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Review Article

Article Reviewing Transdermal Drug Delivery System

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Abstract

Topically applied pharmaceuticals in the form of patches that distribute medications for systemic effects at predefined and controlled rates are known as "transdermal drug delivery systems." The main function of TDDS is penetration of drug through skin. It works extremely simple, with the medicine being put within the patch and is placed on the skin. As a result, a consistent concentration of medication remains in the bloodstream for an extended period. They come in variety of forms, including single-layer drugs in adhesives; inter drugs in adhesives, buffers, and matrix systems. The market price of TDDS products is rapidly expanding. More than 35 items have now been authorized for sale in the United States, and roughly 16 active substances have been approved for usage as a TDDS globally. It is a drug delivery system that has a bright future. It helps in reducing use of syringes for administering a wide range of drugs, but the price is an essential aspect to consider because developing countries like India have the world's second-largest population, but TDDS is a secret part of treatment used for the general population due to rising costs. This review article on transdermal drug delivery systems (TDDS) contains information on the transdermal drug delivery system, Advanced development and the evaluation procedure.

Keywords: TDDS, Drug penetration, Bright future, Rising costs, Evaluation procedure.

INTRODUCTION¹⁻¹¹

TDD is a painless way of systemically administering medications by putting a drug formulation on unbroken and healthy skin. The drug goes through the stratum corneum first, then into the deeper epidermis and dermis, without accumulating in the dermal layer. The medication is available for systemic absorption once it reaches the dermal layer. It can be used as a non-invasive alternative to parenteral methods, avoiding injection fear. The extremely large surface area of skin and ease of access allows for a variety of transdermal absorption, placement choices. Furthermore, medication pharmacokinetic profiles are more consistent and have fewer peaks, reducing the possibility of severe side effects. It can enhance patient compliance by lowering dose frequencies and is also appropriate for patients who are unconscious or vomiting, as well as those who self-administer. Several dosages, insufficient drug delivery, or characteristics of diverse medications typically result in low therapeutic benefits; therefore transdermal drug delivery has piqued the interest of researchers with multiple proposals. In the previous few decades, films or patches, as well as gels, have been extensively designed for skin illnesses or topical care. Drugs for therapeutic purposes can also be included in these dose formulations.

ADVANTAGES AND DISADVANTAGES OF TDDS^{12,13}

Advantages

- Avoids first-pass metabolism and enzymatic breakdown by GIT.
- In a transdermal medication, self-administration is possible.
- Topical patches have a long-lasting medicinal release in the bloodstream.
- Patches are less painful than other methods of delivery.
- Compared to oral methods, transdermal patches offer fewer negative effects.
- GIT incompatibilities are avoided.
- Dose and therapeutic effects are known ahead of time.
- This treatment lasts longer.

Disadvantages

- TDDS is not recommended, for high-dosage drugs.
- Drugs with large molecular sizes are hard to be absorbed.

- It is possible that the skin will get irritated, and the reaction will be hypersensitive.
- It is impossible to manufacture a drug with a long half-life.
- Transdermal drug delivery systems cannot achieve high drug levels in the blood.
- Ionic medicines cannot be delivered by a transdermal drug delivery method.

- The physiological difference in function is a barrier.

ANATOMY AND PHYSIOLOGY OF SKIN

1. Skin^{14,15}

The skin is the biggest organ in the human body, covering roughly 2 square meters and receiving about a third of the blood. It's a useful for a barrier of permeability against transdermal absorption for number of chemical and biological substances. With a thickness of few millimeters, it is body's natural most accessible organs (2.97 0.28 mm).

