IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract:

One of the Controlled released drug delivery through topical route is Transdermal delivery system which can enable to attend steady blood drug level profiles. Transdermal drug delivery system is defined as self-contained discrete dosage forms which are also known as patches. TDDS are dosage forms design to deliver a therapeutically effective amount of drug across a patient's skin. Now days TDDS treatment is available for diseases like motion sickness, diabetes, arthritis, hormonal replacement, and anti-nausea & Alzheimer treatment. In present review we summarized recent advance, development & various modified techniques in transdermal drug delivery to achieve better therapeutic effect for treatments different diseases.

Keywords:Transdermal; permeation pathways; drug delivery; matrix; reservoir.

Introduction:

Transdermal Delivery represent an attractive to oral delivery of drugs and is poised to provide an alternative to hypodermic injection. TDDS are defined as self-contained discrete dosage forms which are also known as "Patches". TDDS are dosage form design to deliver a therapeutically effective amount of drug across a Patients Skin. For thousands of year people have placed substance on the skin for therapeutics effects and in modern era a verity of topical formulation has been developed to treat local indication. The first Transdermal system for systematic delivery – a three day patch that delivers scopolamine to treat motion sickness was approved for use in United States in 1979. The main objective of Transdermal drug delivery system is to deliver drug into systematic circulation through skin at pre determine rate with minimal inter and intra patient variation. A decade later nicotine patches become the first Transdermal blockbuster rising the profile of transdermal delivery in medical and for public in general. Today there are Nemours transdermal delivery system for such drug as estraclios, Fentanyl, lidocaine and testosterone. Combination Patches containing more than one drug for contraception and hormone replacement and ion theoretic and ultra-sonic delivery system for analgesia.

For understanding the concept of TDDS it is important to know the structure and biochemical features of human skin and those characteristics which contributes to the barrier function and the rate of drug access into the body via skin.The skin acts as a formidable barrier to the penetration of drugs and other chemicals;it does have certain advantages which make it an alternative route for systemic delivery of drug.

Number of drugs deliver through TDDS patches for various diseases.

BRAND NAME	DRUG	MANUFACTURER	INDICATION
Nicotine	Nicotine	Novartis	Pharmacological Somking cessation
Martifen	Fentanyl	Nycomed	Pain relief patch
OrthoEuro	Norelgostromine/Ethinyl Estradiol	Ortho-McNeil	Postmenstrual syndrome
Nupatch 100	Diclofenac diethylamine	Zydus cadila	Anti-inflammatory
Neupro	Rigotine	UCB and Schwarz Pharma	Early-stages idiopathic Parkinsons diseases
Alora	Estradiol	Thera/Thec/Proctol and Gamble	Postmenstrual syndrome.
Androderm	Testosterone	Thera/Tech Giaxosmith kine	Hypogonadism Inj.(male)
Nitrodisc	Nitroglycerin	Robert pharmaceuticals	Angina pectoris
Trandermscop	scopolamine	Alza/Norvatis	Motion sickness
Nclvellets	Estrogen/progestrone	Ethical Holdings/scherings	Hormones replacement therapy

SKIN ANATOMY:

The four main layers of human skin can be categorised as follows:

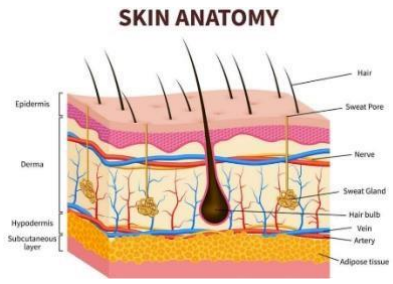
The stratum corneum, which is a non-viable epidermis, is the epidermis.

The dermis lying on top subcutaneous fat's deepest layer.

A skin layer:

Epidermis:

The epidermis is a continuously self-renewing, stratified squamous epithelium that covers the entire outside of the body. It is primarily made up of two types of cells: living or viable cells in the malpighian layer (the viable epidermis), and dead cells in the stratum corneum, also known as the horny layer.[1]The four distinct layers of viable epidermis are further classified.



