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An Overview of the Transdermal Drug Delivery System

Yi-You Huang[1], Chao-Min Cheng[2*], Yunching Chen[2], Fang-Ying Wang[1,3,4]

[1]Department of Biomedical Engineering, College of Medicine, College of Engineering, National Taiwan University, Taipei, Taiwan.
[2]Institute of Biomedical Engineering, National Tsing Hua University, Hsinchu, Taiwan.
[3]Department of Dermatology, Chang Gung Memorial Hospital, Linkou Branch, Taoyuan, Taiwan.
[4]College of Medicine, Chang Gung University, Taoyuan, Taiwan.

***E-mail** ✉ chaomin@mx.nthu.edu.tw

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ABSTRACT

The transdermal drug delivery system (TDDS) has emerged as a significant advancement in drug administration, offering numerous benefits in pharmaceutical treatments. Transdermal patches, which deliver drugs through the skin, provide a systemic effect by allowing the drug to penetrate the dermis. This approach offers advantages such as continuous drug absorption, more stable plasma concentrations, reduced first-pass metabolism, fewer side effects, ease of use, and the ability to terminate treatment by simply removing the patch. TDDS stands out over traditional oral and intravenous drug delivery methods, ensuring controlled drug release for prolonged therapeutic effects. The development of transdermal patches has spurred extensive research into chemical and physical approaches to optimize their performance. Early-generation systems primarily focused on delivering small, lipophilic, low-dose drugs, while more advanced systems incorporate chemical enhancers, ultrasound, and iontophoresis for real-time regulation of drug release. Cutting-edge third-generation systems use technologies such as microneedles, thermal ablation, microdermabrasion, electroporation, and cavitational ultrasound to improve drug permeability through the outer layer of the skin. This article provides an overview of the development of different types of transdermal patches, explores methods for assessing transdermal drug delivery, and highlights the ongoing progress in TDDS technology.

Keywords: Patches, TDDS, Polymers, Transdermal elements, Topical delivery

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Introduction

Transdermal drug delivery systems (TDDS) have garnered significant attention as a promising alternative to traditional oral medications and hypodermic injections [1]. Compared to these conventional methods, TDDS offers several benefits, such as continuous drug release, minimizing hepatic first-pass metabolism, reducing systemic side effects, maintaining consistent blood drug concentrations throughout treatment, and improving patient adherence. Despite these advantages, the widespread use of TDDS is limited by the skin's natural barrier, particularly the stratum corneum, which prevents the entry of foreign substances. Only a select few drugs—typically small, lipophilic, and potent with low molecular weights—can passively penetrate the skin and reach therapeutic concentrations in the bloodstream. In recent years, there has been a surge of interest in developing novel methods to enhance the delivery of existing drugs, aiming to improve treatment efficacy, safety, patient compliance, and overall therapeutic outcomes. TDDS are self-contained, unit-dose forms, commonly referred to as "patches," which provide a convenient alternative to oral drug delivery by alleviating the strain on the digestive system and liver. These patches offer better patient satisfaction, reduce toxic side effects, and simplify medication administration, typically requiring only a single application. By maintaining steady plasma drug levels and increasing bioavailability, TDDS enhances drug efficacy, reduces the frequency of dosing, and prolongs

therapeutic effects while minimizing adverse reactions. Many transdermal patches release the active ingredient at a controlled, zero-order rate for several days, making them ideal for chronic disease management and prevention [2-5].

This article provides an overview of the development of various types of transdermal patches, explores methods for assessing transdermal drug delivery, and highlights the ongoing progress in TDDS technology.

Results and Discussion

Future of transdermal drug administration

Skin's drug absorption mechanisms

The outermost layer of the skin, known as the stratum corneum, plays a crucial role in the skin's barrier function. Composed of approximately 75-80% dry protein, 5-20% lipid, and a small percentage of other components, it is the primary barrier to drug penetration [6]. Beneath the stratum corneum lies the viable epidermis, which is continuously regenerated through cell division in the basal layer [7]. The dermis, located below the epidermis, is thicker and contains capillaries essential for maintaining skin barrier function and temperature regulation. The hypodermis connects the skin layers to underlying tissues and helps protect against mechanical stress [8]. For transdermal drugs to be effective, they must pass through all three layers: the epidermis, dermis, and hypodermis, before entering the bloodstream.

