [25].

Techniques to Enhance Transdermal Transport

Several advanced methods have been developed to enhance transdermal transport [1], [4], [6], [9], [11], [13], [16], [18]:

A. Microneedles

Extremely small needles, either hollow or solid, penetrate the stratum corneum without causing pain, allowing larger molecules to enter the skin [5], [12], [14].

B. Iontophoresis

A mild electrical current drive charged drug molecules through the skin, and delivery rates can be precisely regulated via microprocessor control [6], [15], [17].

C. Thermal Poration

Localized heat creates tiny pores in the skin, facilitating drug passage [7], [16], [18].

D. Electroporation

Short bursts of high-voltage electricity temporarily form pores in the stratum corneum to increase permeability [9], [13], [19].

Chemical Enhancers: Topically applied agents that alter skin properties or drug characteristics to improve absorption [2], [4], [10], [12].

E. Ultrasound (Sonophoresis)

Sound waves disrupt the stratum corneum structure, enhancing drug penetration [3], [11], [15], [20].

These strategies work by temporarily reducing the barrier function of the skin, allowing drugs to reach systemic circulation efficiently while maintaining safety and patient comfort [1], [6], [8], [14], [17].

Role of Skin in Drug Absorption

The skin, being the largest organ of the human body, covers approximately 1.5–2 m² in adults and functions as a protective yet selective barrier for transdermal drug absorption [1], [3], [5]. It comprises three principal layers — the epidermis, dermis, and subcutaneous tissue — each contributing uniquely to the process of drug permeation [10], [11], [13].

1. Epidermis:

The epidermis is a multilayered, keratinized squamous epithelium. Its outermost layer, the stratum corneum, serves as the primary barrier to drug

penetration. Only small, lipophilic, and unionized molecules can effectively diffuse across this layer [6], [7], [19], [27].

2. *Dermis:*

The dermis is a vascular connective tissue layer that contains sweat glands, sebaceous glands, and hair follicles. Once a drug crosses the epidermis, it diffuses through the dermis, aided by the blood vessels and skin appendages [4], [12], [26].

3. *Subcutaneous Tissue (Hypodermis):*

The subcutaneous layer, composed of adipose and connective tissue, connects the skin to underlying muscles and acts as a cushion. It also plays a role in distributing absorbed drugs to deeper tissues [5], [13], [27].

Recent studies suggest that skin hydration, temperature, and the site of application significantly influence drug absorption. Advanced transdermal formulations employing nanoemulsions, lipid carriers, and polymer-based matrices have been developed to overcome the barrier resistance of the stratum corneum, enabling more efficient delivery of both hydrophilic and macromolecular drugs [15], [16], [26]–[29].

V. COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal Drug Delivery Systems (TDDS) are composed of four essential components [2], [3], [5], [7], [11], [13], [15]:

1. *Polymer Matrix*

The polymer matrix provides the structural framework and regulates drug release [3], [5], [7], [12].

Types of Polymers Used:

A. *Natural Polymers:* Cellulose derivatives, gelatin, waxes, starch, natural rubber, and gums [2], [10], [12].

B. *Synthetic Elastomers:* Polybutadiene, silicone rubber, neoprene, hydrin rubber, and acrylonitrile [5], [7], [11].

C. *Synthetic Polymers:* Polyethylene, polypropylene, polyacrylate, polyvinylpyrrolidone, and polymethyl methacrylate [3], [13], [15].

2. *Drug*

The drug is the active pharmaceutical ingredient responsible for therapeutic action. Ideal candidates for TDDS possess the following characteristics [2], [4], [6], [12], [14]:

- Molecular weight below approximately 1000 Daltons.
- Balanced solubility in both lipophilic and hydrophilic environments.
- Low melting point and high potency (effective in small doses).
- Minimal risk of irritation or allergic reactions.
- Stability under controlled release conditions and suitability for long-term administration.

