ABSTRACT
Transdermal delivery builds up one of the most important routes for a new drug delivery system. Since 1981, the Transdermal drug delivery system (TDDS) has been used as a safe and effective drug delivery device. Their potential role in the controlled release is being globally exploited by the scientists with the high rate of enlistment. Today about 74% of drugs are taken orally and are found not to be as efficacious as required. To improve such characters TDDS has emerged. The transdermal drug delivery system is a costly alternative to the conventional formulation. TDDS are dosage forms that involve drug transport to epidermal and or dermal tissues of the skin for local therapeutic effect as long as a very major fraction of drug is transported into the systemic blood circulation. One of the newer technologies to emerge is the delivery-optimized thermodynamic (DOT) patch system, which permits greater drug loading to be achieved a much smaller patch size. Transdermal delivery not only provides controlled, stagnant administration of the drug but also allows continuous Input of drugs with short biological half-lives and repels pulsed entry into the systemic circulation, which mostly causes undesirable side effects. The advantage of the transdermal drug delivery system is that it is a painless technique of administration of drugs.

KEYWORDS: Transdermal drug delivery, Systemic blood circulation, DOT, Painless.
dermatological disorders treatment the most commonly topically applied creams and ointments was used.\textsuperscript{[1]} The transdermal Patches abolish the need for vascular access by syringe or the use of pumps by application to the skin. In 1970s the Transdermal patches were developed and in 1979 the Food and Drug Administration (FDA) was approved first transdermal patches was approved for the treatment of motion sickness. It was a three-day patch that contain scopolamine drug. In 1981, another transdermal patch were approved which contain nitroglycerin, and today there are a number of patches exist that contain drugs such as testosterone clonidine, lidocaine, nicotine, nitroglycerin, oxybutynin, scopolamine, and used for several disease.\textsuperscript{[2]}

For many decades, acute disease or a chronic illness treatment has been accomplished via used of several pharmaceutical dosage forms like tablets, capsules, ointments, liquid aerosols, pills, creams, and suppositories. These dosages form are used as carrier for drug delivery to the site of action. Recently, their several advance techniques have been developed for drug delivery. These innovative methods are adequate of regulate the drug delivery rate, maintain therapeutic action for longer periods of time, and/or targeting drug delivery of drug to specific tissues.\textsuperscript{[3]} Transdermal permeation or percutaneous absorption can be explain as passage of drug substance from skin outside through its several layers in to bloodstream In the transdermal drug delivery system development, some of interrelated essence must be taken in to consideration. These elements are classified in to some areas like drug bioactivity, skin characteristics formulation, adhesion and system design.\textsuperscript{[4]}

Transdermal drug delivery has many advantages like as avert to first pass metabolism, avoid environment of gastric, patient compliance, easy to remove in case of emergent situation. This mini review covers the vital characteristics of skin pertaining to the transdermal drug delivery, and pathways for absorption through skin. Most importantly, will enlighten the readers on the various methods of skin permeation enhancement available and focus more in details for transdermal drug delivery formulation strategies.\textsuperscript{[5]}

**Ideal Characteristics of TDDS**

1. The pH of the solution should be between.\textsuperscript{[5-9]}
2. To attain good therapeutic activity of the drug there is a require for an optimum partition coefficient.
3. The drug melting point should be below (less than 200oC)
4. The Patches size should be less than 40 cm2.
5. There should be shelf life up to 2 yrs.[6]

**Advantages**

1. It can avoid difficulties of drug absorption in gastrointestinal and it covered by gastrointestinal pH, enzymatic activity and drug-food interaction, and other orally administration drug.
2. When the oral route is unsuitable as with vomiting and diarrhea. It can substitute for oral administration of drug.
3. To avoid the first pass effect e.g. transdermal patch containing Nitroglycerin. It is rapidly metabolized by the liner when orally taken.
4. Noninvasive and it can avoid the inconvenience of parenteral therapy.
5. with a single application It give extended therapy, and improving compliance over other dosage forms which are requiring more frequent administration of dose e.g. Transdermal clonidine 7 day.
6. The drugs having a short half-life is increased through the drug reservoir in the therapeutic delivery system.[7]

