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# Transdermal Drug Delivery System: A Complete Review

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**ABSTRACT:** A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of the transdermal drug delivery system is to deliver drugs into systemic circulation through the skin at a predetermined rate with minimal inter and intrapatient variations. This review discusses the detailed structure of the skin, the transdermal patch, and its various components. It also gives a review of the various evaluation parameters of a transdermal patch.

**KEYWORDS**: Transdermal, Patch, Skin, Stratum corneum, Evaluation.

## INTRODUCTION:

Today there are a host of drugs that are used to treat almost every disease condition known to man. These drugs have various forms by which they can enter the human body for therapy like tablets, capsules, injections, aerosols, creams, ointments, suppositories, liquid, etc. Therapy with such concentration involves the maintenance of drug concentration in the body within a therapeutic effective range by the introduction of a fixed dose of the drug at regular intervals into the body. The drawback is that drug concentration in the body follows a peak and through profile leads to changes of therapeutic failure then it was realized that we can use the skin as a source of entry of drug in the systemic circulation, this is known as transdermal administration.[1]

Transdermal Drug Delivery Systems (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches" when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. The main objective of the transdermal drug delivery system is to deliver drugs into systemic circulation the skin through the skin at a predetermined rate with minimal inter and intrapatient variation. Currently transdermal delivery is one of the most promising methods for drug application.[2]

## ADVANTAGES[345]

1. Transdermal medication delivers a steady infusion of a drug over an extended period.
2. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
3. Increases the therapeutic value of many drugs by avoiding specific problems associated with the drug-like GIT irritation, low absorption, decomposition due to hepatic first-pass effect, and short half-life that requires frequent dosing.
4. The simplified medication regimen leads to improved patient compliance and reduces inter and intrapatient variability.
5. Self-administration is possible.
6. The drug input can be terminated at any given point in time by removing the patch.

## DISVANTAGES[67]

1. Skin irritation or contact dermatitis due to the drug, excipients, and enhancers of the drug to increase the percutaneous absorption.
2. The barrier function of the skin changes from one site to another site on the same person, from person to person, and with age.
3. Drugs must have some desirable physicochemical properties for penetration through the stratum corneum.

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4. If the dose of a drug required for therapeutic value is more than 10 mg /day the transdermal drug delivery will be difficult if not possible. A daily dose of 5mg/day is preferred.

**TRANSDERMAL PATCH**

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal patch over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.[8]

**STRUCTURE OF SKIN AND BARRIERS**

To understand TDDS it is important to review the structural and biochemical features of human skin.

**SKIN**

Skin is the largest organ of the human body that covers a surface area of $2m^2$. It receives one-third of all the blood circulating through the body. It acts as a barrier against physical, chemical, and microbial attacks. It acts as a thermostat in maintaining body temperature. It separates the underlying blood network from the outside environment.[9]

When a transdermal patch is applied to the human skin, it may retain the drug or active substance on the surface of the skin, without any absorption, e.g., in the case of cosmetics and antiseptics or it may allow the drug permeation through the skin into the deeper regions i.e., dermis and the epidermis. These formulations are also called dia dermal or endodermal formulations. The third enviable function is to have the drug absorbed systemically.[10,11]

**STRUCTURE OF SKIN**

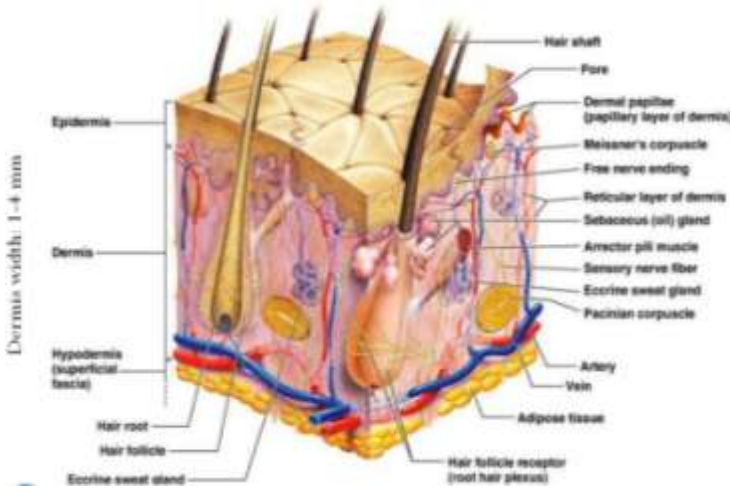


Figure 1: Structure of human skin

Anatomically it has many histological layers but in general, it describes in terms of three major tissue