3. *Permeation Enhancers*

Permeation enhancers are chemically inactive compounds that temporarily increase skin permeability. By interacting with the lipid bilayers of the stratum corneum, they facilitate drug transport into systemic circulation [1], [5], [9], [11], [15].

Table II: Examples of Permeation Enhancers

Type	Mechanism	Advantages	Limitations	Examples
Water	Swells skin layers	Safe, enhances hydrophilic and lipophilic drugs	Limited effect	Water [2, 10]
Hydrocarbons	Disrupt lipid structure	Good for lipophilic drugs; occlusive	Poor for hydrophilic drugs	Alkanes, squalane [3, 12]
Alcohols	Extract lipids; swell skin	Enhances diffusion and drug distribution	Can damage keratinocytes	Ethanol, glycerol [5, 13]

Fatty acids	Disrupt lipids; form drug complexes	Broad applicability; low cost	Less effective for some configurations	Oleic acid, linoleic acid [7, 14]
Fatty acid esters	Alter lipid organization	Enhances penetration	High concentrations may reduce effect	Isopropyl myristate, Transcutol® [11, 15]
Amines Separate	Separate lamellar lipids	Improves distribution of a range of drugs	May irritate skin	Primary, secondary amines [3, 7]
Amides	Integrate into lipid bilayers	Enhances hydrophilic and hydrophobic drugs	Stability issues	Laurocapram (Azone), pyrrolidone [2, 5]

4. Other Excipients

Adhesives secure the patch to the skin, while stabilizers, solvents, and other excipients ensure uniform drug release and overall system performance [1], [4], [6], [12], [13].

VI. ADVANTAGES

- 1) Avoids first-pass metabolism, improving the bioavailability of drugs [2], [3], [7], [12].
- 2) Provides sustained and controlled drug release over an extended period [1], [5], [11], [13].
- 3) Maintains stable and consistent plasma drug levels [2], [4], [10], [15].
- 4) Enhances patient compliance due to simple and convenient application [3], [6], [12], [14].
- 5) Reduces gastrointestinal side effects associated with oral administration [5], [7], [11].
- 6) Minimizes fluctuations in drug concentration within the bloodstream [2], [4], [12], [13].
- 7) Suitable for drugs with short half-lives or narrow therapeutic windows [1], [3], [6], [15].
- 8) Allows easy termination of therapy in case of adverse effects or toxicity [2], [5], [7].
- 9) Enables self-administration and can be used in unconscious patients [4], [10], [12].

- 10) Reduces the overall dosing frequency, improving adherence to therapy [3], [7], [11], [13].

VII. DISADVANTAGE

- 1) Limited to drugs with appropriate physicochemical properties for skin penetration [2], [3], [12].
- 2) Not suitable for drugs requiring high daily doses (usually >5–10 mg/day) [5], [7], [13].
- 3) Ineffective for large-molecule drugs or compounds with poor skin permeability [1], [4], [10].
- 4) Cannot deliver ionic or highly polar drugs efficiently [2], [6], [12].
- 5) May cause local skin irritation, redness, or itching at the application site [3], [5], [11].
- 6) Achieving high plasma drug concentrations is difficult [2], [7], [14].
- 7) Not capable of providing pulsatile or immediate drug delivery [1], [3], [12].
- 8) Long-term use may cause discomfort due to patch adhesion or placement [4], [5], [13].
- 9) Patch performance may vary between individuals and over time [2], [6], [15].
- 10) Production and formulation of patches can be more costly than conventional dosage forms [1], [3], [7], [11].

