Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

A SIMPLE GLANCE AT THE TRANSDERMAL DRUG DELIVERY SYSTEM

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ARTICLE INFO

Received:
02 Apr 2022
Received in revised form:
09 Jun 2022
Accepted:
11 Jun 2022
Available online:
28 Jun 2022

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

ABSTRACT

The Transdermal Drug Delivery Systems (TDDS), which have evolved as elements of the creation of innovative drug administrative systems, is the most important aspect of pharmaceutical dosage. The use of Transdermal patches has a systemic influence due to the penetration of the drug through the dermis. TDDS is also necessary due to its distinctive benefits. Sustained absorption, more constant plasma concentration, less first-pass metabolism, lower adverse outcomes, quick application, and the mouldability to cease medicines easily by clipping out the skin patches are some of the potential positives of transdermal pharmaceutical delivery. This method of drug delivery has many benefits over conventional oral and intravenous techniques. Ensure the fluid is released in a controlled manner with long-term treatment using drugs. As a result, numerous chemical and physical methods for developing transdermal patches are being investigated. The therapeutic application of first-generation transdermal delivery systems has steadily increased for the administration of tiny, lipophilic, low-dose medicines. Second-generation delivery systems that include chemical enhancers, non-cavitational ultrasound, and iontophoresis regulate administration rates in real-time. Third generation TDDS enhanced permeability of drugs through stratum corneum using microneedle, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound technology. This review article explains how to make different types of transdermal patches. Multiple ways for measuring transdermal dosage and the progression of TDDS were also investigated.

To Cite This Article: Chavan YS, Shinkar DM, Jadhav SS, Pingale PL, Boraste SS, Amrutkar SV. A Simple Glance at the Transdermal Drug Delivery System. Pharmacophore. 2022;13(3):72-80. https://doi.org/10.51847/QIRpXSstx5

Introduction

TDDS has piqued attention as a viable alternative to oral medications and hypodermic injections [1]. When especially in comparison to oral or systemic dosing strategies, TDDS allows for sustained release of the drug into patients, minimizing Hepatic first-pass biotransformation effects, lessening systemic adverse outcomes, enhancing dose efficiency during entire treatment by allowing for consistent blood drug profiles, and better patient adherence. However, major usage of TDDS is limited due to the skin's strong barrier function, particularly in the stratified organ, to prevent the introduction of foreign bodies. Only a handful of drugs can infiltrate the skin passively to reach effective blood concentrations and heal diseases. These drugs are generally quite powerful, lipophilic, and have a low molecular weight (under 600 Da). The invention of novel methods for the distribution of present medicinal molecules has received renewed interest in recent years. The innovation of a novel delivery system for already available drug molecules enhances the treatment's efficacy and safety as well as elevates patient compliance and overall therapeutic outcome [2]. TDDS are self-contained, divided dosage forms typically referred to as "patches" [3]. It alleviates the digestive and hepatic strain that the oral route normally involves. It elevates patient satisfaction and lowers the toxic side effects of a dose-by-dose treatment, as well as makes it simple to use transdermally applied medications that only need to be applied once [4]. When compared to lowered standard dose plasma concentrations, this enhances the bioavailability, raises plasma levels, and boosts action duration, leading to lowered dosage frequency, reducing adverse responses, and enhanced treatment with plasma levels sustained until the dosing interval has concluded. For several

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days after the skin is utilized, most skin patches will discharge the main component at zero-order rates. This is excellent for treating chronic conditions as a preventative measure [5].

Prospects for Medication Administration Via the Transdermal Route

Drug Absorption Mechanisms in the Skin

A horny layer of the topmost skin is described as the stratum corneum. The horny layer's obstructive feature is heavily dependent on its components: 75 - 80 % dry protein, 5-20 % lipid, and 10% ondansetron. Corneocypts are buried in a lipid membrane, which is important for establishing skin permeation [6]. Underneath the stratum corneum, there lies a viable epidermis. The epidermis is constantly renewed via cell division in the bottom layer [7]. The dermal layer of the skin beneath the epidermis is 2-5 mm thick. Cutaneous blood flow is critical for body temperature regulation. Capillaries act as a sink for the majority of skin barrier components in this layer, ensuring that dermal permeation is maintained. This is generally regarded as merely gelled water for the administration of transdermal therapeutic drugs, and so represents a minor stumbling block when most polar compounds are administered [8]. Hypoderma maintains the dermis and epidermis. The layer is used to regulate temperature, as well as to strengthen and safeguard mechanically. It connects the major blood veins and nerves to the skin, as well as sensory organs. To enter the bloodstream and administer transdermal medicines, all 3 layers must be infiltrated.