1. Epidermis
2. Dermis
3. Hypodermis

1. **EPIDERMIS**

The epidermis is a continually self-renewing, stratified squamous epithelium covering the entire outer surface of the body and is primarily composed of two parts non-viable epidermis and viable epidermis together make up the epidermis. The stratum corneum is known as the non-viable epidermis whereas the layer below the stratum corneum is called the viable epidermis. The viable epidermis is made of various sublayers of the epidermis which collectively are 50-100 µm thick and cells in this layer are held together by ton fibrils. Blood capillaries and nerve fibers reach the epidermis by passing through the dermis and subcutaneous fat layer. The main cell of the

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epidermis is the keratinocytes which make up 95% of the total cells present in the epidermis. [12–15]

**A. STRATUM CORNEUM**

This is the outermost layer of skin also called a horny layer. It is the rate-limiting barrier that restricts the inward and outward movement of chemical substances. The barrier nature of the horny layer depends critically on its constituents: 75-80% proteins, 5-15% lipids, and 5-10% ondansetron material on a dry weight basis. Stratum corneum is approximately 10 mm thick when dry but swells to several times when fully hydrated. It is flexible but relatively impermeable. The architecture of the horny layer may be modeled as a wall-like structure with protein bricks and lipid mortar. It consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocytes are embedded in a lipid matrix which plays a significant role in determining the permeability of substance across the skin.[16–21]

This is situated beneath the stratum corneumand varies in thickness from 0.06 mm on the eyelids to 0.8mm on the palms.

a. Stratum lucidum (clear layer)- It can only be found in soles and palms
b. Stratum granulosum (granular cell layer)-f 2 to 4 granular cell layers. The thickness of this layer is 3 µm. Cells become increasingly filled with keratin fibers and contain less moisture as compared to basal and prickle cell layers. The shape of these cells becomes much flatter during this process.
c. Stratum spinosum (prickle cell layer)- 10 to 20 layers that lie on top of the basal cell layer. Basal cells, through the process of turn-over, make their shape somewhat flatter and form these layers. The thickness of this sublayer is from 50 to 150 µm.
d. Stratum basal (basal cell layer)- Deepest sublayer of the epidermis and is composed of a single layer of basal cells. Keratinocytes are produced in this sublayer. Melanocytes also lie in this.[18]

**B. VIABLE EPIDERMIS**

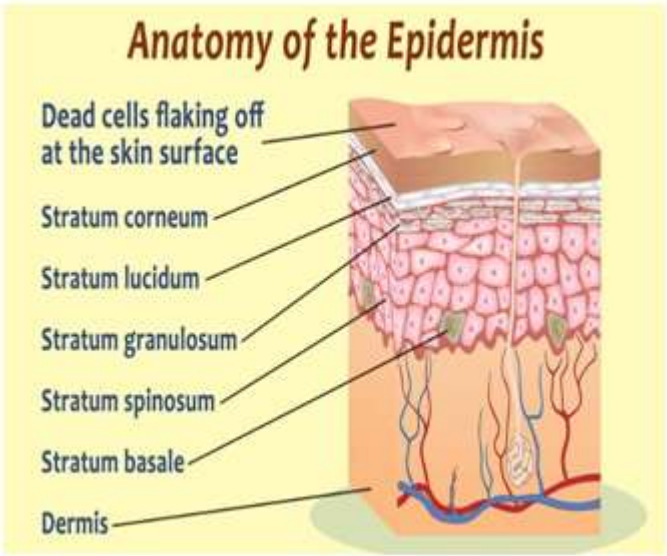


Figure 2: Anatomy of the epidermis

**2. DERMIS**[11]

Once a drug molecule passes through the stratum corneum, it may pass through the deeper epidermal tissues and enter the dermis. The dermis is the layer of skin just beneath the epidermis which is a 3 to 5 mm thick layer and is composed of a matrix of connective tissues, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has an essential function in the regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach within 0.2 mm of the skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation. In terms of transdermal drug delivery, this layer is often viewed as

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essentially gelled water, and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

**3. HYPOSERMSI**[22]

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature and provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, the drug must penetrate through all three layers and reach the systemic circulation.