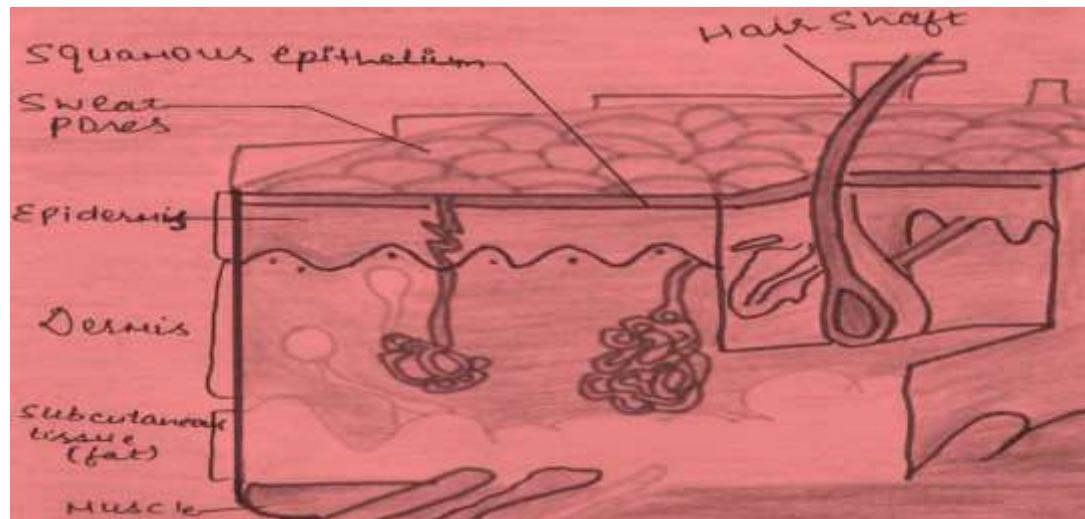


Figure 1: Structure of the skin¹⁶

2. The Epidermis¹⁴

Epidermis is self-renewing, squamous epithelium that covers the entire external surface of body and includes two parts:- living or viable cells in the malpighian layer (viable epidermis) and dead cells in the stratum corneum, also called horny layer. As illustrated in Fig.2, the viable epidermis is classified into four layers.

- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basale

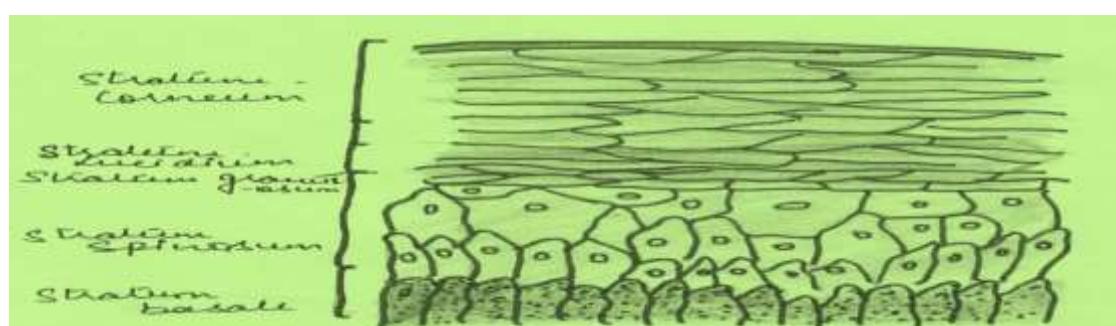


Figure 2: Anatomy of epidermis¹⁵

3. Stratum corneum¹⁷

This is skin's outer covering, sometimes called the horny layer. It is rate-limiting barrier that prevents chemical compounds from moving inward and outward. On a dry weight basis, the horny layer's barrier nature is determined by its constituents: 75-80% protein, 5-15% lipids, and 5% to 10% ondansetron material. When dry, the stratum corneum is around 10 mm thick, but when fully hydrated, it grows

several times its original size. It's malleable but relatively impervious. The horny layer architecture (figure 3) can be described as a wall-like structure made of protein bricks and lipid mortar. It is made up of horny skin cells (corneocytes) that are linked together by desmosomes (protein-rich appendages of cell membrane). Corneocytes are encased in a lipid matrix, which is important in determining the absorability of substances across the skin.

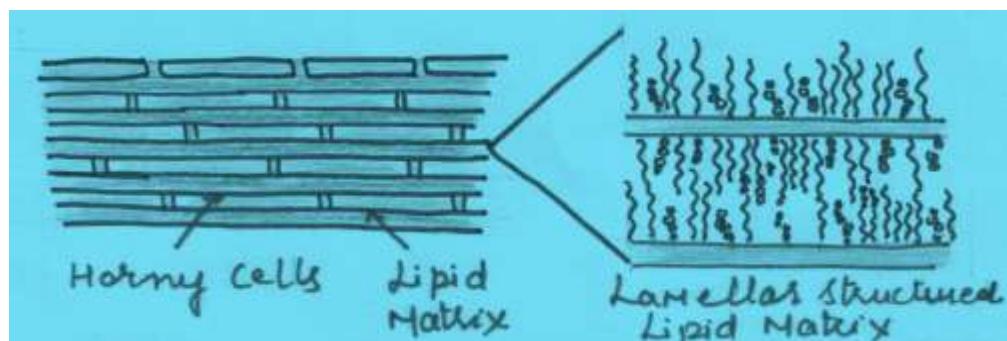


Figure 3: Microstructure of stratum corneum.¹⁷

4. Viable epidermis¹⁸

Thickness of this layer, which lies beneath stratum corneum, varies from 0.06 mm on eyelids to 0.8 mm on palms. The stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale are the several layers that make up the stratum basale. The dermis is constantly renewed in the

base layer by cell mitosis, and this proliferation compensates for the loss of dead horny cells from skin surface. The cells formed by the basal layer change morphologically and histochemically as they travel outward, eventually keratinizing to create the stratum corneum's outermost layer.