**Disadvantage**

1. At the site of application many patients develop contact dermatitis from one or more of the system components.
2. Due to natural limits of drug penetration imposed by the skin's impermeability, only potent drugs are suitable for the transdermal patch.
3. Some drugs e.g. scopolamine transdermal patch placed at the back of the ear, it is uncomfortable.
4. The major disadvantage of this system Long-time adherence of patch is difficult.[8]

**First-generation transdermal delivery systems**

The majority of transdermal patches currently in clinical use are from the first generation of transdermal delivery methods. The current spike in first-generation transdermal patches hitting the market is due to significant advancements in patch technology and popular acceptance. However, this surge will taper off as drugs with ideal properties for this system are enfeable. First-generation transdermal delivery candidates must be lipophilic, low molecular weight, and efficacious at low doses. Because of limited oral bioavailability, the desire or requirement for less consistent delivery profiles or less frequent dosing, or other criteria, transdermal delivery should be more appealing than oral delivery. The first-
generation approach to transdermal delivery is limited primarily by the barrier posed by the skin’s outermost layer the stratum corneum, which is 10 to 20 μm thick, the viable epidermis, which measures 50 to 100 m and is avascular, lies underneath this layer. The dermis, which is 1–2 mm thick and features a dense capillary bed for systemic medication absorption right below the dermal-epidermal junction, is the deepest layer.\[8\]

Second-Generation transdermal delivery systems
Skin permeability augmentation is required to broaden the scope of transdermal medications, according to the second generation of transdermal delivery systems. The ideal enhancer should (i) increase skin permeability by reversibly disrupting stratum corneum structure, (ii) provide an added driving force for transport into the skin (iii) avoid injury to deeper, living tissues. However, enhancement methods discovered in this generation, such as traditional chemical enhancers, Iontophoresis, and non-cavitational ultrasound, have struggled to strike a compromise between increasing distribution over the stratum corneum while avoiding injury to deeper tissues. As a result, this second generation of delivery technologies has mostly improved small molecule distribution for localized, aesthetic, dermatological, and certain systemic applications, while having a limited impact on macromolecule delivery.\[9\]

Anatomy and Physiology of skin
Human skin comprises of three distinct but mutually dependent tissues: The stratified, vascular, cellular called as “epidermis” Underlying dermis of connective tissues, Hypodermis.

1. Epidermis
The multilayered epidermis varies in thickness, depending on the number of cell layers of the epidermis, and cell size, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. The stratum corneum is the outermost layer of skin also called a horny layer. When dry, it is around 10 mm thick, but when fully hydrated, it swells to several times that thickness. Corneocytes are dead, keratinized cells that are arranged in 10 to 25 layers. It is flexible but relatively impermeable. The stratum corneum is the principal barrier to drug penetration. The architecture of the horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar.” The lipids are arranged in multiple bilayers. There is sufficient amphiphilic material in the lipid fraction, such as cholesterol and polar free fatty acids, to maintain a bilayer form. The viable epidermis is situated below the stratum corneum and varies in thickness from 0.06 mm on
the eyelids to 0.8 mm on the palms. Going interior, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basal. In the basal layer, mitosis of the cells constantly renew the epidermis and this proliferation compensates for the loss of dead honey cells from the skin surface. As the cells produced by the basal layer move outside, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of the stratum corneum.\textsuperscript{[10]}

2. **Dermis**

The Dermis is a 3 to 5 mm thick layer. It is composed of a matrix of connective tissue, which contains lymph vessels, blood vessels, and nerves. The cutaneous blood supply plays a critical role in body temperature regulation. It also provides nutrients and oxygen to the skin while removing waste products and toxins. 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 a permeate very low and the resulting concentration difference across the epidermis provides an essential concentration gradient for transdermal permeation.

3. **Hypodermis**

The subcutaneous or hypodermis fat tissue supports the dermis and epidermis. It performs as a fat storage area. This layer helps to regulate temperature, provides nutritional support, and mechanically protection. It may contain sensory pressure organs and carries major blood vessels and nerves to the skin. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in the case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.\textsuperscript{[11]}

The structure of the skin was shown in Figure 1.