**PERCUTANEOUS ABSORPTION:**[23]

To undergo percutaneous absorption, a compound is released from its formulation, encounters the skin surface, establishes a stratum corneum reservoir, penetrates the stratum corneum barrier, diffuses into the viable epidermis, and finally gains access to the systemic compartment through the vascular system

Percutaneous absorption involves the passive diffusion of a substance through the skin.

By two mechanisms

A.Trans epidermal absorption - Passage through the epidermis

B. Trans follicular absorption- Diffusion through the shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands vs epidermalroute**:**

**TRANSEPIDERMAL ABSORPTION**- In trans epidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intracellular pathway. Both polar and nonpolar substances diffuse via transcellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated stratum corneum whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the stratum corneum. Thus, the principal pathway taken by a penetrant is decided mainly by the partition coefficient

The main route of transport for water-soluble molecules is transcellular. It involves the passage through the cytoplasm of corneocytes and the lipid arrangement of the stratum corneum.

Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants traverse the stratum corneum via the intercellular route. Most molecules pass the stratum corneum by both routes. The pathway of transport for lipid-soluble molecules is intercellular; it implicates the passage apparently through the endogenous lipid within the stratum corneum.

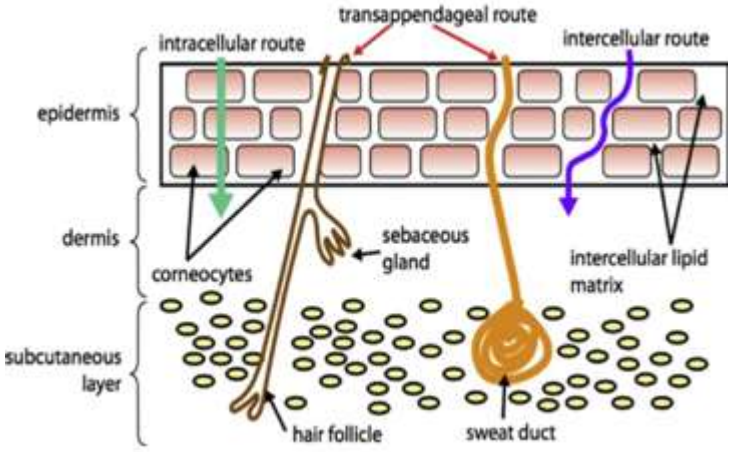


Figure 3: Transepidermal route

**TRANS FOLLICULAR ROUTE (SHUNT PATHWAY):**

This route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. Although these routes offer high permeability, they are of minor importance because of their relatively small area, approximately 0.1% area of the total skin. This route seems to be most important for ions and large polar molecules which hardly permeate through the stratum corneum.[23–27]

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**COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM**

A. Polymer matrix / Drug reservoir.
B. Drugs.
C. Permeation enhancers.
D. Pressure-sensitive adhesive (PSA).
E. Backing laminates.
F. Release liner.
G. Other excipients like plasticizers and solvent.

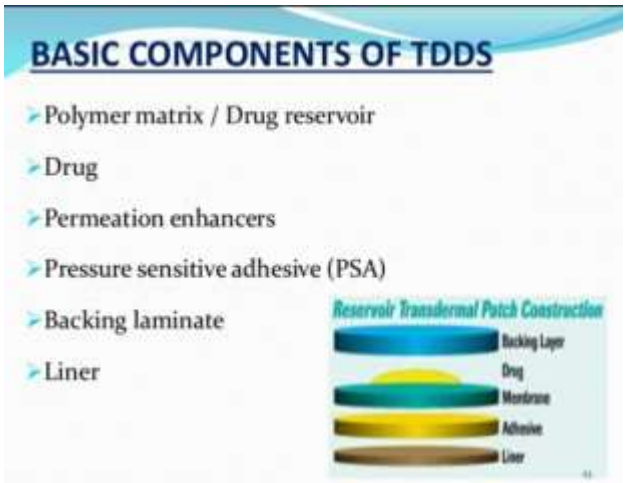


Figure 4: Basic components of transdermal drug delivery system

**A. POLYMER MATRIX / DRUG RESERVOIR.**[23,28,29]

Polymers are the heart of TDDS, which control the release of the drug from the device. The polymer matrix can be prepared by dispersion of drugs in liquid or solid-state synthetic polymer bases. Polymers used in TDDS should have good stability and compatibility with the drug and other components of the system and they should provide effective release of a drug throughout the device with safe status.

