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Transdermal Route: A Promising Approach for Drug Delivery

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KEYWORDS

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ABSTRACT:

Transdermal drug delivery systems (TDDS) provide a controlled, non-invasive route for systemic administration of medications by facilitating drug permeation through the skin into the bloodstream. By bypassing gastrointestinal degradation and first-pass hepatic metabolism, TDDS can improve bioavailability, reduce systemic side effects, and enhance patient compliance. However, the skin's outermost layer—the stratum corneum—acts as a formidable barrier, limiting TDDS applicability to relatively low-molecular-weight and lipophilic drugs or those aided by permeation enhancers. This review first outlines skin anatomy—including the keratinized brick-and-mortar structure of the stratum corneum, the viable epidermis, dermis, and hypodermis—and explains how each layer influences drug absorption. Next, it categorizes TDDS into six principal types: reservoir, matrix, adhesive, microreservoir, iontophoretic, and microneedle-based systems, illustrating each with representative examples (e.g., nicotine patches, fentanyl patches, iontophoretic lidocaine). The mechanism of transdermal delivery is described in sequential steps: drug release from the patch, penetration of the stratum corneum, diffusion through the epidermis, absorption into the dermis, and eventual systemic circulation. Methods to enhance permeation—such as electrical currents (iontophoresis), electroporation, microneedles, heat, and ultrasound—are discussed. Key factors affecting delivery include skin condition, drug physicochemical properties, and formulation design. The review details evaluation parameters, including physicochemical tests (thickness, weight uniformity, drug content, moisture content), adhesive performance (shear and peel tests, tack measurements), in vitro release (USP apparatus adaptations), and in vivo studies using animal models and human volunteers. Finally, applications and recent advances—particularly "drug-in-adhesive" technology and tailored adhesives—are highlighted, underscoring TDDS's potential for chronic conditions (e.g., pain management, smoking cessation, hormone replacement) and future directions in formulation research.

Introduction:

Transdermal patches, also referred to as skin patches, utilize a specialized membrane to regulate the passage of the liquid drug from the reservoir within the patch into the bloodstream through the skin. Certain medications require additives like alcohol to enhance their skin penetration for effective delivery through a transdermal patch. Common drugs administered through transdermal patches include scopolamine for motion sickness, nicotine for smoking cessation, estrogen for menopause and osteoporosis prevention, nitroglycerin for angina, and lidocaine for shingles pain relief. However, large molecules such as insulin and certain other substances are unable to permeate the skin barrier. Transdermal patches offer a needle-free alternative to vascular access via syringes or pumps. The FDA approved the first transdermal patch in 1979 for motion sickness treatment, signaling their emergence in the 1970s. (1,2).

Oral conventional dosage forms like tablets and capsules are commonly used for drug delivery, but they often encounter issues such as gastric drug/enzyme instability and first-pass metabolism. Additionally, the oral route presents challenges like unpleasant taste, odor, and color, which can contribute to patient non-compliance. In contrast, transdermal drug delivery systems (TDDS) offer an appealing alternative by providing sustained drug release over a specific period, while being gentle on the skin and non-invasive. TDDS aim to optimize drug absorption through the skin into the bloodstream while minimizing drug retention and metabolism in the skin(3). Compared to traditional multi-dose treatments, TDDS can enhance drug bioavailability by bypassing hepatic first-pass metabolism. Consequently, various innovative drug delivery systems, including TDDS, controlled-release systems, and transmucosal delivery systems, have been developed to overcome the limitations associated with conventional oral dosage forms. (4)

In transdermal drug delivery, the skin's protective barrier properties pose a major challenge, as the skin's complex structure does not readily allow drug permeation. The outermost layer, the stratum corneum, is composed of keratin and lipids that effectively prevent water loss and chemical penetration. This layer, measuring 20 mm in thickness, accounts for the majority of the total diffusional path length of 300-500 mm. To overcome this barrier, drugs must be able to diffuse across the sequential, repeated structure of the skin's bilayers, which can accommodate both hydrophilic and lipophilic compounds (5).

1.1 Definition:

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a

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specific dose of medication through the skin and into the bloodstream (6).