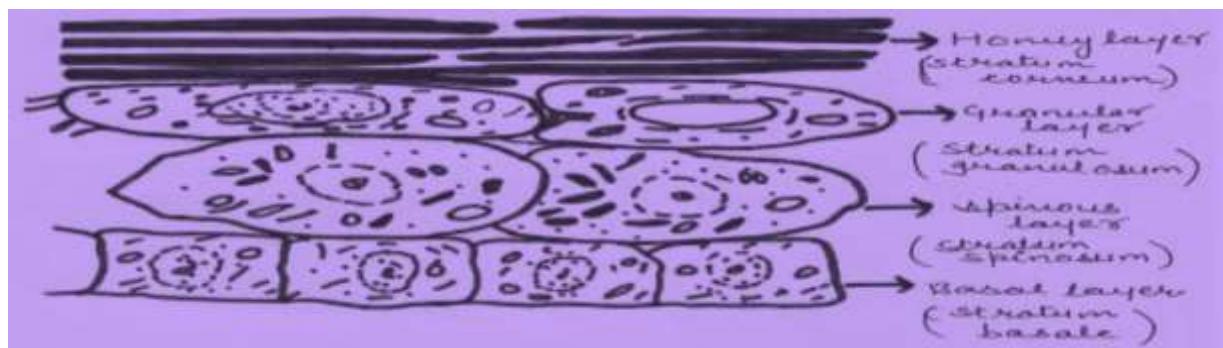


Figure 4: Different layers of epidermis¹⁸

5. Dermis¹⁶

It is 3-5 mm thick layer of skin that lies beneath the epidermis and is made of matrix of connective tissues that contain blood vessels, lymph vessels, and nerves. The cutaneous Body temperature regulation plays an important role in blood supply. It also feeds skin with nutrients and oxygen while eliminating impurities and debris. Capillaries stretch to within 0.2 mm of skin's surface and act as sinks for most molecules that pass via the skin barrier. As result of the blood supply, the dermal concentration of permeate is kept very low, and the ensuing concentration differential across epidermis provides the necessary driving force for transdermal permeation. This layer is frequently seen as simply gelled water in terms of TDDS, and hence provides a minor barrier to the absorption of most polar medicines, while the dermal barrier can be considered when delivering very lipophilic compounds.

6. Hypodermis¹⁸

The dermis and epidermis are supported by the hypodermis or subcutaneous fat tissue. It is a fat storage compartment. This layer aids in temperature regulation, nutritional support and mechanical defense. Transdermal drug delivery requires the medicine to permeate all three layers and enter the systemic circulation.

DRUG PENETRATION THROUGH SKIN¹⁹

In cutaneous responses to xenobiotics, medications, and other chemicals, drug penetration through the skin is an essential factor. The size of the compartments is one of the most difficult aspects of appropriately assessing percutaneous absorption. When used topically, a semisolid

dosage form, such as a gel, ointment, or cream, is usually applied to a thickness of less than 10 m. The stratum corneum is also about 10 m thick, whereas the viable epidermis, dermis, and, to a lesser extent, the systemic compartment operate as a major sink for ingested poisons, diluting them to levels undetectable by all but the most sensitive techniques. As a result, it's technically difficult to sample time-dependent variations in a compound's concentration in separate compartments.

Drugs can pass through the skin in a variety of ways.

- Via hair follicular penetration;
- Via transcorneal penetration;
- Via intracellular route;
- Via transcellular route.

EVALUATION PARAMETERS

1. Thickness²⁰

The thickness of matrix patches was measured with a screw gauge.

2. Weight uniformity²¹

Before testing, the manufactured patches must be dried at 60°C for about 4 hours. A defined patch area must be split into distinct sections and weighed on a digital balance. Individual measurements will be used to establish the average weight and standard deviation.

3. Folding endurance²¹

A strip of a specified area must be cut uniformly and folded continuously at the same location until it breaks. The value of the foldable endurance was determined by the number of

repetitions, the film might be folded in the same location without breaking.

4. Drug content²²

A certain region of the patch must be dissolved in a precise volume of a solvent. The solutions are then filtered through a filter media, and the drug content is determined using the appropriate method (UV or HPLC). The average of 3 samples is shown by each value.

5. WVTR (Water vap. transmission rate)²³

Vials of the same size as the cells were used, cleaned, and dried. CaCl₂ (1.0 gm) was added to the cells, and 2.076 cm² patches were inserted at the brim. Following the weighing, the cells were placed in a desiccator with KCl and a humidity of 80-90 percent. Cells were taken out and weighed every day for seven days. Equation was used to determine WVTR.

$$\text{WVTR} = \frac{WF - WI}{TXA} \times 100$$

Where, WI=Weight Initial, WF= Weight Final, T=Time, A=Area

6. Flatness²⁴

Matrix patches measuring 1.5cm in length were cut from the produced film. Following that, the length differences due to flatness uniformity were calculated using the formula below:

$$\text{Constriction (\%)} = \frac{LF - LI}{LI} \times 100$$

Where LF stands for final length and LI stands for initial length.