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

Stratum corneum:

The horny layer, which is the skin's outermost layer, is present here. Chemical substances cannot move both inward and outward because of the rate limiting barrier. The horny layer's constituents—75–80% proteins, 5–15% lipids, and 5–10% ondansetron material on a dry weight basis—have a significant impact on the barrier properties of the layer. When fully hydrated, stratum corneum expands to a thickness of several times its normal 10 mm thickness. Despite being somewhat impermeable, it is flexible. Protein bricks and lipid mortar can be used to simulate the architecture of the horny layer (figure 3). It is made up of horny skin cells (corneocytes) that are joined together by desmosomes, which are protein-rich extensions of the cell membrane. The lipid matrix that surrounds the corneocytes significantly influences how permeable the skin is to substances.[2]

. Viable epidermis

Under the stratum corneum, this layer ranges in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale are some of the layers that make up the interior. The basal layer's continuous cell renewal by mitosis makes up for the epidermis' loss of dead horny cells from the skin's surface. The basale layer's outwardly migrating cells undergo morphological and histochemical changes as they undergo keratinization to form the stratum corneum's top layer.[3]

Dermis

The dermis is a 3 to 5 mm thick layer of connective tissue that lies just below the epidermis and is made up of nerves, lymphatic vessels, and blood vessels.

In order to control body temperature, the cutaneous blood supply is crucial. In addition, it nourishes and oxygenates the skin while eliminating toxins and waste. In order for most molecules to pass through the skin barrier, capillaries must be within 0.2 mm of the skin's surface. As a result, the blood supply keeps the dermal concentration of permeate at an extremely low level. The resulting concentration difference across the epidermis then acts as the primary driving force for transdermal permeation. Although the dermal barrier may be significant when delivering highly lipophilic molecules, this layer is frequently thought of in terms of transdermal drug delivery as essentially gelled water and thus provides a minimal barrier to the delivery of most polar drugs.[4]

Hypodermis

The dermis and epidermis are supported by the subcutaneous fat tissue, or hypodermis. It acts as a spot to store fat. This layer offers nutritional support, mechanical protection, and assistance with temperature regulation. It may contain sensory pressure organs and major blood vessels and nerves that supply the skin. In order for a drug to be delivered transdermally, it must cross all three layers and enter the bloodstream.[3]

PATHWAYS OF DRUGS ABSORPTION THROUGH THE SKIN:

A.Transfollicular route:

Trans follicular route is the shortest pathway that drugs has to follow to reach the systemic circulation that provide a large area for diffusion of drugs.

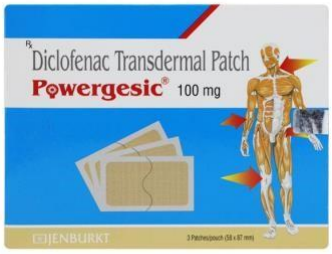
B.Transcellular route:

Drugs delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathways.The drugs passes through the corneocytes of stratum corneum.

C. Inert cellular route.

In intercellular pathway the drug diffuses through the continuous lipid matrix present between cells.

TRANSDERMAL PATCH



A transdermal patch, also known as a skin patch, is an adhesive patch that contains medication and is applied to the skin in order to deliver a specific dose of medication through the skin and into the bloodstream. In December 1979, the U.S. Food and Drug Administration approved the first prescription patch for motion sickness that contained scopolamine. The nicotine patch, which releases nicotine to aid in quitting tobacco use, was the transdermal patch with the highest sales in the United States. In 2007, Europe approved the first commercially available vapour patch to help people quit smoking.

Various other patches, such as nitroglycerin patches for angina and lidocaine patches marketed under the name Lidoderm, which reduce shingles-related peripheral pain, are also offered on the market. As an analgesic for moderate to severe chronic pain, buprenorphine is sold under the brand name Bu Trans. In addition, it is now frequently used off-label to treat chronic pain and the pain from recent injuries. Flector (Diclofenac Epolamine) patch is a topical NSAID used to treat acute pain brought on by minor contusions, sprains, and strains. Additionally, it is used to treat fibromyalgia, arthritis, and other chronic conditions that benefit from NSAIDs in terms of pain and inflammation. ADHD, or excessive activity. The FDA revealed in 2005 that they are looking into reports of fatalities and other grave adverse events connected to narcotic overdose.fentanyl transdermal patch users who use Duragesic for pain relief.[26]

Components of the transdermal patch:

Transdermal patches' primary ingredients are a polymer matrix/drug reservoir, the active substance (drug), permeation enhancers, pressure-sensitive adhesive (PSA), backing laminates, release liner, and other excipients like plasticizers and solvents.

