World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Review topic: A detailed analysis of transdermal drug delivery system

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World Journal of Biology Pharmacy and Health Sciences, 2024, 20(03), 292–300

Publication history: Received on 30 October 2024; revised on 05 December 2024; accepted on 07 December 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.20.3.0999

Abstract

Transdermal drug delivery systems (TDDS) are a novel approach for administering medications through the skin, offering several advantages over conventional methods like oral or intravenous delivery. TDDS allow for controlled and consistent drug release, effectively bypassing the gastrointestinal tract and avoiding first-pass metabolism, which can enhance bioavailability and reduce systemic side effects. However, the skin's barrier properties present significant challenges for drug permeation, particularly for larger or hydrophilic molecules. To address these challenges, various methods have been developed, including chemical permeation enhancers, microneedles, iontophoresis, and sonophoresis, to facilitate drug delivery.

The typical components of TDDS include an active pharmaceutical ingredient, an adhesive matrix, a release liner, and a backing layer, each contributing to the controlled release and stability of the system. Despite these advancements, TDDS are primarily effective for small, lipophilic drugs, and issues such as skin irritation and limited permeation for larger molecules continue to be significant challenges. Recent innovations, such as the use of nanoparticles, 3D printing technology, and personalized delivery systems, show promise in overcoming these limitations. This review examines the principles, benefits, challenges, and recent developments in transdermal drug delivery systems, highlighting their potential applications in chronic disease management, hormone therapy, and vaccine delivery, as well as future directions for enhancing their efficacy and expanding their therapeutic range.

Keywords: Patch; Topical administration; Systemic circulation; Transdermal drug delivery system

1. Introduction

Transdermal Drug Delivery Systems (TDDS) are defined as self-contained discrete dosage forms, commonly known as "patches." When these patches are applied to intact skin, they deliver drugs at a controlled rate into the systemic circulation. The drugs can have effects on tissues adjacent to the application site or can exert their effects after being distributed through the circulatory system. The drug initially penetrates through the stratum corneum and then moves through the deeper layers of the epidermis and dermis without accumulating in the dermal layer.TDDS provide a non-invasive alternative that can enhance patient compliance and minimize side effects. This method involves formulating the drug into patches or gels that release the active ingredient slowly over time, allowing for sustained therapeutic effects. One of the primary advantages of TDDS is its ability to bypass the gastrointestinal tract and first-pass metabolism, which can degrade many drugs when taken orally. Additionally, transdermal systems can offer controlled drug release, leading to stable plasma drug concentrations and reduced peaks.

Transdermal patches, also referred to as adhesive patches or skin patches, are designed to deliver a controlled dose of drug through the skin over a specified period. These patches utilize a special membrane to regulate the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and enter the bloodstream. Some

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drugs may need to be combined with substances, such as alcohol, to enhance their ability to penetrate the skin for effective use in patches. The transdermal device is considered a membrane-moderated system.

The first transdermal system, Transdermal SCOP, was approved by the FDA in 1979 for the prevention of nausea and vomiting associated with travel. TDDS have gained significant attention for managing chronic conditions such as pain, hormone replacement therapy, and cardiovascular diseases, making them a versatile option in modern therapeutics. Currently, transdermal delivery is regarded as one of the most promising methods for drug application, as it reduces the burden that the oral route typically places on the digestive tract and liver.

2. History

The concept of transdermal drug delivery has ancient origins, with various cultures employing topical remedies like ointments and poultices for medicinal purposes. Indigenous populations worldwide have historically used plant extracts and other substances directly on the skin to treat ailments. The formal recognition of transdermal delivery as a drug administration route gained traction in the early 20th century. The first transdermal drug delivery system (TDDS) was developed in 1980, specifically the scopolamine patch for motion sickness, providing 72-hour prophylaxis. Additionally, during the 19th century, the use of adhesive plasters infused with medicinal substances became quite popular.