Drug Molecule Penetration Via the Skin

The first law of Fick Diffusion states that a drug molecule diffuses from a higher concentration area to a lower concentration area until equilibrium is established. The slope from higher to lower concentration drives the mechanism of molecular diffusion. The medicine is released from the dosage form, and its travel to the dermis for treatment of skin problems is governed by a sequence of processes. After passing through the epidermal layer, the therapeutic phytoconstituent partitions and diffuses into the dermis. The phytoconstituent enters the bloodstream and is utilized to treat skin diseases [9].

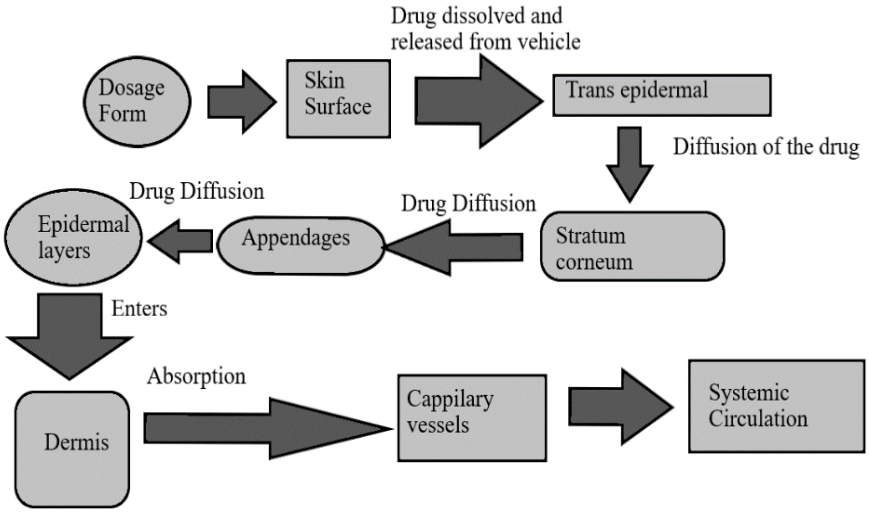

Figure 1. Drug Absorption Mechanism via skin

The dosage form is applied to the skin surface which diffuses through a horny layer and reaches appendages and later diffuses through the epidermal layer to the dermis. Absorption through the dermis in capillary vessels takes place and hence it reaches the systemic circulation depicted in **Figure 1**.

Percutaneous Absorption

Percutaneous absorption is the most common term for the delivery of drugs through the skin, however other terms utilized in the literature include sorption, perception, permeation, and penetration. Briefly defined, percutaneous absorption occurs when substances penetrate different layers of the skin and enter the bloodstream through the epidermis shown in **Figure 2** [10].

Percutaneous absorption is accomplished in two ways.

- *Trans-Epidermal Absorption*

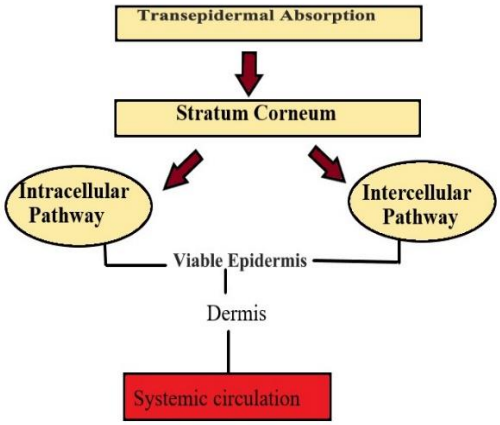

Figure 2. Mechanism of trans-epidermal absorption

In trans-epidermal transference, molecules pass through the undamaged horny layer. There are two probable micro routes: intracellular and intercellular. Polar and non-polar substances diffuse across intracellular and intercellular routes in a variety of ways. Polar molecules are largely disseminated throughout the polar channel by the moistened corneal stratum, whereas nonpolar molecules decrease and are distributed via the stratal cornea's non-hydrated lipid matrix [11].