**IDEAL PROPERTIES OF A POLYMER TO BE USED IN A TRANSDERMAL SYSTEM:**

a. Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
b. Stable.
c. Nontoxic
d. Easily manufactured
e. The polymer should be inexpensive
f. The polymer and its degradation product must be nontoxic or non-antagonistic to the host.
g. Large amounts of the active agent are incorporated into it.

**B. DRUGS**[23,28]

**1. PHYSICOCHEMICAL PROPERTIES:**

The drug should have a molecular weight of fewer than 1000 Daltons. The drug should have an affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin. The drug should have a low melting point. Along with these properties, the drug should be potent, have a short half-life, and be non-irritating.

**2. BIOLOGICAL PROPERTIES:**

The drug should be very potent, i.e., it should be effective in a few mg/days. The drug should have a short biological half-life. The drug should not be irritant and non-allergic to human skin. The drug should be stable when in contact with the skin. They should not stimulate an immune reaction in the skin. Tolerance to the drug must not develop under a near zero-order release profile of transdermal delivery. The dose is less than 50 mg per day and ideally less than 10 mg per day. The drug should not get irreversibly bound in the subcutaneous tissue. The drug should not get extensively metabolized in the skin.

**C. PERMEATION ENHANCERS**[23,28–33]

These compounds are useful to increase the permeability of the stratum corneum by interacting with structural components of the stratum corneum i.e., proteins or lipids to attain higher therapeutic levels of the drug 23. They alter the protein and lipid packaging of the stratum corneum, thus chemically modifying the barrier functions leading to increased permeability 24. Some examples are Dimethyl sulfoxide, Propylene glycol,2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Surbiton monolaurate, Pluronic, Cardamom oil,

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Caraway oil, Lemon oil, Menthol, limonene, Linoleic acid

These are compounds that promote skin permeability by altering the skin as a barrier to the flux of the desired penetrant. Compounds having the ability to enhance the stratum corneum ability are

1. **SOLVENTS**:

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples: water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethylacetamide and dimethylformamide

2. SURFACTANTS

These compounds are proposed to enhance polar pathway transport, especially hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length

Anionic Surfactants: e.g., Dioctyl sulfosuccinate, Sodium lauryl sulfate, Dodecyl-methyl sulfoxide, etc.

Nonanoic Surfactants'. Pluronic F127, Pluronic F68, etc.

Bile Salts: e.g., Sodium taurocholate, Sodium deoxycholate, Sodium Tauro glycocholate.

Binary system: These systems open the heterogeneous multilaminate pathway as well as the continuous pathways. Propylene glycol-oleic acid and 1, 4-butanediol- linoleic acid.

Miscellaneous chemicals: These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness is sparse. These include eucalyptol, di-o-methyl-cyclodextrins, and soybean casein

**D. PRESSURE-SENSITIVE ADHESIVES**

Material that helps in maintaining intimate contact between the transdermal system and the skin surface. The fastening of all transdermal devices to the skin is done by using a pressure-sensitive adhesive. Adhesion involves a liquid-like flow resulting in wetting of skin upon applying pressure, when pressure is removed adhesive sets in the state. It should adhere with not more than applied finger pressure. It should be removable from the smooth surface without leaving residue. It must be skin-compatible, causing minimal irritation or sensitization. In addition, they must be able to dissolve drug and excipient in quantities sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability.

Examples polyacrylate, polyisobutylene, and polysiloxane

**E. BAKING LAMINATES**

They are flexible which provides a good bond to the drug reservoir. It prevents the drug from leaving the dosage form through the top. It is an impermeable substance that protects the product during use on the skin, for example, metallic plastic. While designing a backing layer the consideration of chemical resistance and excipients may be compatible because of the prolonged contact between the backing layer and the excipients, drug, or penetration enhancer through the layer. They should have a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. aluminum vapor coated layer, a plastic film, and heat real player.

For example, Cellulose derivatives and polypropylene silicon aluminum vapor coated layer, a plasticfilm and heat real player.