![Figure 1: Structure of human skin.](image)

**Basic components of transdermal drug delivery systems**
1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Backing Laminate
5. Release Liner
6. Other excipients

1. Polymer matrix
   The Polymer controls the drug release from the device. Possible useful polymers for transdermal devices are:
   a. Natural Polymers e.g., cellulose derivatives, Shellac, Waxes, Zein, Gelatin, Proteins, Gums and their derivatives, Natural rubber, Starch, etc.
   b. Synthetic Elastomers e.g., polybutadiene, Polysiloxane, Hydrin rubber, Silicone rubber, Butyl rubber, Styrenebutadiene rubber, Nitrile, Acrylonitrile, Neoprene, etc.
   c. Synthetic Polymers e.g., polyvinyl alcohol, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polyvinylchloride, Polyethylene Polymethylmethacrylate, etc.

2. Drug
   Drug for successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

   Physicochemical properties
   a. 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.
   b. The drug should have a low melting point.
   c. The drug should have a molecular weight of less than approximately 1000 Daltons. Along with these properties, the drug should be potent, having a short half-life, and be non-irritating.[12]

3. Permeation enhancers
   Permeation enhancers are the chemical compounds that increase the permeability of the stratum corneum to attain higher therapeutic levels of the drug candidate. Penetration
enhancers interact with structural components of the stratum corneum i.e. lipids or proteins. They change the stratum corneum’s lipid and protein packing, chemically altering the barrier functions and increasing permeability. Over the last 20 years, a tremendous amount of work has been directed towards the search for specific chemicals, a combination of chemicals, which can act as penetration enhancers. Some of the permeation enhancers are Esters and Fatty acid, Ethanol, Pyrrolidones, Dimethyl sulfoxide, etc.

4. **Backin laminate**

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should be considered because the prolonged contact between and the excipients and backing layer may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drugs, or penetration enhancers through the layer. An overemphasis on chemical resistance, on the other hand, may result in stiffness and excessive occlusivity to moisture vapor and air, causing patches to lift and potentially irritate the skin over time. The most comfortable backing will be the one that exhibits the lowest modulus or high flexibility, good oxygen transmission, and a high moisture vapor transmission rate. Examples of some backing materials are polyethylene, vinyl, and polyester films.

5. **Release liner**

During storage, the patch is covered by a protective liner that is discharged and removed 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. However, as the liner is in intimate contact with the delivery system, it should meet certain standards regarding permeability to the medication and chemical inertness, penetration booster, and water. Typically, the release liner is composed of a base layer that may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of Teflon or silicon. Other materials used for TDDS release liner include and metalized laminates polyester foil.

6. **Other excipients**

Various solvents such as acetone, chloroform, methanol, isopropanol, and dichloromethane are used to prepare drug reservoirs. In addition plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added to provide plasticity to the transdermal patch.\[13\]
TDDS classification based on their technical sophistication

A. Rate pre-programmed drug delivery system
B. Activation modulated drug delivery system
C. Feedback regulated drug delivery system
D. Carrier-based drug delivery system

A. Rate pre-programmed drug delivery system
It involves the system design that delivers medicaments by controlling the molecular diffusion of drug molecules across the skin barrier within or surrounding the delivery system.

1. Polymer membrane permeation controlled drug delivery system
The drug is enclosed within a drug reservoir. This is covered by the semi-permeable membrane of polymer which regulates the release and having a specific permeability. There is some potential development with the process of membrane permeation are as microporous membrane permeation controlled gastrointestinal delivery device, gastric fluid resistance intestinal targeted controlled release gastrointestinal device, and gel diffusion controlled drug delivery system.

2. Polymer matrix diffusion controlled drug delivery system
It is developed by fling drug particles in a carrier matrix (in a homogenous manner) that is rate-controlling i.e. Nitro-Dur. It is designed for application onto intact skin for 24 h that provide the consistent transdermal infusion of nitroglycerine.

3. Micro reservoir partitioned controlled drug delivery system
It involves dispersion of micro particles of suspension of a drug (aqueous) in a polymer using high energy dispersion. e.g. Syncromate implant.

B. Activation modulated drug delivery system
This type of delivery system can be achieved by-

1. Physical means
   a. Osmotic pressure-activated drug delivery system.
   b. Hydrodynamic pressure controlled drug delivery system.
   c. Vapor pressure-activated drug delivery system.
   d. Mechanically activated drug delivery system.
   e. Magnetically activated drug delivery system.
   f. Electrically activated drug delivery system.
g. Ultrasound-activated drug delivery system.

h. Hydration activated drug delivery system.