- *Trans-Follicular Absorption*

Hair follicles as well as sebaceous glands are transported by the sweat glands in this route. Although these routes are extremely permeable, their size (about 0.2 & of total skin) is assumed to be insignificant. For ions and large polar chemicals that are unable to permeate the horny layer, this channel appears to be more important. Skin appendages are only possible through secondary permeation channels. Because the aperture of the follicular pores via which the hairpin departs the skin is fairly large, the follicular route is an important conduit for percutaneous absorption [12].

The Stages Involved in Medication Transdermal Penetration

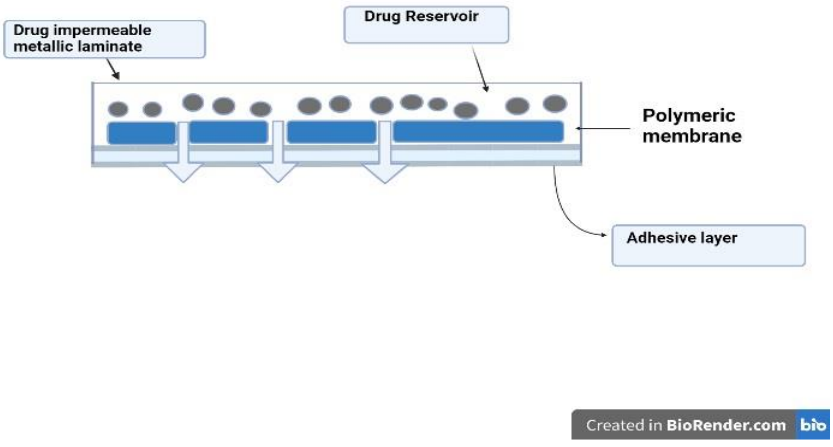

Figure 3. Mechanism of transdermal patch

The medication must be well absorbed and rates utilized to obtain and sustain consistent, blood, and medicinal concentrations throughout its utilization in the transdermal route of drug delivery. When a drug molecule penetrates the stratum barrier, it enters the deeper dermis swiftly and readily, allowing for systemic absorption **(Figure 3)** [13].

Transdermal Permeation Is Influenced by A Variety of Factors

- **Drug molecule's physical and chemical properties**
  - Partition ratios
  - pH environment
  - Concentration level of the medicine

- **Drug Delivery System Physicochemical Properties**
  - Features of the release
  - Utilization of penetration enhancers
  - Drug Delivery System Formulation
- **Skin's pathophysiological state**
- Horny Layer's reservoir effect
- Skin hydration
- Lipid film
- The temperature of the skin [14]

Demand for a Transdermal Patch

The transdermal patch method is a non-invasive method for delivering active chemicals to the bloodstream via the skin's epidermis, the body's main and even more responsive organ. The first transdermal patch for treating disease induced by motion was authorized in 1981. Including over 25-30 FDA-approved patches in the market in North America and thus greater than Forty in clinical trials, the Food and Drug Administration approved $6 trillion in funding [15]. Eleven pharmaceutical compositions were based upon patches of fentanyl, nitro-glycerine, estradiol, ethinylestradiol, norethindrone-acetate, testosterone, clonidine, nicotine, lidocaine, prilocaine, and scopolamine. 2 recently approved transdermal patches (a tablet containing ethinylestradiol and nasal elgestrom) and a bladder patch delivering hyperactive oxybutynin to cure. Transdermal delivery has several advantages over traditional and oral injections.