Here are the advantages and disadvantages of the transdermal route of administration:

Advantages:

1. **Improved bioavailability**: Transdermal route bypasses first-pass metabolism, increasing bioavailability (6).

2. **Reduced side effects**: Minimizes gastrointestinal side effects associated with oral medications (7).

3. **Enhanced patient compliance**: Easy to apply and maintain, reducing dosing frequency (8).

4. **Targeted delivery**: Directly delivers medication to the affected area, reducing systemic exposure (9).

5. **Long-term therapy**: Suitable for chronic conditions, such as pain management and hormone replacement (10).

6. **Non-invasive**: Avoids injections and oral medications, reducing patient discomfort (11).

Disadvantages:

1. **Skin irritation**: Common adverse effect, especially with prolonged use (12).

2. **Dose limitations**: Limited by skin permeability and surface area (13).

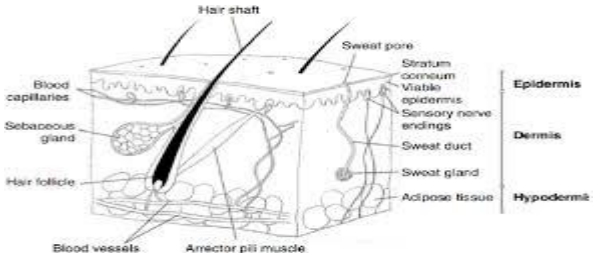
3. **Skin variability**: Inter-individual differences in skin permeability affect drug absorption.

4. **Delayed onset**: Slower onset of action compared to injectable or oral routes.

5. **Limited drug compatibility**: Not suitable for all medications, especially large molecules.

6. **Adhesion issues**: Patch adhesion problems can affect drug delivery (14).

Anatomy and physiology of skin



Human skin comprises of three distinct but mutually dependent tissues: The stratified, vascular, cellular called as “epidermis” Underlying dermis of connective tissues, Hypodermis (Figure 1).

Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum. This is the outermost layer of skin alsocalled as horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horny layer may be modeled as a walllike structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar.” The lipids are arranged in multiple bilayers.

There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form. Viable epidermis is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

Dermis

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanically protection. It

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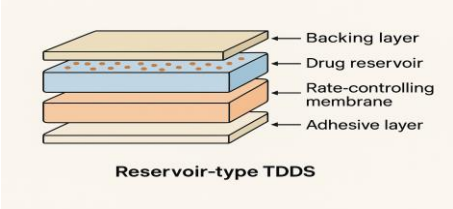
carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.(15)

The types of Transdermal Drug Delivery Systems (TDDS) are

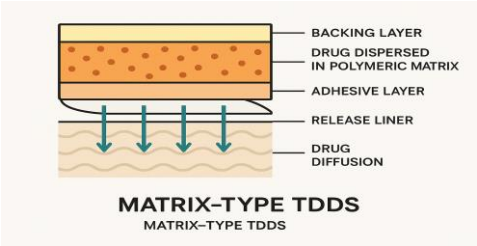
1. Reservoir-type TDDS

- Definition: Drug reservoir separated from skin by rate-controlling membrane. These systems consist of a liquid or gel-like reservoir containing the drug, which is separated from the skin by a rate-controlling membrane. The drug is released at a controlled rate, providing steady drug levels in the systemic circulation. [16]
- Examples: Scopolamine patch, Clonidine patch



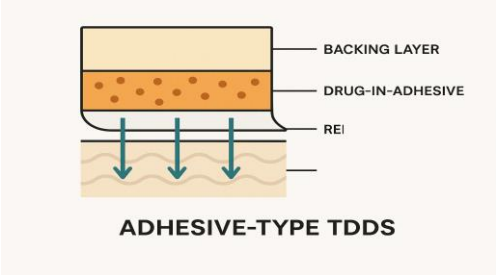
2. Matrix-type TDDS

- Definition: Drug dispersed in polymer matrix. In this design, the drug is dispersed in a polymer matrix, which controls the release of the drug. The matrix is placed in direct contact with the skin, allowing for drug diffusion [17]
- Examples: Nicotine patch, Estradiol patch