Drug molecule penetration through the skin

According to Fick's first law of diffusion, drug molecules move from areas of higher to lower concentration until equilibrium is reached. This process drives the diffusion of drug molecules through the skin. After being released from the drug formulation, the molecules travel through the epidermal layer, partition into the dermis, and subsequently enter the bloodstream. This mechanism allows the drug to treat targeted skin conditions effectively [9].

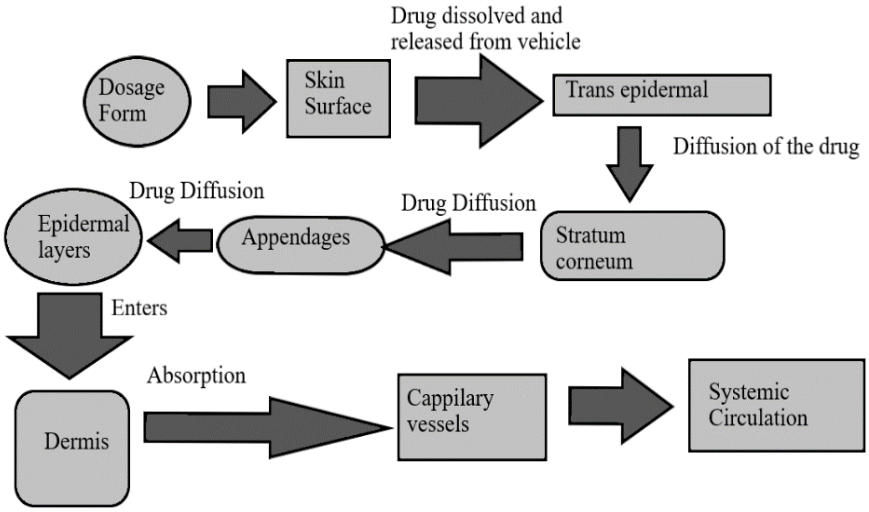

Figure 1. Drug absorption mechanism via skin

The application of the dosage form on the skin surface allows it to pass through the outer layer and penetrate the skin appendages. It continues its journey by diffusing through the epidermis to reach the dermal layer, where it is absorbed by capillaries and enters systemic circulation, as shown in **Figure 1**.

Percutaneous absorption

Percutaneous absorption is a widely used term to describe the process of delivering substances through the skin, although other terms like sorption, permeation, perception, and penetration are sometimes used in scientific literature. In essence, percutaneous absorption involves substances moving through the skin layers and entering the bloodstream via the epidermis, as illustrated in **Figure 2** [10]. This absorption can occur in two main processes:

Trans-epidermal absorption

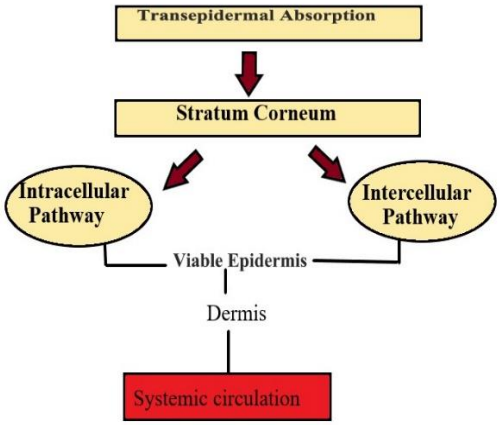

Figure 2. Mechanism of trans-epidermal absorption

In trans-epidermal transport, molecules traverse the intact stratum corneum. Two main pathways are involved: intracellular and intercellular. Both polar and non-polar molecules can pass through these routes, albeit in different manners. Polar molecules tend to move along the hydrated channels within the stratum corneum, while non-polar molecules navigate through the non-hydrated lipid-rich matrix of the stratum corneum [11].

Trans-follicular absorption

This pathway involves the transportation of substances through hair follicles and sebaceous glands, often assisted by sweat glands. Although these routes are highly permeable, they account for only about 0.2% of the skin's surface area, making them relatively minor. However, they become significant for larger polar compounds and ions that are unable to penetrate the stratum corneum. Skin appendages function as secondary pathways for permeation. The follicular route plays a critical role in percutaneous absorption, as the follicular pores, where hair emerges from the skin, are quite large and facilitate the movement of substances [12].