**F. RELEASE LINERS**

During storage, the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to the skin. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form for delivering the drug. A release liner is composed of a base layer that may be non-occlusive (e.g., paper fabric) or occlusive (e.g., polyethylene, polyvinyl chloride) and a release coating layer made up of silicon or Teflon. It should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer, and water.

**G. OTHER EXCIPIENTS**

Various solvents such as chloroform, methanol, acetone, isopropanol, and dichloromethane are used to prepare drug reservoirs 18, 32. In addition plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added to provide plasticity to the transdermal patch.[34]

**PENETRATION ENHANCERS**

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. There are two types of penetration enhancers.

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A. CHEMICAL PENETRATION ENHANCERS
B. PHYSICAL PENETRATION ENHANCERS

**A. CHEMICAL ENHANCERS**[35]

Chemical substances temporarily diminish the barrier of the skin and are known as accelerants or sorption promoters that can enhance drug flux.Several types of chemical enhancers are known.Sulfoxides and similar chemicals- Dimethyl sulfoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. DMSO alone has been applied topically to treat systemic inflammation. It is one of the most widely studied penetration enhancers. It is a powerful aprotic solvent in which hydrogen bonds with itself rather than with water. However, at these relatively high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing some skin proteins results in erythema, scaling, contact urticaria, stinging, and burning sensations.Since DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically related material as an accelerant. DMAC and DMF are similarly powerful aprotic solvents.

**AZONE**- Azone was the first molecule specifically designed as a skin penetration enhancer. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics, and antiviral agents. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone molecules may exist dispersed within the barrier lipoid or separate domains within the bilayer.[36,37]

**PYRROLIDONE**- The pyrrolidone partition well into the human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidone has been used to generate reservoirs within the skin membrane. Such a reservoir effect offers potential for sustained release of a permeant from the stratum corneum over extended periods. [38]

**FATTY ACIDS**-Percutaneous drug absorption has been increased by a wide variety of long-chain fatty acids, the most popular of which is oleic acid. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold through human skin membrane in vitro. The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a long-chain fatty acid with cis- configuration. [36,39,40]

**ESSENTIAL OIL, TERPENES, AND TERPENOIDS**- One mechanism by which this agent operates is to modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue. Many terpenes permeate human skin well and large amounts of terpene have been found in the epidermis after application from a matrix-type patch. [41–43]

**Urea**- Urea promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, the enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism.[44]

**PHYSICAL PENETRATION ENHANCERS**

**1. IONTOPHORESIS**: It is defined as the permeation of ionized drugs through electrical impulses of 0.5 mA/cm by either galvanic or voltaic cells.It contains a cathode and anode which attract positively charged ions and negatively charged ions, respectively.In other words, it is a technique that uses a slight electric current to improve the transportation of the drug via an electric circuit consisting of two drug reservoirs (anode and cathode) deposited on the skin surface.Drugsdrew into the skin directly proportional to the current applied. The higher the pH of the skin will be the permeability of drugs in the skin.Iontophoresis, which utilizes small electric currents, can enhance transport across the skin by different mechanisms such as electromigration and electroosmosis. Electromigration (electro repulsion): In this mechanism, ions are repelled by the electrode of the same charge and attracted by the electrode of the opposite charge.Charged ions are attracted to positively charged electrodes.In electroosmosis, neutral substances are transported with the solvent flow.[45–53]

**2. ELECTROPORATION:** Electroporation is a method of application of short, high-voltage electrical pulses to the skin. That has been suggested to induce the formation of transient pores. (Nano-sized) High voltages (1000v) and short-term duration (milliseconds) are most frequently employed. This technology is used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, and proteins.

Peptides, oligonucleotides) including biopharmaceuticals with a molecular weight greater than 7 KDA. The formation of nanosized pores increases the passage of ions and macromolecules through the skin. This technique works in either of the two ways: first is pore formation in lipid

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bilayers, corneocytes but small-charged molecules cannot pass via this route and the second is applying a high voltage which automatically creates aqueous pores through the epidermis which are helpful in permeation across five to six lipid membranes.

Reversible Electric pulses cause a short-term increment in permeation enhancement and the cell survives. This approach has its application in biotechnology and medicine.