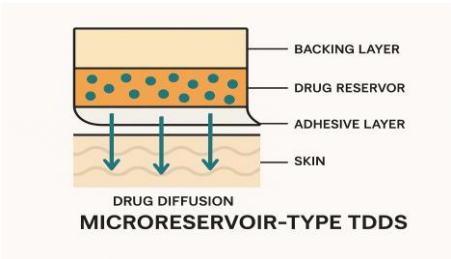
3. Adhesive-type TDDS

- Definition: Drug incorporated into adhesive layer. In adhesive TDDS, the drug is directly incorporated into the adhesive layer. The adhesive serves a dual function: securing the patch to the skin and acting as the drug matrix. [18]
- Examples: Fentanyl patch, Lidocaine patch



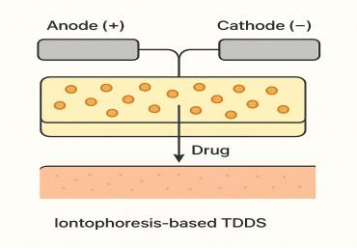
4. Microreservoir-type TDDS

- Definition: Microencapsulated drug in polymer matrix. These systems combine the properties of reservoir and matrix systems. The drug is stored in micro-reservoirs embedded within a polymer matrix. [19]
- Examples: Microencapsulated insulin, Microencapsulated vaccines



5. Iontophoresis-based TDDS

- Definition: Electrical current enhances drug delivery. Iontophoresis uses a small electrical current to enhance the delivery of ionized drugs through the skin. This system is particularly effective for delivering peptides and proteins. [20]
- Examples: Iontophoretic delivery of lidocaine, Iontophoretic delivery of fentanyl



6. Microneedle-based TDDS

- Definition: Microscopic needles create microchannels. These systems use tiny needles to create microchannels in the skin, facilitating drug delivery without significant pain. The drug can be in a solid, liquid, or patch form [21]

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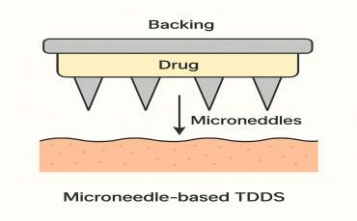
- Examples: Microneedle-based delivery of influenza vaccine, Microneedle-based delivery of lidocaine



Mechanism of Transdermal Drug Delivery Systems (TDDS),:

Step 1: Drug Release from the System

- Drug is released from the TDDS due to diffusion, osmosis, or other mechanisms [22]
- Release rate is controlled by the system's design and materials [23]

Step 2: Penetration through the Stratum Corneum

- Released drug penetrates the stratum corneum (SC), the outermost skin layer [24]
- SC's lipid bilayer structure and corneocytes regulate drug diffusion [25]

Step 3: Diffusion through the Epidermis

- Drug diffuses through the epidermis, the layer beneath the SC [26]
- Epidermal cells and lipids influence drug diffusion rates [27]

Step 4: Absorption into the Dermis

- Drug is absorbed into the dermis, the layer beneath the epidermis [28]
- Dermis's blood vessels and lymphatic system facilitate systemic absorption [29]

Step 5: Systemic Absorption

- Drug is absorbed into the bloodstream, reaching systemic circulation [30]
- Systemic absorption rates depend on factors like skin permeability and blood flow

Mechanisms Enhancing Transdermal Delivery

- Iontophoresis: electrical current enhances drug delivery
- Electroporation: electrical pulses create temporary pores
- Microneedles: microscopic needles create microchannels
- Thermal and ultrasound-based methods: heat or ultrasound enhance drug delivery

Factors Influencing Transdermal Delivery

- Skin type and condition
- Drug properties (e.g., molecular weight, lipophilicity)
- Formulation characteristics (e.g., pH, solvent)
- Application site and duration [31]

Evaluation Parameters:

1. **Physicochemical evaluation**
2. **In vitro evaluation**
3. **In vivo evaluation**

Evaluation parameter of transdermal patches are as follows:

1. **Physicochemical evaluation**

Thickness: The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight.

Adhesive studies: -

(a) Shear adhesion test: - The cohesive strength of an adhesive polymer is determined by this test. The value of strength can be affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers added. An adhesive coated patch is stacked on plate made of stainless steel and specified weight hung from the patch

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parallel to this plat. The time taken to pull off the patch from the plate determines the cohesive strength. More the time taken, greater is the shear strength.