Stages of transdermal penetration

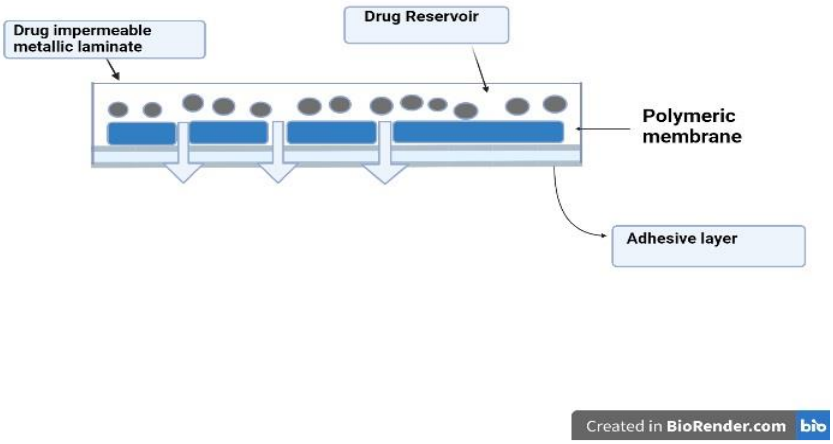

Figure 3. Mechanism of transdermal patch

For effective transdermal drug delivery, the drug must be absorbed efficiently, with appropriate rates used to maintain consistent blood and therapeutic concentrations throughout its application. Once a drug molecule crosses

the stratum corneum barrier, it quickly penetrates the underlying dermis, facilitating systemic absorption **(Figure 3)** [13].

Factors affecting transdermal permeation

Transdermal permeation is influenced by several factors, including

The physical and chemical characteristics of the drug molecule

- The partition coefficient
- The pH of the surrounding environment
- The concentration of the drug

The physicochemical properties of the drug delivery system

- The characteristics of the drug release
- The use of penetration enhancers
- The formulation of the drug delivery system

The skin's pathophysiological condition

- The reservoir effect of the stratum corneum
- Skin hydration
- The lipid layer
- Skin temperature [14]

Need for transdermal patches

Transdermal patches offer a non-invasive method for transporting active compounds into the bloodstream through the skin, a key organ in drug delivery systems. The first patch, designed to treat motion sickness, received approval in 1981. Presently, North America has more than 25 FDA-approved transdermal patches, with over 40 still undergoing clinical trials. In total, $6 trillion in funding has been allocated to this field [15]. Approved patches include medications such as fentanyl, nitroglycerin, estradiol, and nicotine, among others. Recently introduced patches include ones that treat conditions like hyperactive bladder, using drugs like oxybutynin. Compared to traditional oral or injectable methods, transdermal delivery has many advantages.

Benefits of TDDS [16-19]

- Avoids the first-pass metabolic effect.
- Helps maintain consistent blood pressure and regulate circulation.
- Mimics aspects of intravenous treatments.
- Does not disrupt gastrointestinal fluids.
- Allows for easy self-administration and avoids injection-related discomfort.
- Effective for drugs that struggle with absorption or degradation in the digestive system.
- More economical than conventional drug delivery methods.

Challenges of transdermal drug delivery

- Not suitable for cationic drugs.
- Requires specific chemical and physical attributes for effective penetration.
- Struggles to reach ideal serum drug concentrations.
- Managing pulsatile release is challenging.
- Maintaining consistent use over time can be difficult.
- May cause skin irritation due to the drug or excipients.

Mechanisms of transdermal drug absorption

Understanding the dynamics of transdermal absorption is key to improving these systems. Key mechanisms include:

- Passage through the outer skin layer (stratum corneum)
- Movement across deeper skin layers
- Absorption in the epidermal-dermal papillae

Factors impacting transdermal absorption

Various factors influence the efficiency of transdermal drug delivery. These include genetic aspects like skin type, age, blood flow, and ethnicity, as well as physiological conditions such as skin moisture, pH, and temperature. Drug-related characteristics, including loading capacity, diffusion rate, partition coefficient, and molecular size, also play a significant role. Furthermore, environmental conditions, such as temperature extremes, air quality, and sunlight, can impact how well drugs are absorbed through the skin [19-21].

Impact of temperature on transdermal patches

Temperature significantly influences the absorption of drugs through transdermal systems. External heat sources, such as hot water bags or heaters, should not be used during application, as they can alter the patch's functionality. Higher body temperatures can accelerate drug absorption, but the patch should be removed immediately if it causes excessive heat. Proper storage in its original packaging, kept cool and protected, is essential until the patch is ready to be applied to maintain its efficacy [14, 22].

Formulation of transdermal drug delivery systems

A well-designed transdermal system must incorporate factors like appropriate system size, precise targeting of the application site, repeatable delivery mechanisms, and efficient drug release, ensuring that it provides consistent performance over time [23-25].