- Early 20th Century: In this period, various methods were experimented with to enhance drug absorption through the skin. These early efforts included the use of chemical permeation enhancers and simple transdermal patches.
- 1950s-1960s: The modern era of TDDS development began in the mid-20th century, with researchers investigating patches for more effective drug delivery. In 1952, the first transdermal patch, known as the “Scop” patch, was developed for motion sickness. This patch contained scopolamine and proved the feasibility of transdermal drug delivery.
- 1970s: The introduction of the first commercially available transdermal patch, the nitroglycerin patch for treating angina, marked a significant milestone in TDDS development during the 1970s. This innovation paved the way for the delivery of other drugs through the skin.
- 1980s-1990s: The following decades saw substantial advancements in TDDS technology. The 1980s introduced fentanyl patches for chronic pain management, while the 1990s brought nicotine patches for smoking cessation and hormonal patches for birth control and hormone replacement therapy. Numerous transdermal drug delivery systems have since been launched in the global prescription drug market.[1]

2.1 Types of Transdermal Patches

The types of transdermal patches are :-

- Single-layer drug in adhesive
- Multi-layer drug in adhesive
- Reservoir
- Matrix
- Vapour patch

2.2 Single-layer drug in adhesive

Adhesive layer of this system contains the drug. In this type of patch, the adhesive layer not only serves to bond the various layers together and attach the system to the skin but is also responsible for the drug release. The rate of drug release from this system is influenced by the diffusion process across the skin. Surrounding the adhesive layer are a temporary liner and a backing layer.

2.3 Multi-layer drug in adhesive

The multi-layer drug-in-adhesive patch is comparable to the single-layer system in that both adhesive layers play a role in drug release. One layer is designed for the immediate release of the drug, while the other layer facilitates controlled release from the reservoir. Furthermore, the multi-layer patch consists of a temporary liner and a permanent backing.

2.4 Reservoir

Unlike the single-layer and multi-layer drug-in-adhesive systems, the reservoir transdermal system features a separate drug layer. This drug layer is a liquid compartment that contains a drug solution or suspension, which is separated by the adhesive layer. The patch is also supported by a backing layer, as shown in the figure. In this type of system, the rate of drug release is zero-order.

2.5 Matrix

The Matrix system design as shown in Fig. has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlying it.

These type of patches are also known as monolithic device.

2.6 Vapour patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controlled vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a mouth are also available on the market.

2.7 Basic Components Of TDDS

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents [2]