2. Chemical means

a. pH activated drug delivery system
b. Ion activated drug delivery system
c. Hydrolysis activated drug delivery system

C. Feedback regulated drug delivery system

The release of the drug molecules from the transdermal system is facilitated by an agent that triggers the release of the drug, such as biochemicals in the body, and also regulated by its concentration through some feedback mechanism.

b. Bio-responsive drug delivery system.
c. self-regulated drug delivery system.

D. Carrier-Based drug delivery system

Colloidal particulates carrier system: This involves vesicular systems like hydrogels, nanoparticles, polymeric complexes, microspheres, nano erythrosomes, transferosomes, dendrimers, aquasomes, etc.\cite{14,15}

Types of transdermal patches


In a single layer, the drug-in-adhesive system drug is dispersed in the adhesive layer of the patch. The adhesive layer is responsible for both adhering the multiple layers together and releasing the medicine in this sort of patch. The adhesive layer is surrounded by a temporary liner and a backing layer.

2. Multi-layer Drug-in-Adhesive

In a multi-layer drug-in-adhesive system drug is dispersed in the adhesive layers of the patch.
same as in a single-layer drug in adhesive. But the only difference is that it contains multiple layers of the drug in adhesive separated by a membrane. This patch also has a temporary liner–layer and a permanent backing layer.

3. Drug Reservoir-in-Adhesive
Reservoir transdermal system has a separate drug layer enclosed in a rate-controlling nonporous or microporous membrane and an impermeable backing laminate. The drug layer is a liquid compartment containing a drug suspension or solution separated by the backing layer. The release rate of the drug is determined by the abrasion rate, diffusion, permeability, and thickness of the membrane. In this type of system, the rate of release is zero order.

4. Drug Matrix-in-Adhesive
In the drug matrix-in-adhesive approach, the drug reservoir is prepared by homogenously dispersing drug particles in a lipophilic or hydrophilic polymer matrix. The adhesive layer in this patch surrounds the drug layer partially overlapping it. It also has an occlusive base plate, absorbent pad, and backing laminate on the back.[16]
Various methods for preparation of TDDS

1. **Asymmetric TPX membrane method**

A prototype patch can be fabricated for this a heat-sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. A drug sample is dispensed into the concave membrane, which is then covered by a TPX asymmetric membrane and sealed with an adhesive. [(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a predetermined thickness with a Gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in a coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].\(^{[17]}\)

2. **Circular teflon mold method**

Solutions containing polymers in various ratios are used in an organic solvent. A calculated amount of drug is dissolved in half the quantity of the same organic solvent. Enhancers are dissolved in the other half of the organic solvent and then added in various concentrations. Di-N-butyl phthalate is added as a plasticizer into a drug-polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mold. The molds are to be placed on a leveled surface and covered with an inverted funnel to control solvent vaporization in a laminar flow hood model with an airspeed of 0.5 m/s. For 24 hours, the solvent is allowed to evaporate. To eliminate aging effects, the dried films must be held for another 24 hours at 250.5°C in a desiccator containing silica gel before being evaluated. The type of films is to be evaluated within one week of their preparation.

3. **Mercury substrate method**

In this method drug is dissolved in a polymer solution along with a plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured into a leveled mercury surface, covered with an inverted funnel to control solvent evaporation.

4. **By using the "IPM membranes" method**

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in a magnetic stirrer. Buffer pH 7.4 can be used
to obtain solution gel if the drug solubility in an aqueous solution is very poor. The formed gel will be incorporated into the IPM membrane.

5. **By using the "EVAC membranes" method**

To prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene-vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. The drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The medicine (in gel form) is applied to a backing layer sheet that covers the desired area. A rate-controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak-proof device.[18]

6. **Aluminum-backed adhesive film method**

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminum backed adhesive film method is a suitable one. For the preparation of the same, chloroform is the choice of solvent, because most of the drugs, as well as adhesive, are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom-made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks.