(b) Peel adhesion test: - The measure of patch strength between an adhesive and a substrate is defined as adhesion. The force required removing adhesive coating from the steel used as test substrate. The type and amount of polymer molecular weight and the composition of polymers determine the adhesive properties. The single patch is adhering to test substrate (Steel) and it pulled from the substrate at 1800 angle. No residue on the test substrate indicates failure of adhesive.

(c) Tack properties: - Tack is the ability of polymer to adhere to a substrate with little figure pressure it's important in transdermal systems which are applied with little figure pressure. Tack is dependent on molecular weight as well as composition of polymer and tackifying resins used in the polymer.

Tests for tack include: -

(a) Thumb tack test: - This is subjective test in which evaluation is done by pressing the thumb in to the adhesive. Experience is required for using the test.

(b) Rolling ball tack test: - This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. The diameter of ball is 7/16o inches and it released on inclined track having angle 22.50. More the distance travelled, less the tacky polymer. Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive pol

(c) Peel tack or quick stick test: - The peel force is the force required to break the bond between the adhesive and the test substrate. The patch is pulled away from the substrate at 90o with speed 12 inches/minute. The value of force is expressed in grams/inch or ounces/inch.

(d) Probe tack test: - In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive an probe, removal of probe at a fixed rate away from the adhesive which break the bond. The force required to break the bond is recorded as tack and it is expressed in grams.

IN VITRO RELEASE STUDIES: - Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system there are various methods available for determination of drug release rate of TDDS.

The Paddle over Disc: - (USP apparatus 5/ Ph Eur 2.9.4.1) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C.

The Cylinder modified USP Basket: (USP apparatus 6 / Ph Eur 2.9.4.3) this method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C. The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages.

Preparation of skin for permeation studies: - An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2)

IN VIVO STUDIES: - In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using: [31]

Animal Models, Human volunteers 1. Animal models: - Considerable time and resources are required to carry

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out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man. [32]

Human models: - The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. [33-38]

Stability studies: - The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines.

Applications of transdermal patches: -

1)Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

2)Nitroglycerine patches are also sometimes prescribed for the treatment of Angina. 3)Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflamatory drug are also available in the form of transdermal patches.

4)Transdermal form of the MAOI selegiline became the first transdermal delivery agent for an antidepressant.

5)Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

Advance development in TDDS

Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch polymer is required. TDDS realistic practical application as the next generation of drug delivery system. [39, 40]

Conclusion

Transdermal drug delivery systems (TDDS) have emerged as a versatile and patient-friendly alternative to traditional oral and parenteral routes. By bypassing gastrointestinal degradation and first-pass hepatic metabolism, TDDS can offer improved bioavailability, more consistent plasma levels, and enhanced compliance—particularly for chronic therapies such as hormone replacement, pain management, and smoking cessation. Nevertheless, key challenges remain. The stratum corneum continues to limit delivery primarily to small, moderately lipophilic compounds or those formulated with effective permeation enhancers. Skin irritation, interpatient variability in permeability, and limitations in total dose deliverable via a finite patch area also impose constraints on widespread adoption.

Recent advances—such as microneedle arrays, iontophoretic and electroporation-based systems, and “drug-in-adhesive” formulations—have demonstrated substantial promise in broadening the scope of molecules amenable to transdermal administration and in reducing lag times. Ongoing optimization of polymer matrices, rate-controlling membranes, and adhesive chemistries continues to improve skin adhesion, reduce local irritation, and fine-tune release kinetics. Furthermore, developments in microreservoir technologies and combination approaches (e.g., microneedles plus permeation enhancers) are pushing the boundaries of what can be delivered noninvasively.

Moving forward, successful translation of these innovations will depend on rigorous in vitro–in vivo correlation studies, standardized evaluation protocols, and well-designed clinical trials that assess both efficacy and long-term safety. As materials science, formulation engineering, and skin biology converge, TDDS is poised to become a mainstream platform for delivering not only small-molecule drugs but also peptides, vaccines, and perhaps even gene-based therapies. In summary, while the skin barrier remains a formidable obstacle, integrated technological strategies—coupled with careful patient-centric design—hold the key to unlocking the full potential of transdermal delivery.

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