2.8 Skin Information

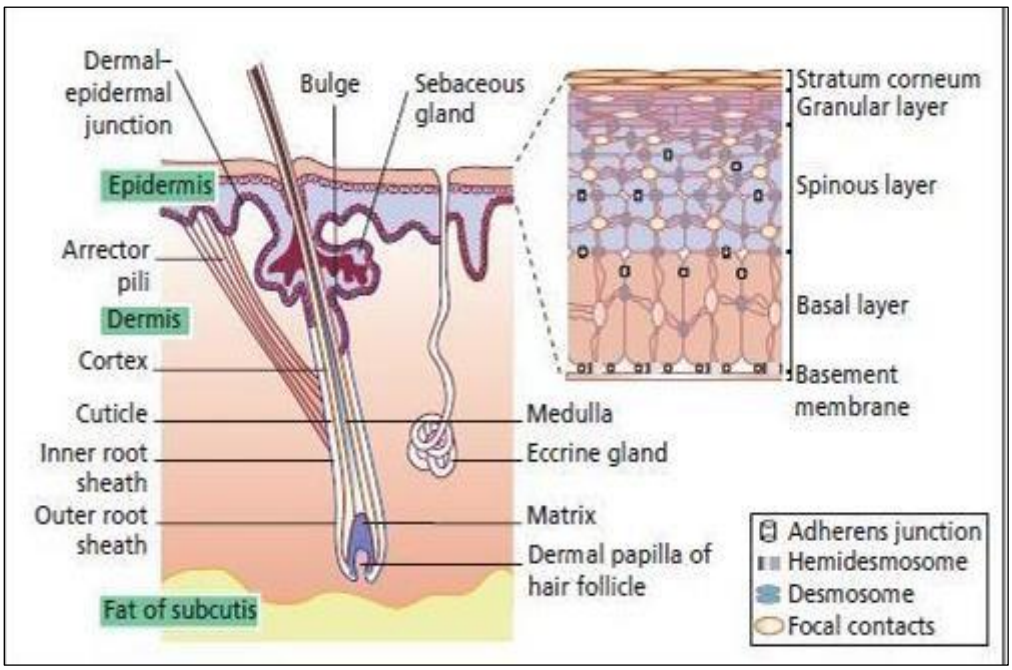

Figure 1 Anatomical and physiological structure of skin

The skin is the largest organ of the human body, covering an approximate surface area of 2 square meters and accounting for about one-third of the body's blood circulation. It serves as a permeability barrier against the transdermal absorption of various chemicals and biological agents. The skin significantly influences several drug

delivery aspects, such as the permeation and absorption of drugs across the dermis. It is generally described in terms of three tissue layers: the epidermis, the dermis, and the hypodermis.

2.9 Epidermis

The outer layer of skin, made of epithelial cells, plays a vital role in maintaining the skin's unique integrity. The epidermis is thickest on the palms and soles, gradually thinning over the trunk's ventral surface. It consists of two main parts: the stratum corneum and the stratum germinativum.

The stratum corneum, the outermost layer of the epidermis, is composed of many layers of compacted, flattened, dehydrated, keratinized cells in a stratified arrangement. This layer acts as a barrier, limiting the movement of substances in and out. The stratum corneum is about 10 mm thick when dry but can swell significantly when fully hydrated. Cells in the basal cell layer of the stratum germinativum slowly move upward, serving as the regenerative layer of the epidermis. In thicker skin areas, the transition from living cells in the germinativum zone to dead cells in the stratum corneum is facilitated by three layers: the stratum spinosum, the stratum granulosum, and the stratum lucidum. Removing these upper epidermal layers can lead to water loss and increased skin permeability

2.10 Dermis

Dermis is layer of skin just under epidermis which is 3 to 5 mm thick layer & is composed of matrix of connective tissues, which contain blood vessel, lymph vessel & nerves. It provides nutrients & oxygen to skin, while removing toxin & waste products. The blood supply keeps dermal concentration of permeate very low & resulting concentration difference across epidermis provides essential driving force for transdermal permeation.

2.11 Hypodermis

It is subcutaneous outer layer of dermis. It is elastic layer. Large amount of fat cells which will be present & it contains thickness in 4-9mm. It carries principal blood vessel & nerves to skin & may contain sensory pressure organs. [3]

2.12 Routes of skin penetration

There are three potential entry routes of drug to the viable tissue (dermis) 1)

- Via the sweat ducts.
- Hair follicles and their associated sebaceous glands
- Across the continuous stratum corneum.

The skin permeation of most neutral molecules at steady state can thus be considered primary a process of passive diffusion through the stratum corneum in the index follicular region.[4-5]

3. Technologies Of Developing Transdermal Drug System

This technology can be classified into four basic approaches:

3.1 Polymer membrane permeation Controlled TDDS

In this type of controlled drug delivery system (CDDS), a drug formulation is either fully or partially encapsulated. The drug reservoir compartment has a drug-releasing surface that is covered by a rate-controlling polymeric membrane. The drug reservoir can consist of a dispersion of solid drug particles or a concentration of drug solution in either a liquid or solid dispersing medium.