7. **Preparation of TDDS by using Proliposomes**

The pro liposomes are prepared by carrier method using film deposition technique. The prior reference medication and lecithin in the ratio of 0.1:2.0 can be utilized as an optimized one. The pro liposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at a 60-70°C temperature and the flask is rotated at 80-90 rpm and dried mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round-bottomed flask at 37°C after complete drying. It's time to add the second aliquots (0.5ml) of the solution. After the final loading, the flask holding pro liposomes is linked in a lyophilizer, and the drug-loaded mannitol powders (pro liposomes) are desiccated overnight and sieved through 100 mesh. The gathered powder is placed in a glass bottle and kept frozen until it is time to characterize it.
8. **By using the free film method**
A free film of cellulose acetate is prepared by casting on a mercury surface. A polymer solution of 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of the polymer weight. Five ml of the polymer solution was poured into a glass ring which is placed over the mercury surface in a glass petri dish. By placing an inverted funnel above the petri dish, the rate of solvent evaporation can be adjusted. After the solvent has completely evaporated, observe the mercury surface for the formation of a film. The dry film will be separated and stored between the sheets of wax paper in a desiccator until use. Free films of different thicknesses can be prepared by changing the volume of the polymer solution.[19]

**Properties that influence transdermal drug delivery**

Three components, namely the drug, the skin, and the vehicles, can be used to develop effective transdermal medication administration. So the factors affecting can be divided into two classes as biological factors and physicochemical factors.

**A. Biological factors**

1. **Skin condition**

   Acids and alkalis, many solvents like methanol, chloroform damage the skin cells and promote penetration. The diseased state of the patient shifts the skin conditions. Although undamaged skin is a better barrier, the factors stated above have an impact on penetration.

2. **Skin age**

   Young skin is more permeable than older. Children are more sensitive to skin absorption of toxins. Thus, skin age is one of the factors affecting the penetration of drugs in the transdermal drug delivery system.

3. **Blood supply**

   Some changes in peripheral circulation can affect transdermal absorption.

4. **Regional skin site**

   Nature of stratum corneum, Thickness of skin, and density of appendages vary site to site.

   These factors affect significantly penetration.
5. Skin metabolism
Skin metabolizes hormones, steroids, chemical carcinogens, and some drugs. So skin metabolism determines the efficacy of drugs permeated through the skin.

6. Species differences
The skin thickness, density of appendages, and keratinization of skin vary from species to species, so affects the penetration.

B. Physicochemical factors
1. Skin hydration
In contact with water the permeability of skin increases significantly. Hydration is the most important factor in increasing the permeation of skin. So the use of humectant is done in transdermal delivery.

2. Temperature and Ph
The permeation of the drug increases ten folds with temperature variation. The diffusion coefficient decreases as the temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa values. The proportion of unionized drugs determines the drug concentration in the skin. Thus, pH and temperature are important factors affecting drug penetration.

3. Diffusion coefficient
Penetration of drug depends on the diffusion coefficient of the drug. At a constant temperature, the diffusion coefficient of the drug depends on the properties of the drug, diffusion medium, and interaction between them.

4. Molecular Size and Shape
Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.\(^{20}\)

5. Partition co-efficient
Drugs possessing both water and lipid solubility are favorably absorbed through the skin. The permeability coefficient of the skin has a linear relationship with the partition co-efficient. Varying the vehicle may also alter a lipid/water partition coefficient of a drug molecule. The partition coefficient of a drug molecule may be altered by chemical modification without affecting the pharmacological activity of the drug.
6. Drug concentration

Transdermal permeability across mammalian skin is a passive diffusion process and this depends on the concentration of penetrant molecules on the surface layer of the skin.[21]

Approaches for permeation enhancement:

There are mainly three approaches for penetration enhancement.