Benefits of TDDS [16-19]

- Keeping the first-pass impact at bay.
- Blood pressure is maintained at a constant level, and circulation is managed.
- Aspects of iv drip that are similar.
- Transdermal delivery has no effect on the liquids in the stomach and intestines.
- Self-administration is possible, and it also eliminates the unpleasantness associated with injectable medication.
- For providing medications that are not simply absorbed from the gut or degraded by the hepatic, transdermal patches are preferred.
- The expense transdermal patches are a great choice for the conventional method.

Limitations of Transdermal Drug Delivery System

- Transdermic distribution for cationic medications is not possible.
- To stratify corneal penetration, the drug should have the necessary physical and chemical properties.
- Inability to achieve the highest drug levels in serum.
- Drugs are to be distributed in a pulsatile manner.
- It's difficult to stick to a routine for a long time.
- Drug or excipient-induced skin irritation.

Kinetics of Transdermal Permeation

Transdermal dynamics are critical for the successful invention of transdermal gadgets.

- "Horny layer absorption"
- “Drug absorption across skin layers”
- “The drug's absorption in the epidermal-dermal papillae”

Factors Affecting Transdermal Permeation

Genetic factors included skin conditions, age, blood circulation, regional skin location, skin biotransformation, and race differences. Dermal moisture, temperature, and pH, as well as the rate of diffusion, drug loading, coefficient of partition, and molecule shape and size, are all physio-chemical factors. Transdermal permeation is affected by climate elements such as sunlight, cold season, air pollution, and heat [20-22].

Effect of Heat on Transdermal Patch [23, 24]

The temperature has generated a high absorption of transdermal medicines. External temperature elements, such as bags containing water and water heaters, should not be used at the operation location. Patients are encouraged to do so. Drugs delivered by transdermal delivery can improve even high body temperatures. In this case, the patch should be dislocated quickly. Topically applied medicine patches were properly stored in packaging and kept cool and safe till they are ready for use.

Formulations [25]

Transdermal drug delivery is designed to have all of the characteristics listed above, as well as reasonable system size, application site definition, highly repeatable requirements of the proposed, zero delivery processes, and efficient supply [26, 27].

Components of Transdermal Drug Delivery System

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

- *Polymer Matrix / Drug Reservoir:* Polymeric materials that control the delivery of activity from the apparatus are at the heart of Transdermal drug delivery. Distributing the medication into artificial fluids or a solid foundation can create a polymer structure. Formulating polymers should be stable and compatible with medicament as well as other elements of the system, and they should effectively deliver pharmaceuticals within safe environments [28].
- *Selection of Drugs:* The chemical and physical features of the drug have a role in TDDS drug selection. The transdermal delivery method is probably more suited to having drugs [29].
- *Permeation Enhancers:* Such substances serve to boost a stratum corneum's porosity by combining with structural components of the horny layer, such as proteins and lipids, resulting in a larger medical therapy potential. Chemical alterations in membrane integrity modify stratum corneum proteins and lipids to promote penetration. (DMSO and oleic acid are an example of the same [30, 31].
- *Pressure Sensitive Adhesives:* The transdermal pharmaceutical provider's pressure-sensitive adhesive (PSA) adheres securely to the body. It must be firmly and constantly attached with merely provided finger pressure, and it should have a strong grip strength. It should also be removed from the single layer without leaving any trace. Skin compatibility, little irritation or sensitivities, and removal without physical stress or remains are all requirements. Furthermore, medications and inactive ingredients should be soluble at amounts that are appropriate for the required pharmacological effects while maintaining compliance and epidermal tolerability. In currently available transdermal devices, polyacrylates, polyisobutylene, and poly-siloxane are employed [32, 33].
- *Backing Laminate:* The resources should be adaptable while keeping a strong tensile property. Opaque, colorful, or metalized polyolefin, polyester, and epoxies are often utilized materials. Elastic polymers with a low density, such as polyethylene, respond to body motion better quickly and provide better adhesion than the fewer components, including polyester. Substances should have a low rate of water vapor transfer to promote greater skin moisture and, as a result, greater skin penetration. For devices keeping pharmaceuticals in liquids and gels, the backpack ingredients should be heat-stable to enable fluid-tight packing of the medicinal stock utilizing the form-fill-section procedure [34].
- *Release Liners:* While storing, the patches are covered with such a protecting lining, which would be quickly dismissed and discharged for topical application. As a result, instead of being an element of the active ingredient, this relates to the distribution of the medication as an element of the primary packaging [35, 36].
- *Other Excipients:* Drug reservoirs are made with a variety of solvents, including chloroform, methanol, acetone, isopropanol, and DCM. Plasticizers such as dibutyl phthalate, triethyl-citrate, polyethylene glycol, and propylene glycol are also used to plasticize the transdermal patch [37].