The polymeric membrane can be made from various materials, including homogeneous or heterogeneous, non-porous polymers, as well as micro-porous or semi-permeable membranes. These formulations can be prepared using techniques like molding, encapsulation, or micro-encapsulation. Different sizes and shapes of drug delivery systems can be designed. The release of the drug from the system depends on factors such as the partition coefficient, the liquidity of the drug molecule, and the thickness and characteristics of the rate-controlling membrane. Examples include transdermal patches and sub-dermal implants.

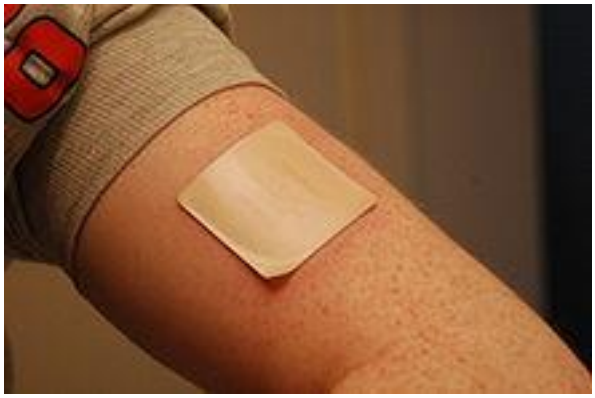

Figure 2 Membrane permeatation Controlled Transdermal patch

3.2 Polymeric Matrix Diffusion CDDS

In this type of controlled drug delivery system (CDDS), the reservoir is created from a homogeneous dispersion of drug particles in either a lipophilic or hydrophilic polymer matrix. The drug dispersion can be achieved through several methods:

- By blending a dose of finely ground drug particles with a viscous liquid or semi-solid polymer, followed by cross-linking of the polymer chains.

- By mixing solid drug particles with melted polymer at an elevated temperature. The resulting drug-polymer dispersion is then molded to create specific sizes and shapes for targeted applications.

- By dissolving both the drug and polymer in a common solvent, followed by the evaporation of the solvent at elevated temperatures.These techniques allow for the customization of the drug delivery system to meet specific therapeutic needs.

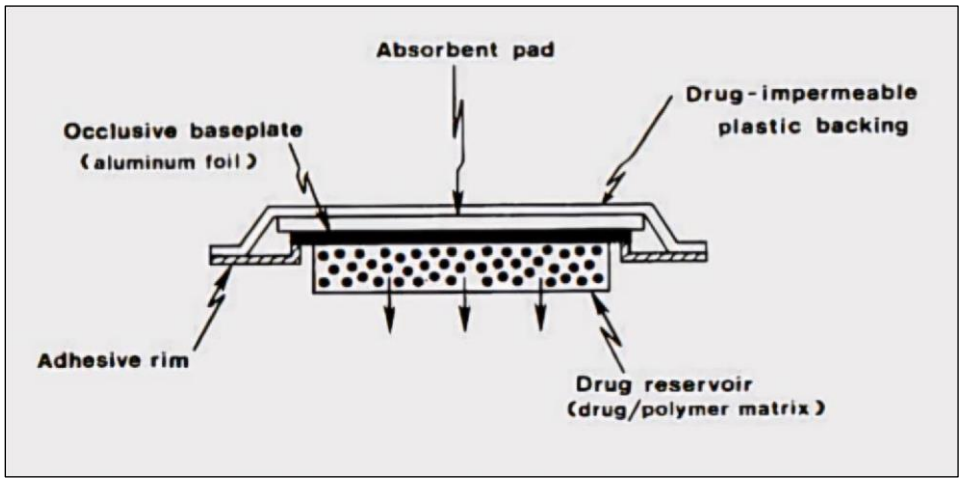

Figure 3 Polymeric Matrix Diffusion System**.**

3.3 Polymeric Membrane/ Matrix hybrid type DDS

This type of controlled drug delivery system (CDDS) combines the approaches of polymer membrane permeation and polymer matrix systems. It is often referred to as a sandwich type of CDDS. In this system, a rate-controlling non-medicated polymeric membrane is applied to coat the surface of the drug-dispersing polymer matrix. This dual mechanism allows the system to follow both dissolution and diffusion-controlled release.