1. Chemical approach
2. Biochemical approach
3. Physical approach

1. Chemical approach

Mechanism: Penetration enhancers follow three main routes, they are:

1. Causing disruptions in the highly organized structure of the stratum corneum.
2. Interaction with proteins presents intercellularly.
3. Improved drug partitioning the stratum corneum with help of co-enhancer (i.e. solvent)
4. Permeation enhancers have been developed and utilized for decades to help mankind, one of the more extensively used ones are shown below:

1. Alcohols can increase skin permeation by various mechanisms such as lipids and protein extraction, stratum corneum swelling, and thus improving partitioning of drug into host skin or drug solubility in the formulation. Propylene glycol promotes flux of heparin sodium hydrochloride and verapamil hydrochloride and also ketoprofen. At high concentrations, propylene glycol stops the flux of ketoprofen. When propylene glycol is coupled with azone, the flow of cyclosporine A and methotrexate is increased. SC keratin is solvated by PG, which fills the sites with hydrogen bonds. When PG is combined with an azone, large amounts of glycolate the tissue to increase intracellular drug diffusion. The drug flux is directly proportional to the length of the carbon chain (up to six carbon atoms) in n-alcohols. These alcohols improve absorption by promoting the extraction of lipids from SC. The flow of 5-FU was increased by making a saturated terpene solution in a PG-water co-solvent system (fluorouracil). The activity of terpenes was related to PG content and the maximum flux was obtained from drugs with 80% PG content. Also, PG increases the partitioning of the drug. PG in conjunction with 5% oleic acid showed an increase in the flux by 10 times.[22]

2. 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 nontoxic and biodegradable compounds that contain 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.

3. Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g., mannitol and 5-fluorouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2-pyrrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch.

4. 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. Many penetration enhancers, such as azone, have saturated or unsaturated hydrocarbon chains, and some structure-activity relationships have been drawn from Aungst's extensive studies, which used a variety of fatty acids, acids, surfactants, alcohol sulfoxides, and amides as naloxone enhancers. studied various penetration enhancers like glycols (diethylene glycol and tetramethylene glycol), fatty acids (lauric acid, myristic acid, and capric acid), an anionic surfactant (polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearyl ether) on the release of triprolidine.\(^\text{[23]}\)

2. Physical approach
   1. Iontophoresis passes a few mill amperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Electrorepulsion and electroosmosis are the two main mechanisms by which iontophoresis improves drug delivery across the skin. The permanent effect of an applied electric field on a charge is known as electron repulsion. The second process, electroosmosis, is based on the fact that at physiological pH, the skin supports a net negative charge. Iontophoresis is a non-invasive method used to boost the high concentration of a charged substance, generally, medication or bioactive agents, transdermally by repulsive electromotive force using a small electrical current applied to an Iontophoresis chamber containing a similarly charged active agent and its vehicle. These movements are measured in units of chemical flux, commonly \(\mu\text{mol/cm}^2\text{h}\). This technique is based on the general principle that like charges repel each other. Thus, during Iontophoresis, if delivery of a positively charged drug (D+) is desired, the charged
drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode in this example. Pilocarpine is primarily used to promote perspiration as part of a cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.[24]

2. Ultrasound is also termed or sonophoresis or phonophoresis. In this enhancement technique, permeation is increased via ultrasonic waves which means the frequency is 420 kHz. Its Mechanism involves either of the two ways: First, application of sound waves to the skin increases the fluidity of lipids and increases permeation via a transcellular pathway, or second, formation of bubbles which generates pores which even allows large molecular weight drugs such as protein or vaccines. Trainers prefer this method to permeate dexamethasone, lidocaine, or ketoprofen in patients. But this technique has some limitations, i.e. formation of attenuation which is because sound waves transform to heat energy.

3. Stratum corneum removed Microdermabrasion is introduced as a method to increase skin permeability by removing the stratum corneum. The depth of slash depends on the patient’s requirement. This technique is a boon to large molecular weight drugs like peptides, vaccines, and insulin. In this method, complete removal of the epidermis is not employed. Skountzou et al. observed transcutaneous immunization using topical delivery of influenza vaccine. The outer skin barrier can be overcome through the use of mild chemical and/or physical treatments, including ethanol-water hydration and stripping, which allows large vaccine molecules or even particulate antigens to gain access to the skin’s immune cells.

4. Thermal Energy application of ultrasound on skin leads to an increase in temperature. Thus there is an increase in skin permeability which leads to the drug entering the systemic circulation. This approach has been mimicked by Zars, They developed a mini heating unit CHADD, which gives heat for a certain time at a certain intensity. The full form of CHADD is a Controlled Heat-aided Drug Delivery system. Oxidation reaction occurs within the heating unit.[25]

**Evaluation of transdermal patches**

The transdermal patches can be characterized in terms of the following parameters.