1. Polymer matrix:

Transdermal drug delivery systems are built on polymers. Systems for transdermal delivery are made of multilayered polymeric laminates, which have two polymeric layers sandwiching a drug reservoir or drug polymer matrix between them. The outer impervious backing layer prevents drug loss through the backing surface, and the inner polymeric layer serves as an adhesive and/or rate-controlling membrane. When attempting to meet the various requirements for the creation of reliable transdermal delivery systems, polymer selection and design must be taken into account. The design of a polymer matrix poses the greatest challenge, which is then followed by optimisation of the drug-loaded matrix with regard to its adhesion

cohesion balance, physical and chemical characteristics, compatibility, and stability with other system components as well as with skin. The polymers utilized for TDDS can be classified as

(1) Natural polymers: cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, chitosan, etc,

(2) Synthetic elastomers: polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butyl rubber, etc,

(3) Synthetic polymers: polyvinyl alcohol,polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyurea, polymethylmethacrylate etc.

2. Drug:

The drug must meet the necessary physicochemical and pharmacokinetic requirements, which are the main requirements for TDDS. Drugs that undergo extensive first-pass metabolism, have a limited therapeutic window, or have a short half-life that necessitates frequent dosing and results in non-compliance have a lot to gain from transdermal patches.

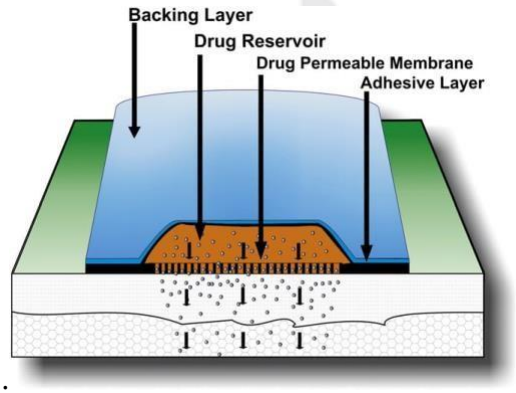
3. Permeation enhancers: Permeation enhancers interact with the proteins or lipids that make up the structural elements of the stratum corneum in order to increase its permeability and increase the therapeutic levels of the drug. The partial leaching of the epidermal lipids by the chemical enhancers, which improves the skin conditions for wetting and for trans-epidermal and trans-follicular permeation, is thought to be the cause of the enhancement in the absorption of oil-soluble drugs. The increased transdermal permeation of watersoluble may be caused by the enhancers' miscibility and solution properties.

4. Pressure-sensitive adhesive (PSA): A PSA keeps the patch and the skin's surface in close proximity. It should be aggressively and permanently tacky, adhere with no more than finger pressure, and exert a strong holding force. Adhesives based on silicon, polyisobutylene, and polyacrylates are among them, according to World Journal of Pharmacy and Pharmaceutical Sciences. Numerous elements, such as the patch design and drug formulation, influence the choice of adhesive. PSA shouldn't affect drug release and should be compatible with physicochemical and biological processes. The PSA may be placed on the device's face or inside the device's back and extending outward.

5. Backing laminate: Support is the backing laminate's main purpose in life. Because prolonged contact between the backing layer and the excipients may result in additives leaching out or may result in excipients, drugs, or permeation enhancers diffusing through, the backing layer should be chemically resistant and excipients compatible. They ought to have a slow rate of moisture vapour transmission. Their elasticity, flexibility, and tensile strength must be at their best.

6. Release liner: The release liner stops contamination during storage as well as drug loss that has migrated into the adhesive layer. Therefore, rather than being a component of the dosage form for dispensing the medication, it is viewed as a part of the primary packaging material. The base layer of the release liner can be either non-occlusive or occlusive, and the release coating layer is made of silicon or Teflon. Polyester foil and metalized laminate are additional materials used to make the TDDS release liner.

7. Other excipients: Drug reservoirs are made using a variety of solvents, including dichloromethane, acetone, chloroform, methanol, and methanol. Additionally, plasticizers like dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added to the transdermal patch to give it plasticity.[27]



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DESIGN OF TRANSDERMAL DELIVERY SYSTEM: The drug is dissolved or dispersed in an inert polymer matrix, which serves as support and a platform for drug release, as the fundamental component of any transdermal delivery system. The patch system's two fundamental designs, which determine the drug release characteristics and patch behaviour, are as follows:

Matrix or Monolithic: The inert polymer matrix binds with the drug and controls its release from the device.