Irreversible Electric pulses lead to membrane permeation which leads to cell death or necrosis or apoptosis. This approach has its application in the food industry and sterilization.

Application of Electroporation

1. S Arora (2012). Eriksson et al. (2013) studied that DNA vaccine (coding for the prostate specific antigen to treat prostate cancer) can be given transdermally with the help of an electroporation technique.
2. It has positive applications in the delivery of proteins, oligonucleotides, small molecules, heparin, insulin, dextran, and vitamin C.[54–56]

**3.SONOPHORESIS**

It is also termed phonophoresis or the use of ultrasound

Use of ultrasound Application of ultrasound, particularly low-frequency ultrasound, has been shown to enhance the transdermal transport of various drugs including macromolecules. It is also known as sonophoresis.

In this enhancement technique, permeation is increased via ultrasonic waves

Ultrasound conditions are as follows: Diagnostic ultrasound (High frequency, 3-10 MHz); Therapeutic ultrasound (Medium frequency, 0.7-3 MHz); Regulator ultrasound (Low frequency, 18 to 100 kHz). The use of low frequency is a viable technique for local, regional, and systemic transdermal drug delivery, which reduces the side effects associated with oral and intravenous delivery. When ultrasound passes through

Mechanism

When the US passes through a medium, energy is partially absorbed. In the human body, ultrasound energy absorbed by tissue causes a local temperature increase that is dependent upon ultrasound frequency, intensity, area of the ultrasound beam, duration of exposure, and the rate of heat removal by blood flow or conduction. The resultant temperature increase of the skin may enhance permeability due to an increase in diffusivity of the skin

The mechanism involves either of the two ways: (a) application of sound waves to the skin increases the fluidity of lipids and increases permeation via a transcellular pathway or (b) formation of bubbles that generates pores that even allow large molecular weight drugs such as protein or vaccines.

Uses of Sonophoresis

Efficiently deliver several types of drugs regardless of their electrical characteristics.

Trainers prefer a method of formation of bubbles that generates pores to permeate dexamethasone, ketoprofen, or lidocaine in patients.[57–60]

**H. MICRONEEDLES**

Microneedles are micron-sized needles, generally, microneedles have a length of 100-500 µm, made of a diversity of materials and shapes. Micro needles are used to open holes into the skin to create a pathway for the following delivery of drugs, and thus, microneedles can penetrate the higher layer of the skin without reaching the dermis and are almost painless. Then, the drug diffuses through the rest of the epidermis into the dermis where it is absorbed into the blood circulation.

**EVALUATION OF TRANSDERMAL DRUG DELIVERY**

**1. THICKNESS**: Determined by traveling microscope, dial gauge, screw gauge, or micrometer at different points of the film.

EXPERIMENT: The thickness of the patch was measured by using a screw gauge at five positions of the patch and an average of three was taken.[61]

**2. UNIFORMITY OF WEIGHT:**

The individual patches are weighed in a digital balance

EXPERIMENT: 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.

Ensures that film containsthe proper amount of excipient and API.[62]

**3. DRUG CONTENT DETERMINATION:**

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

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**3. MOISTURE CONTENT**:

The prepared films are weighed individually and kept in 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. The percent moisture content is calculated using the following formula.

% Moisture content = Initial weight – Final weight X 100 4

**4. TENSILE STRENGTH**

The tensile strength of the film was determined with a universal strength testing machine. The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one is fixed and the upper one is movable. The test film of size (4 × 1 cm2) is fixed between these cell grips and force is gradually applied till the film breaks. The tensile strength of the film is taken directly from the dial reading in kg. Tensile strength is expressed as follows. Tensile strength =Tensile load at break / Cross-section

**6. FOLDING ENDURANCE**

It checks the ability of the sample to withstand folding. Checks the no of folds that either break the specimen or develop visible cracks. Checks the elasticity of the film. Checks the brittleness (less folding endurance gives more brittleness).

EXPERIMENT: A patch of 2cm was cut evenly and repeatedly folded at the same place till it breaks, the number of times film was folded without breaking gives the folding endurance

**7. %MOISTURE UPTAKES:**

It is defined as the quantity of moisture transmitted through a unit area of film in unit time.