An example of this type of system is the nitroglycerin implant, which effectively delivers the drug over an extended period while maintaining controlled release characteristics. This design enhances the efficacy and safety of the drug administered.

4. Micro reservoir partition

It is a type of drug delivery system (DDS) where the drug reservoir consists of a suspension of solid drug particles in an aqueous solution of a water-miscible polymer like polyethylene glycol (PEG). This creates a homogeneous dispersion of many discrete, unreachable microscopic drug reservoirs within a biocompatible polymer, such as silicone or elastomers.

Micro dispersion is typically achieved using high-energy dispersion techniques. Various shapes and sizes of drug formulations can be created from this micro reservoir type of controlled release drug delivery system (CRDDS) through molding or extrusion techniques. The drug release mechanism primarily follows diffusion, allowing for controlled and sustained release of the drug. An example of this type of system is a transdermal contraceptive device, which effectively delivers hormones over time.[6-7]

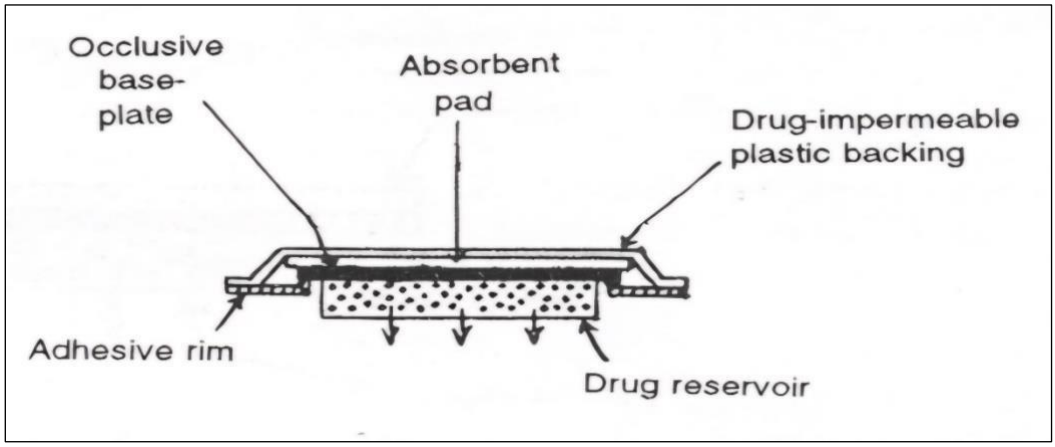

Figure 4 Micro reservoir partition system**.**

5. Evaluation methods

The evaluation methods for transdermal dosage form can be classified into following types:

- Physicochemical evaluation
- In vitro evaluation
- In vivo evalution

5.1 Physicochemical evaluation

- Drug Excipients Interaction Studies: It's crucial to confirm that the drug and excipients are compatible to create a stable product. Interaction studies help identify any physical or chemical interactions. Common techniques include thermal analysis, FT-IR spectroscopy, UV spectroscopy, and chromatographic methods. These methods compare physicochemical characteristics such as assay, melting endotherms, characteristic wave numbers, and absorption maxima.
- Drug Content: To determine the drug content, a specific area of the patch is dissolved in a suitable solvent of a defined volume. The solution is then filtered through a filter medium, and the drug content is analyzed using appropriate methods like UV or HPLC. The results represent the average of three samples.
- Weight Uniformity: Before testing, the prepared patches should be dried at 60°C for 4 hours. A specified area of the patch is cut into different parts, and each part is weighed using a digital balance. The average weight and standard deviation are calculated from the individual weights to assess uniformity.
- Thickness of the Patch: The thickness of the drug-loaded patch is measured at various points using a digital micrometer. The average thickness and standard deviation are calculated to ensure consistent thickness across the patch.
- Flatness Test: Three longitudinal strips are cut from each film at different locations (one from the center, one from the left side, and one from the right side). The length of each strip is measured, and the variation in length due to non-uniformity in flatness is assessed by calculating the percent constriction, where 0% constriction indicates 100% flatness.