Reservoir or Membrane: Drug release is not governed by the polymer matrix. Instead, a rate- regulating membrane that is sandwiched between the drug matrix and the adhesive layer acts as the rate-limiting barrier for drug release from the device.[5]

PREPARATION OF TRANSDERMAL PATCHES: Transdermal drug delivery patches can be prepared by various methods

Mercury Substrate Method: This method involves dissolving the required amount of drug in a solution of polymer and plasticizer. The aforementioned mixture should be stirred for a while to create a homogenous dispersion. It should then be set aside until all air bubbles have been eliminated before being poured into a glass ring that will be placed over the mercury surface in a glass petri dish. By putting an inverted funnel over the petri dish, the rate at which the solvent evaporates can be managed. The films that have dried out must be kept in a desiccator[6-7].

Circular Teflon Mould Method: In an organic solvent, solutions with different ratios of polymers are used. The drug is dissolved in half as much of the same organic solvent as was calculated. Drug polymer solution contains a plasticizer. After thoroughly stirring the mixture, it should be poured into a teflon mould that is circular. Inverted glass funnels on teflon moulds were used to control the rate of solvent vaporisation. 24 hours are given for the solvent to evaporate. The dehydrated films must be kept in a desiccator[8-9].

Glass Substrate Method: The polymeric solutions are set aside to swell before the necessary amounts of plasticizer and drug solution are added, followed by a 10-minute stirring period. It is also allowed to stand for a while to release any trapped air before being poured into a dry, clean anumbra petriplate. Inverting a glass funnel over the petri plate regulates the rate of solvent evaporation. The dried films are removed from the overnight drying process and placed in a desiccator[10-11]

By Using IPM Membranes Method: This method involves dispersing the drug over a 12-hour stirring period in a solution of water and propylene glycol that contains carbomer 940 polymers. Triethanolamine will be added to the dispersion to neutralise it and make it viscous. If the drug is very poorly soluble in aqueous solution, a buffer pH 7.4 can be used to create solution gel. The gel will be formed and integrated into the IPM membrane[12-13]

By Using EVAC Membranes Method: Rate control membranes made of polyethylene (PE), ethylene vinyl acetate copolymer (EVAC), and 1% carbopol reservoir gel can be used to prepare the target transdermal therapeutic system. When making a gel, propylene glycol is used if the drug is not soluble in water. The drug is dissolved in propylene glycol, and then carbopol resin is added to the mixture before it is neutralised with 5% w/w sodium hydroxide solution. The medication is applied to a backing layer sheet that covers the designated area and is in the form of a gel. To create a leak-proof device, the gel will be covered with a rate-regulating membrane, and the edges will be heated to seal them.[12-13]

Aluminium Backed Adhesive Film Method: If the loading dose is greater than 10 mg, transdermal drug delivery systems may result in unstable matrixes. Using adhesive film with an aluminium backing is a good option. Due to the fact that most drugs and adhesives are soluble in chloroform, it is the preferred solvent for preparation of the same. Adhesive material will be added and dissolved in the drug solution after the drug has been dissolved in chloroform. Aluminium foil is used to line a specially made aluminium former, and snugly fitting cork blocks are used to blank off the ends[11-14]

Asymmetric TPX Membrane Method: A prototype patch can be created using a heat sealable polyester film (type 1009, 3m) with a backing membrane concave of 1 cm in diameter. A TPX "poly (4-methyl-1pentene)" asymmetric membrane is used to cover the concave membrane, which is then filled with the drug sample and sealed with adhesive[15].

EVALUATION TEST OF TRANSDERMAL PATCH

Studies on Drug Excipient Interactions: The medicine and excipients need to get along for the product to work well. Stable product, so it's critical to find any possible defects. Physical and chemical forces interacting One category of research that examines human interaction is the interaction studies study. In this technique, thermal analysis is frequently performed. FT-IR by comparing the assay, melting, and other physiochemical wave numbers, maxima, etc. with UV and chromatographic procedures. [15]

Drug Content: A specific volume of an appropriate solvent needs to be used to dissolve a section of the patch. The solution will next be filtered via a filter media. Determine the drug's composition using the proper technology (UV or X-rays). The HPLC method). Every sample value represents the average of three values.[16-17]