Methods for preparation of Transdermal Drug Delivery System

- *Asymmetric TPX Membrane Preparation:* The watery reversal devices have been manufactured. To make a hydrogel, the TPX is mixed in liquid (cyclohexane) and non-solvent mixtures at 60°C. The polymeric solution is kept at 40°C and poured with a pruning blade upon a glass screen with a predetermined depth. After the forming layer has been vaporized for thirty seconds at 50°C, each glass slide must be quickly plunged into a [coagulation bath at a temperature of 25°C].
- Following ten minute of soaking, the barrier can be withdrawn and dried in a circulation furnace at 50°C for 24 h.) [38, 39].
- *Mercury Substrate Method:* Inside this procedure, the drug solubility is in a suitable solvent together with the lubricant. With above solution should be spun for 10-15 minutes in distribution and then poured onto a level surface. After that, the mixture is switched to solvent removal control [40].
- *Circular Teflon Mould Technique:* In chemical reagents, polymer mixtures are used in various ratios. The drug is predicted to be half the rate of organic liquid. The stimulants are dissolved and introduced in various amounts to another portion of the organic liquid. Di-N-butyl phthalate is used as a lubricant in a liquid for the medication polymer. All components in spherical Teflon moulds must be spun for 12 hours. In a half m/second airspeed laminar flow hood, the moulds are mounted on a level pad and feature a reversed feeder to alter damper liquids. After 24 hours, the liquid may

vaporize. To minimize the occurrence of fading, keep the dried film in a silica gel-containing desiccator for additional 24 hrs at 250.5°C. Within one week, such videos must be evaluated [41].

- *By Utilizing the Free Film Technique:* A cellulose acetate mercury surface is used to create dry films. A 2 percent w/w polymeric solution is produced via chloroform. Plasticizers are used at a 40 percent W/P of polymer weight percentage. On the mercury surface of a Petri plate, a ringed of glass was poured with 5 ml of a suitable solvent. Putting an upturned disc cover the petri dish controls the rate of solvent removal. Monitoring of the mercurial surfaces after full solvent removal reveals the film's creation. Between both the wax paper sheets, the dried film is separated and preserved in the desiccator. To make free films of varying depths, the number of suitable solvents can be modified.

Methods of Evaluation [42]

a. Physicochemical Evaluation

- *Thickness*
  A digital micrometer is utilized at several spots on the patches to measure the thickness of the medication and to make sure that the thickness of the developed film is consistent. The fault and maximum thickness were measured.
- *Weight Uniformity*
  The produced films must be dried at 60°Celcius for 4 hours before evaluation. A patched region must be sliced and weighted in the electronic balance at numerous points throughout the patch. The average and standard deviations of the distinct values should be calculated.
- *Drug Content Determinations*
  A very well section of the patch (approximately 100 mg) is added to 100 ml of appropriate solvent, stirred for 24 hours constantly in shaking flasks, as well as the liquid is solvable. The entire liquid is then stirred continuously. The liquid measures measure the absorbance of the individual dilution after sonification and subsequently filtering.
- *Content Uniformity Test*
  Whenever the material of nine in ten patches varies from 85 percent to 115 percent, whereas the quantity of one patch ranges from 70 percent to 125 percent, transdermal drug delivery is used to maintain consistency in the content test. If three patches contain a content of 75 percent to 125 percent, another 20 patches will be examined for drug content. The transdermal patches are evaluated to see if the range of the 20 patches is between 85 and 115 percent.
- *Moisture Uptake*
  To preserve Relative humidity at 84 percent, the formulations should be independently measured and kept in a desiccator with a potassium chloride saturated solution. The film must be measured after 24 hours and the moisture intake calculated by using the procedure below.