Key components of transdermal drug delivery systems

- *Polymer matrix/drug reservoir*: The polymeric material that controls drug delivery is central to the transdermal system. These polymers must be stable, compatible with the drug and other system components, and allow for safe and controlled drug release [26].
- *Drug selection*: The physical and chemical properties of the drug are crucial for determining its suitability for transdermal delivery. Drugs with characteristics that facilitate skin penetration are ideal for this delivery method [27].
- *Permeation enhancers*: These substances help to increase the permeability of the skin's outer layer by interacting with its proteins and lipids, thereby promoting enhanced drug absorption. Examples include DMSO and oleic acid [28, 29].
- *Pressure-sensitive adhesives (PSA)*: The adhesive used in transdermal patches must ensure a firm bond to the skin with minimal effort. It should provide strong adhesion, be gentle on the skin, and not leave residues when removed. The adhesives must be compatible with both the drug and the skin, ensuring effective delivery and minimizing irritation. Materials like polyacrylates, polyisobutylene, and polysiloxane are commonly used in these applications [30, 31].
- *Backing laminate*: This component must be flexible, durable, and able to withstand body movement. Polyolefin, polyester, and epoxies are often used materials, as they also reduce water vapor transfer, enhancing skin moisture and drug absorption [32].
- *Release liners*: Protective liners are used to cover the patch during storage, which are removed before application. This ensures the patch remains intact and effective until it is ready for use [33, 34].
- *Other excipients*: Solvents and plasticizers are included in the formulation of transdermal patches. Solvents like chloroform, acetone, and isopropanol, along with plasticizers like dibutyl phthalate and triethyl-citrate, help improve the flexibility and drug delivery properties of the patch [35].

Techniques for creating transdermal drug delivery systems

- *Asymmetric TPX membrane method*: This method involves preparing hydrogel-based reversal devices by mixing TPX with a combination of a solvent (cyclohexane) and a non-solvent at 60 °C. The polymer solution is kept at 40 °C before being poured onto a glass slide, using a blade to ensure the correct depth. After allowing the formed layer to vaporize at 50 °C for 30 seconds, the glass slide is quickly dipped into a coagulation bath at 25°C. The barrier is left to soak for 10 minutes before being dried in an oven at 50 °C for 24 hours [26, 36].
- *Mercury substrate technique*: In this approach, the drug is dissolved in a suitable solvent along with a lubricant. The resulting solution is then spun for 10-15 minutes to ensure uniform distribution, before being spread onto a flat surface. Solvent removal is then carried out under controlled conditions [37].

- *Circular Teflon mould approach*: Chemical reagents are mixed with polymers in specific ratios. The drug is added in an amount equal to half the organic liquid's rate. Activators are dissolved and incorporated into a separate portion of the organic liquid. Di-N-butyl phthalate is used as a lubricant for the medication polymer. The mixture is spun in Teflon moulds for 12 hours. The moulds are positioned in a laminar flow hood with a 0.5 m/s airspeed and adjusted using a reverse feeder. After 24 hours, the solvent evaporates. The dried film is then kept in a desiccator containing silica gel at 25 °C for an additional 24 hours to prevent fading. These films should be tested within a week [38].
- *Free film method*: This process involves creating dry films on a cellulose acetate mercury surface. A 2% w/w polymeric solution is made using chloroform, with plasticizers added at 40% of the polymer weight. The solution is poured onto the mercury surface of a Petri dish, and an inverted disc is placed over it to control the rate of solvent evaporation. Once the solvent has completely evaporated, the film is formed and removed between two wax paper sheets before being stored in a desiccator. The film's thickness can be varied by adjusting the amount of solvent used.

Evaluation methods for transdermal drug delivery systems [39]

Physicochemical analysis

Thickness measurement

A digital micrometer is used to assess the thickness of the patches at various points to ensure uniformity in the film's thickness. Both the maximum and minimum thickness values are recorded.

Uniformity of weight

The films are dried at 60 °C for 4 hours before being weighed. Different sections of the patch are cut and weighed using an electronic balance at multiple locations. The average and standard deviation of the weight measurements are then calculated.

Drug content determination

A small portion (approximately 100 mg) of the patch is placed into 100 ml of a suitable solvent. The mixture is stirred for 24 hours in a shaking flask to dissolve the drug. After sonification and filtering, the absorbance of the solution is measured to determine the drug content.