VIII. MARKETED TRANSDERMAL PATCHES

Table III : Marketed Transdermal Patches

Drug	Brand / Product	Therapeutic Use	Duration of Application	Patch Type	Reference(s)
Scopolamine	Transderm-Scop	Prevents motion sickness	72 hours	Reservoir / Membrane	[1, 5, 12]

Nitroglycerin	Transderm-Nitro / Nitro-Dur	Angina relief	12–14 hours	DIA / Microreservoir / Matrix	[1, 5, 13]
Clonidine	Catapres-TTS	High blood pressure	7 days	Reservoir / Membrane	[1, 5, 13]
Estradiol	Estraderm / Climara / Vivelle-Dot / Alora / Menostar / Minivelle	Menopause / Hormone therapy	3–7 days	Reservoir / Membrane / Matrix	[1, 5, 13, 16]
Fentanyl	Duragesic / MatrifenR	Chronic pain management	72 hours	Reservoir	[1, 5, 13]
Nicotine	Nicoderm CQ / Habitrol / Nicorette / Nicorette Invisipatch	Smoking cessation	16–24 hours	Matrix / Reservoir / DIA	[1, 5, 13, 16]
Testosterone	Androderm / Testoderm / Axiron	Low testosterone	24 hours	Reservoir / Membrane / Topical solution	[1, 5, 16]
Lidocaine	Lidoderm / Iontocaine / Synera	Pain relief / Local anesthesia	12–30 min / 12 hours	DIA / Eutectic mixture	[5, 12, 16]
Oxybutynin	Oxytrol	Overactive bladder	3–4 days	Matrix	[5, 13, 16]
Rivastigmine	Exelon	Alzheimer's / Dementia	24 hours	Matrix	[5, 13, 16]
Rotigotine	Neupro	Parkinson's / Restless legs syndrome	24 hours	DIA	[5, 12, 16]
Selegiline	Emsam	Depression	24 hours	DIA	[5, 12, 16]
Estradiol / Norethindrone	Combipac	Menopause / Hormone therapy	3–4 days	DIA	[5, 13, 16]
Ethinyl Estradiol / Norelgestromin	Ortho Evra	Contracepti	7 days	DIA	[5, 13, 16]
Estradiol / Levonorgestrel	Climara Pro	Menopause / Hormone therapy	7 days	DIA	[5, 13, 16]
Buprenorphine	Butrans	Pain / Opioid dependence	7 days	DIA	[5, 12, 16]
Methylphenidate	Daytrana	ADHD management	Up to 9 hours	DIA	[5, 12, 16]
Granisetron	Sancuso	Nausea & vomiting due to chemotherapy	Up to 7 days	DIA	[5, 12, 16]

Capsaicin	Qutenza	Neuropathic pain	Single 60 min	DIA	[5, 12, 16]
Diclofenac epolamine	Flector	Acute pain	12 hours	DIA	[5, 12, 16]

IX. FUTURE SCOPE

Over the last decade, the application of transdermal patches for medications such as nicotine, nitroglycerin, clonidine, scopolamine, and estradiol has remained relatively stable, with few novel drugs introduced in patch form [1], [5], [12], [13]. This is primarily due to the stringent molecular size, lipophilicity, and potency requirements necessary for effective transdermal delivery [3], [7], [11]. Moreover, the specialized nature of patch manufacturing often encourages companies to retain in-house production to ensure quality control and maximize profitability [16], [18].

Ongoing research focuses on enhancing adhesive formulations and excipients to improve skin adhesion, drug stability, and delivery efficiency [8], [10], [17], [19]. Since no single adhesive is universally suitable for all drugs, customizing adhesive chemistry is crucial to optimize patch performance [9], [14]. Additionally, innovative approaches have explored the use of mechanical energy to temporarily modify the skin barrier or increase the energy of drug molecules, thereby enhancing transdermal permeation [20], [21], [24].

X. CONCLUSION

Transdermal drug delivery systems (TDDS) offer a reliable, non-invasive method for systemic drug administration, bypassing first-pass metabolism and reducing the risk of adverse effects [1], [3], [5], [12]. These systems enable precise and consistent drug release over a defined period while maintaining stability until the drug reaches the target site [7], [11], [13], [16]. Furthermore, TDDS enhances the absorption of poorly bioavailable drugs and facilitates prolonged administration of therapeutically effective doses safely and efficiently [8], [10], [17], [19].

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