- Percentage Moisture Uptake: The weighed films are placed in desiccators at room temperature for 24 hours to measure moisture uptake. This helps determine the stability and shelf life of the patches.

These evaluations are vital for ensuring that the transdermal patches are effective, consistent, and safe for use.

6. *In vitro* Evaluation

6.1 *In vitro* skin permeation studies

In vitro permeation studies using diffusion cells are crucial for evaluating the transdermal delivery of drugs. Here's a detailed overview of the procedure based on your description:

- Preparation of Skin: Full-thickness abdominal skin from male Wistar rats weighing between 200 to 250 grams is used. Carefully remove hair from the abdominal area using an electric clipper to avoid damaging the skin. Clean the dermal side of the skin thoroughly with distilled water to eliminate any remaining tissues or blood vessels.
- Equilibration: The cleaned skin is equilibrated for one hour in a dissolution medium, such as phosphate buffer at pH 7.4, to ensure that the skin is hydrated and ready for the permeation study.
- Diffusion Cell Setup: The skin piece is then mounted between the donor and receptor compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. This orientation is essential for simulating the transdermal delivery process.
- Temperature Control: The temperature of the diffusion cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. This temperature mimics the conditions of human skin.
- Stirring: A magnetic stirrer with a small magnetic needle is placed in the receptor compartment to ensure uniform distribution of the diffusant throughout the medium.
- Sampling: At regular intervals, a specific volume of the solution is removed from the receptor compartment for analysis. An equal volume of fresh medium is added to maintain the volume in the receptor compartment.

7. *In-vivo* studies

In-vivo evaluations play a crucial role in truly understanding how a drug performs in a real-life setting. Here's a breakdown of how in-vivo evaluations of Transdermal Drug Delivery Systems (TDDS) can be conducted using animal models and human volunteers:

- **Animal Models**

Various animal species are utilized for evaluating TDDS, including mice, hairless rats, hairless dogs, hairless rhesus monkeys, rabbits, guinea pigs, and more. These animal models help researchers simulate the effects of transdermal drug delivery before moving on to human trials.

- **Human Models**

When it comes to the final stages of developing a transdermal device, human volunteers are essential. Clinical trials with human participants provide valuable pharmacokinetic and pharmacodynamic data after applying the patch. These trials help assess the device's efficacy, potential risks, side effects, patient compliance, and overall performance in a human context.

By incorporating both animal and human models in the evaluation process, researchers can gain a comprehensive understanding of how TDDS function and perform under real-world conditions. It's a vital step in ensuring the safety and effectiveness of transdermal drug delivery systems.[8-10]

8. Factors Affecting TDDS

8.1 Physio-chemical factors

- Partition coefficient
- Molecular size
- Solubility
- pH condition
- Enhancement of transdermal permeation
- Composition of drug delivery system

8.2 Biological factors

- Skin age
- Skin hydration
- Skin temperature
- Pathological injury to skin
- Blood supply
- Regional skin site
- Skin metabolism[11-12]

9. Conclusion

Recent advances in technology have made the transdermal route of drug administration increasingly popular, allowing for the delivery of drugs directly to the site of action without damaging the skin barrier. This article serves as a valuable resource for researchers focused on the formulation and evaluation of transdermal drug delivery systems (TDDS). It highlights the potential of TDDS to effectively deliver both hydrophobic and hydrophilic active substances, making them suitable for a wide range of medications.

To optimize these drug delivery systems, a deeper understanding of the various biological interactions and the role of polymers is essential. The advancements in TDDS position them as a realistic and practical application for the future of drug delivery, representing the next generation of therapeutic solutions. With ongoing research and development, TDDS could significantly enhance the efficacy and convenience of medication administration.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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