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

- *Folding Toleration*
  A section of a stripe is sliced and folded continuously until it breaks. At the very same location. The patch could be folded without tearing because of its amount and toleration.
- *Flexibility Strength*
  To test flexibility strength, polymeric sheets are distinctly bonded between stoppered, longitudinal metal slabs. A metal screening secures one end of the film, while a free-moving thread connects another. The weights are slowly introduced to the pot and fastened to the swinging end of the thread. A marker on the thread is utilized to monitor the patch's stretch. The patch's mass is enough to fracture.
- *Tack Properties*
  It refers to a polymer's ability to adhere to a material with reduced contact force. The molecular tackle determines the molecular mass, content, and use of confronting resin in polymers.
- *Thumbtack Test*
  Tack is a measurement of how hard it is to get your thumb out of the adhesive.
- *Peel Tack Test*
  At ambient temperature, the tapestry is taken from the substrate at a rate of 13 inches per minute. The required peeling ability is calculated and expressed as a tack value in grams per inch of width.

b. In-Vitro Release Studies

To assess the flow of medication from the produced patches, utilize the disc paddle (USP appliance V) approach. Drying sheets of familiar thickness must be slashed into a specific form, measured, and adhered to a glass slide with glue. The glass slide was then fitted, and the apparatus was adjusted to 32 0.5°C using 500 mL saline phosphate buffer pH 7.4. The paddle was then set at a distance of 2.5 cm from the glass plate and worked at 50 rpm. The HPLC

or UV spectrophotometer can be used to extract specimens (5-ml aliquot) at any moment for up to 24 hrs. The test must be repeated 3 times, with the mean value calculated [43].

c. In-Vivo Studies

- *Animal Models*

  Because human studies require a significant amount of time and resources, animal trials on a small scale are suggested. The frequent animal species utilized in testing transdermal pharmaceutical systems are the mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, and guinea pig. Various studies have outcomes that hairless animals are preferred to hairy animals in both in vitro and *In-vivo* testing. One of the most produces precise transdermal delivery *in-vivo* measuring models is Monkey Rhesus [44].

Applications of Transdermal Patches

- The nicotinic patches are the most popular transdermal patch in the United States, as it distributes nicotine in controlled amounts to help people quit smoking.
- Fentanyl (marketed as Duragesic) and buprenorphine are major opioid medicines used to alleviate extreme pain 24 hours a day, seven days a week (marketed as BuTrans).
- For the management of angina, nitro-glycerine patches might be used instead of buccal pills.
- The topical form of the Monoamine oxidase inhibitor selegiline was the first antidepressant transdermal delivery medication.
- The Anti-hypertensive drug in the form of a transdermal Clonidine

Scope of Transdermal Delivery System [45]

- Dexamethasone iontophoretic treatment is a tennis elbow remedy.
- Try out the Varenicline smoking cessation patch and the high-dose nicotine patch for rapid metabolizers.
- Selegiline Patch is used to treat elderly depression and drug habits.
- Sufentanil is a novel cancer pain patch.
- Transdermal stroke glyceryl trinitrate, to name a few.

Conclusion

In transdermal systems, reasonable treatment program methods (safe, effective, and cost-effective) drug delivery instruments are used. Because of the TDDS's numerous advantages, many more studies are now being conducted to incorporate new drugs into the program. Drug reservoirs, liners, adhesives, porosity enhancers, laminates, plasticizers, and solvents are all critical elements of a transdermal patch, and they all play a role in modern medical distribution through the epidermis. Using TDDS core parts, many ways of producing these patches are used. After the manufacture of transdermal patches, they are tested for physical-chemical, in-vitro, skin rashes, and stability. However, before they can be commercialized, all transdermal patches that have been designed and tested must be indicated for the treatment. The level of flexibility and the expansion of available drugs are likely to be the top priorities for TDDS's growth prospects. Transdermal dosage forms could give doctors more therapy options to help their patients get the most out of their treatments.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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