EXPERIMENT: Glass cells were filled with 2g of anhydrous calcium chloride and a film of a specified area was affixed to the cell rim. The assembly was accurately weighed and placed in a humidity chamber

%Moisture uptake = Final weight -Initial weight *100

**IN VITRO EVALUATION**

In vitro skin permeation studies were performed with a Franz diffusion cell with a receptor compartment capacity of 22.5 ml. The excised rat abdominal skin was mounted between the donor and the receptorcompartment of the diffusion cell.

EXPERIMENT: Formulated patches were placed on the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer of ph. 7.4.The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was continuously and constantly stirred using magnetic beads at 50 rpm and the temperature was maintained at 32.50 degrees Celsius or 31.05 degrees Celsius. An aliquot (3ml) of the receptor medium withdrawal at equal intervals (1,2,3,4,5,6,7, and 8 hours) were withdrawn at different time intervals and analyzed for drug content spectrophotometrically.

The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentage of drug permitted for each square cm of patches was plotted against the time

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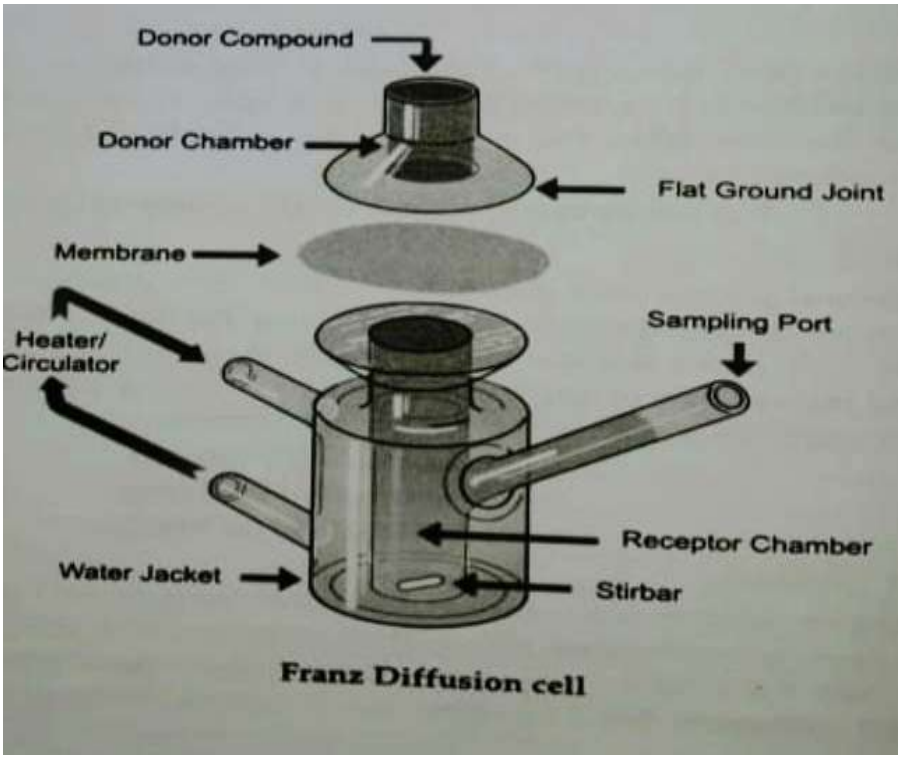


Figure 5: Franz diffusion cell

**IN VIVO EVALUATION**

Transdermal patches can be in vivo evaluated in terms of In vivo evaluations are the true depiction of the drug performance. The variables which cannot be considered during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using animal models of human volunteers.

**ANIMAL MODELS**

Considerable time and resources are required to carry out human studies, so animal studies are preferred on a small scale. The most common animal species used for evaluating transdermal drug delivery systems are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig, etc. Various experiments conducted led to the 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.26

**HUMAN MODEL**

The final stage of the development of a transdermal device involves the collection of pharmacokinetic and pharmacodynamic data following the application of the patch to human volunteers.39 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 many patient populations and phase IV trials at post-marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources best to assess the performance of the drug.

## CONCLUSION

Transdermal delivery offers several advantages over oral routes for controlled drug delivery, viz., avoidance of hepatic first-pass metabolism, the ability to control drug delivery for a longer time than the GIT transit of oral dosage form, the ability to avoid changing physiological environment, and chemical or metabolic degradation, the ability to discontinue administration by removal of the system.

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