Patch Thickness : By using a digital micrometre to measure the patch's thickness at multiple locations, the average thickness and width of the drug-loaded patch are found. To confirm the thickness of the constructed patch, find the standard deviation for the same[18]

Moisture loss : each of the generated films, then store them in a calcium chloride-filled desiccator at 40˚C. The movies will be screened the next day. Utilizing the procedure below, reweigh and determine the percentage of moisture loss [13]. % Moisture Loss = [Start weight–End weight] × 100[19]

Swellability: The 3.14 cm2 patches were weighed and then allowed to drink in 10 ml of double-distilled water in a petri plate. A rise in mass. Patches were chosen at prearranged intervals until a decision was made. It was found that the weight did not change. To calculate the swelling degree (S), use the formula S(%) = Wt-Wo/Wo ×100. Wt is the weight of the patch at time t, Wo is the weight of the patch at time zero, and S is the percentage swelling[20]

In- vivo Studies: Studies conducted in vivo provide the most precise picture of a drug's effectiveness. In-vitro research allows for the full consideration of variables that are not possible to consider. Studies on invivo research have been conducted. To carry out TDDS, the following techniques can be tested in vivo: Animal-based models Human race volunteers[21]

Models of Animals: Mice, hairless rats, and other animals are the most often employed animal species for transdermal drug delivery system testing. Examples of hairless animals include guinea pigs, hairless dogs, hairless rhesus monkeys, and rabbits.

Human Models : The last stage in developing a transdermal patch for pharmaceutical pharmacokinetics is gathering human models. After the patch is applied, pharmacodynamic data is collected from a group of human volunteers. Among other things, clinical trials have been conducted to ascertain efficacy, risk, side effects, and patient compliance..

Stability Studies: Stability studies must be conducted by storing the TDDS in compliance with ICH regulations. Samples were maintained at 40.5% RH and 40.5% C for six months. Samples were obtained at 0, 30, 60, 90, and 180 days in advance. Examine the medication's contents with due diligence. [18-22]

GENERAL CLINICAL CONSIDERATIONS IN THE USE OF TDDS:[23]

The patient should be informed of the general rules listed below. To help the skin regain its normal permeability and to prevent skin irritation, the application site should be rotated15. To clean, dry skin that is largely hair-free and not oily, inflamed, irritated, or broken skin, TDDS should be applied. Drug permeation time can be sped up on moist or wet skin. Skin that is too oily can make patches less adherent. If hair is present at the site, it should be carefully cut, rather than wet shaved or removed with a depilatory agent, as this may affect the rate and extent of drug permeation by removing stratum corneum. Skin lotion shouldn't be applied where it will be applied**.** Mainly because lotions can change the drug's partition coefficient and have an impact on the skin's hydration. In order to preserve the integrity of the system, the patient shouldn't physically alter the TDDS. Take care not to touch your fingertips when removing the protective backing. For about 10 seconds, press the heel of your hand firmly against the TDDS skin site. An area where a TDDS won't be exposed to movement or clothing rubbing off should be chosen for placement. While bathing, showering, or swimming, TDDS should be left on. A TDDS should be used as directed by the product's instructions, which include wearing it for the recommended amount of time before removing it and changing to a new system. Following the application of a TDDS, the patient or carer

should wash their hands. When handling the system, the patient shouldn't touch their mouth or rub their eyes. The patient should request reevaluation if they show signs of sensitivity or intolerance to TDDSs or experience excessive skin rashes. To prevent re-use, a used TDDS should be folded in half with the adhesive layer together after removal. In a way that is safe for kids and pets, the used patch was disposed of. applying a transdermal patch Use a different application site each day to prevent skin sensitivity. The recommended rotation is Day 1: Upper right arm, Day 2: Upper right chest, Day 3: Upper left chest, and Day 4: Upper left arm, then repeat from Day 1.

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE USED: When a patient needs an alternative drug delivery method because they have intolerable side effects (like constipation) from oral medication and are unable to swallow it (due to dysphagia), they turn to transdermal patches. where reliable administration could enhance the control of the pain. Patients with cognitive impairment or those unable to use their analgesia to self-medicate for other reasons may find this helpful.[24-25]

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE NOT USED: The use of transdermal patch is not suitable when:

(1) A remedy for severe pain is necessary.

(2) In situations that call for quick dose titration.

(3) Where the dosage requirement is equal to or less than 30 mg/24 hours.[24-25]

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