Content uniformity test

The content uniformity test ensures consistency in drug delivery. For this, nine out of ten patches must have a drug content between 85% and 115%, with the tenth patch ranging from 70% to 125%. If three patches fall within 75% to 125%, an additional 20 patches are tested. The drug content of these patches should range between 85% and 115%.

Moisture uptake

To maintain a relative humidity of 84%, the patches are stored in a desiccator with a potassium chloride-saturated solution. After 24 hours, the patches are weighed, and the moisture uptake is calculated using the following formula:

$$\% \text{ Moisture uptake} = (\text{Final weight} - \text{Initial weight})/\text{Initial weight} \times 100 \quad (1)$$

Folding endurance

A section of the patch is repeatedly folded at the same location until it breaks, indicating its durability and folding tolerance without tearing.

Flexural strength

To evaluate the flexibility, the polymer film is attached to a set of metal slabs. One end of the film is secured, while the other is connected to a free-moving thread. Weights are added gradually, and the film's stretch is monitored by a marker on the thread until the patch breaks.

Tack properties

Tack refers to the ability of a polymer to adhere to a surface with minimal force. It is influenced by the molecular weight, content, and resin used in the polymer.

Thumbtack test

This test measures the ease with which a thumb can be removed from the adhesive layer, indicating its tackiness.

Peel tack test

In this test, the patch is peeled from the substrate at a rate of 13 inches per minute, and the force required to peel the patch is measured, giving a tack value in grams per inch of width.

In vitro release studies

The in vitro drug release from transdermal patches is evaluated using the disc paddle method (USP apparatus V). Patches of the desired thickness are cut into a specified shape, weighed, and adhered to a glass slide using an adhesive. The glass slide is then placed in the apparatus, with the temperature adjusted to 32 ± 0.5 °C using 500 mL of phosphate-buffered saline at pH 7.4. The paddle is positioned 2.5 cm from the glass surface and operates at a speed of 50 rpm. Samples (5 mL) are taken periodically for up to 24 hours, and the drug concentration can be analyzed using HPLC or UV spectrophotometry. The experiment is repeated three times, and the average release value is calculated [40].

In vivo studies

Animal models

Due to the high cost and time required for human trials, small-scale animal testing is recommended. Common animal models for transdermal drug delivery studies include mice, hairless rats, hairless dogs, hairless rhesus monkeys, rabbits, and guinea pigs. Studies suggest that hairless animals provide more accurate results than their hairy counterparts for both in vitro and in vivo testing. The rhesus monkey is considered one of the best models for precise transdermal delivery in vivo [41].

Applications of transdermal patches

- Nicotine patches are widely used in the U.S. to aid individuals in quitting smoking by delivering controlled amounts of nicotine.
- Fentanyl patches (Duragesic) and Buprenorphine Patches (BuTrans) are opioid medications designed for continuous pain relief over 24 hours.
- Nitroglycerin patches offer an alternative to buccal tablets for managing angina.
- Selegiline is the first transdermal antidepressant used for the treatment of depression.
- Clonidine Patches are used as a transdermal treatment for hypertension.

Scope of transdermal drug delivery systems [42]

- Dexamethasone iontophoretic patch is used for treating tennis elbow.
- Varenicline smoking cessation patches and high-dose nicotine patches are designed for rapid metabolizers to help quit smoking.
- Selegiline patch is used for treating elderly depression and addressing drug dependencies.
- Sufentanil patch is a new method for managing cancer-related pain.
- Transdermal glyceryl trinitrate is used in the treatment of stroke, among other applications.

Conclusion

Transdermal drug delivery systems (TDDS) offer a promising approach to drug administration, utilizing methods that are safe, efficient, and cost-effective. Due to the numerous benefits of TDDS, ongoing research is focused on incorporating additional drugs into these systems. Key components of transdermal patches, such as drug reservoirs, liners, adhesives, porosity enhancers, laminates, plasticizers, and solvents, each contribute to the effective delivery of medications through the skin. A variety of techniques are employed in the production of these patches, followed by extensive testing for physicochemical properties, in-vitro performance, skin irritation, and stability. Before commercialization, all developed and tested transdermal patches must undergo clinical validation

for their intended therapeutic applications. The future development of TDDS will likely prioritize enhancing flexibility and expanding the range of drugs that can be delivered effectively. This technology could offer healthcare professionals a broader spectrum of treatment options, maximizing the benefits of therapies for patients.

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