Patches with zero percent constrictions were regarded to be 100% flat.

7. In vitro release tests²⁵

The Franz cell was made locally for this study. This cell has two compartments: a donor compartment and a receptor compartment. The receptor compartment has a sampling port that collects samples for examination. Rubber bands connect the two sections. The magnetic bead was used to rotate the receptor compartment, which was filled with pH 7.4 buffer. Aluminum foil was used to create a patch. A one-milliliter sample was taken every seven hours and examined with a UV spectrophotometer at 232nm. Each time the sample was taken out, a new buffer was inserted to replace it.

8. Drug release kinetic data analysis²⁶

For the kinetic models, release data was analyzed using PCP disso software. The models of Zero, Higuchi, and Peppa were studied.

9. Stability studies²⁷

Matrix patches of two batches were identified to be the best formulations based on several evaluation factors. These two formulations were submitted to a three-month accelerated trial at various temperatures. Two batches of formulations were airtight packed and stored at 40°C for three months (75 percent RH). The absorbance of the samples was measured using a UV spectrophotometer set at 232 nm. The amount was calculated based on the calibration curve.

10. Thumbtack test²⁸

This is a qualitative test used to measure the adhesive's tack properties. The relative tack property is detected simply by pressing the thumb on the glue.

11. Shear adhesion test²⁹

This test is used to measure the adhesive polymer's cohesive strength. The degree of cross-linking, the molecular weight, the polymer nature, and the number of tackifiers present influence the strength value. A stainless steel plate is covered with an adhesive-coated patch, and a prescribed weight is hanged from the patch parallel to the plate. The cohesive strength is determined by the time it takes to remove the patch from the plate. The greater the shear strength, the longer time it takes.

12. Peel adhesion test³⁰

The strength of a patch between an adhesive and a substrate is measured by adhesion. The amount of force needed to remove the adhesive coating from the steel test substrate. The adhesive characteristics are influenced by the type and amount of polymer used, as well as the molecular weight and content of the polymers. The single patch adhered to the test substrate (Steel) and was dragged away from it at an angle of 180 degrees. If there is no residue on the test substrate, the adhesive has failed.

ADVANCED DEVELOPMENT OF TDDS

The advancements in transdermal delivery methods that have occurred to date can be divided into three generations of development.

1. First generation
2. Second generation
3. Third Generation

1. First generation

The first generation encompasses the advancement of patches that are now in use. A reservoir with an impermeable backing membrane on one side and an adhesive layer on the other side that contacts the skin. Some designs use a medication that is dissolved in a liquid or gel-based reservoir, allowing liquid chemical enhancers to be used. All of this is classified as first generation.³¹

2. Second generation

The advancements exhibited in the second generation are similar to increased skin permeability. The second generation of transdermal delivery systems understands the need of improving skin permeability in order to expand the range of transdermal medications. However, enhancement methods established in this generation, such as traditional chemical enhancers, non-cavitational ultrasound, and iontophoresis, still struggled to strike a compromise between increasing distribution over the stratum corneum while avoiding injury to deeper tissues.

3. Third Generation

Via targeted permeabilization of skin's stratum corneum, the third generation will permit transdermal delivery of small molecule medicines and macromolecules (containing proteins and DNA). Because it primarily directs its effects to the stratum corneum, the third generation of transdermal drug delivery system methods was set to have a substantial impact on medication delivery. This method allows for nearly total rupture of the stratum corneum wall, allowing for more effective transdermal medication distribution while simultaneously safeguarding deeper tissues. In human clinical trials, innovative chemical enhancers, cavitational ultrasound, electroporation, and more recently micro needles, thermal ablation, and microderm abrasion (Arora et al) have all been shown to transfer macromolecules over the stratum corneum, including vaccinations and therapeutic proteins.^{32,33}

Microneedles are another advanced technology in TDDS

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Microneedle is a microstructured transdermal system that comprises an array of microstructured projections coated with medication or vaccination and applied to the skin to deliver active substances that would not otherwise pass the stratum corneum. Microneedles are similar to ordinary needles, however, they are made on a smaller scale. They usually have a diameter of one inch and a length of one to one hundred. Metals, silicon, silicon dioxide, polymers, glass, and other materials have all been used to produce microneedles.

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CONCLUSION

Transdermal drug delivery system isn't a new concept, and it's no longer limited to adhesive patches. It is becoming the most frequently accepted route of drug absorption because of recent technological improvements and the integration of the drug into the site of action without breaking the epidermal membrane. It has the potential to eliminate the use of needles for the administration of a wide range of pharmaceuticals in the future.

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