1. Physicochemical evaluation
2. In vivo evaluation
A. Physicochemical evaluation
Transdermal patches can be physicochemically evaluated in terms of these parameters:

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

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

3. Folding endurance
Assessment of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it shatters. The number of times the films could be folded at the same place without breaking is folding endurance value.

4. Tensile strength
To evaluate tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the film is kept fixed with the help of an iron screen and another end is attached to a freely movable thread over a pulley. The weights are added gradually to the pan attached to the hanging end of the thread. A pointer on the thread is used to measure the distension of the film. The weight just sufficient to break the film is noted.[26]

5. Percentage of moisture content
The films should be weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a stagnant weight. The percentage of moisture content was calculated as the difference between initial and final weight.[27]

\[
\text{% Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

6. Content uniformity test
10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of
content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have ranged from 85% to 115%, then the transdermal patches pass the test.

7. **Drug content**

A specified area of the patch is to be dissolved in a suitable solvent in a specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Each value represents an average of three different samples.

8. **Shear adhesion test**

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross-linking, and the composition of polymer, type, and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a the specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time taken for removal, the greater is the shear strength.\cite{Shear}

B. **In vivo evaluation**

In vivo evaluation is the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using animal models and human volunteers.

1. **Animal models**

Considerable time and resources are required to carry out human studies, so animal studies are preferred at 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 lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.\cite{Rhesus}
2. Human volunteers
The final stage in the development of the transdermal device involves the collection of pharmacokinetic and pharmacodynamic data following the application of the device to human volunteers. An in vivo evaluation using human subjects should give pertinent information with minimum risk to the subjects within a reasonable period. In vivo evaluation using human models involve the determination of percutaneous absorption by an indirect method of measuring radioactivity in excreta following topical application of the labeled drug. C14 is generally used for radio-labeling Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the body, or excreted by routes not monitored. This necessitates the measurement of dose absorbed. However this method has certain limitations, to overcome the limitations inherent in this method, various refinements have been made.[30]

Advance development in TDDS
Adhesive drug delivery has become the most popular method for passive transdermal distribution; adhesives and excipients are two areas of formulation study. Adhesive research focuses on modifying the adhesive to improve skin adhesion over time, improve medication stability and solubility, decrease lag time, and boost delivery rate. Because there is no one-size-fits-all adhesive that can accommodate all medication and formulation chemistries, the transdermal formulator can maximize the transdermal patch's efficacy by personalizing the adhesive chemistry. The development of transdermal technologies that use mechanical energy to improve drug flow over the skin by either modifying the skin barrier (mainly the stratum corneum) or increasing the energy of the drug molecules has been a rich field of research over the last 10 to 15 years. These so-called “active” transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low-frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetophoresis or the use of magnetic energy to boost medication flux over the skin has been studied.[31]

Applications of transdermal patches
1. The nicotine patch, which distributes nicotine in controlled dosages to aid in the cessation of tobacco smoking, is the most popular transdermal patch in the United States.
2. Fentanyl (marketed as Duragesic) and Buprenorphine, two opioid drugs used to offer 24-hour pain relief, are frequently administered as patches (marketed as BuTrans).

3. Estrogen patches are sometimes used to treat menopausal symptoms and osteoporosis after menopause. The contraceptive patch is another type of transdermal patch for hormone delivery (marketed as Ortho Evra or Evra). Nitroglycerin patches are sometimes prescribed for the treatment of angina instead of sublingual pills.

4. The anti-hypertensive drug Clonidine is available in transdermal patch form.

5. The transdermal form of the MAOI selegiline became the first transdermal delivery agent for an antidepressant.

6. Transdermal delivery agent for Attention Deficit Hyperactivity Disorder (ADHD).[32]

CONCLUSION
Transdermal drug delivery is hardly an old technology, and this technology no longer is just adhesive patches. Transdermal medication administration is becoming the most frequently accepted route of drug administration because of recent technological improvements and the integration of the medication to the site of action without rupturing the epidermal membrane. It promises to eliminate needles for the administration of a wide variety of drugs in the future.

REFERENCE


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