

TRANSDERMAL DRUG DELIVERY PATCHES: AN OVERVIEW**Onkar Raje*¹, Prof. Prashant Khade² and Dr. Ashok Bhosale³**^{1,2,3}Department of Pharmaceutics, Shankarrao Ursal College of Pharmacy, Kharadi, Pune, Maharashtra, India.Article Received on
18 Dec. 2020,Revised on 08 Jan. 2021,
Accepted on 29 Jan. 2021DOI: <https://doi.org/10.17605/OSF.IO/9QXP5>***Corresponding Author****Onkar Raje**Department of
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India.**ABSTRACT**

Transdermal drug delivery (TDD) is a non-invasive route of drug administration, but its application is limited by the low permeability of the skin. It's an attractive alternative technique to the conventional techniques for the administration of systemic approaches. The major site of application is skin for both local and systemic effects. However, the main barrier is the stratum corneum to penetrate the drug through the skin membrane. As a result, completely different approaches to penetration enhancement are used to avoid stratum corneum and to expand the flow through the skin membrane. The new active rates of controlled transdermal drug delivery system (TDDS) technology have been identified, developed, and marketed for the TDD. This review

presents, the structure of the skin, the pathways of penetration through the skin, completely different approaches to enhance penetration, transdermal patches to optimize the transdermal delivery system into a good drug delivery system.

KEYWORDS: Transdermal patches, Penetration enhancers, Transdermal Drug Delivery System (TDDS).

INTRODUCTION^[1]

Currently, transdermic drug delivery is one of the foremost promising methods for drug application. Increasing the number of medications is being added to the list of therapeutic agents that will deliver to the circulation via the skin. The transdermal route offers significant benefits over conventional dosage forms such as tablets and injections, including preventing the first-pass metabolism by the liver. In transdermal drug delivery system contain drug at the defined surface area which delivers a specific amount of drug to the surface of skin at a predefined rate. This technique overcomes the disadvantages associated with oral products.

Therefore, the aim of this article is to explain the structure, routes, criteria of selection, approaches, etc.

Advantages of patches over other dosage forms^[2-4]

- Eliminate the first-pass metabolism
- Give steady delivery/ blood vessels
- Increase compliance/ convenience
- Reduce systemic drug interaction
- Will minimize abuse/ diversion
- Allow dose discontinuance via removal
- Provides product life cycle extension opportunities at a lower cost with lower risks.
- Improved bioavailability
- Longer period of action
- More uniform plasma levels

Limitations of TDDS^[5]

- Chances of local irritation at the site of application
- Erythema, itching, and local swelling is caused by the drug, the adhesive, or other additives in the patch formulation.

Structure of skin barrier^[6-8]

Skin is the largest human organ of our body composed of many layers: the stratum corneum (uppermost layer), the viable epidermis, the dermis, and also the lower layers of adipose tissue (fig.1). The stratum corneum consists of flat, roughly hexagonally shaped, partially overlapping cells, with a thickness of 0.3 μm and a diameter of 30 μm . Slightly below the stratum corneum is the viable epidermis, which made of three layers: the stratum granulosum, spinosum, and basal. It has a cell thickness of between 50-100 μm . Beneath the viable epidermis dermis is present. Dermis thickness is concerning 2000-3000 μm and consists of a matrix of loose connective tissue composed of fibrous protein enclosed in associate amorphous ground substance. For the past few years, the transdermal route has been selected for the delivery of certain drugs. However, its use is limited due to the low permeability of the skin to many drugs.

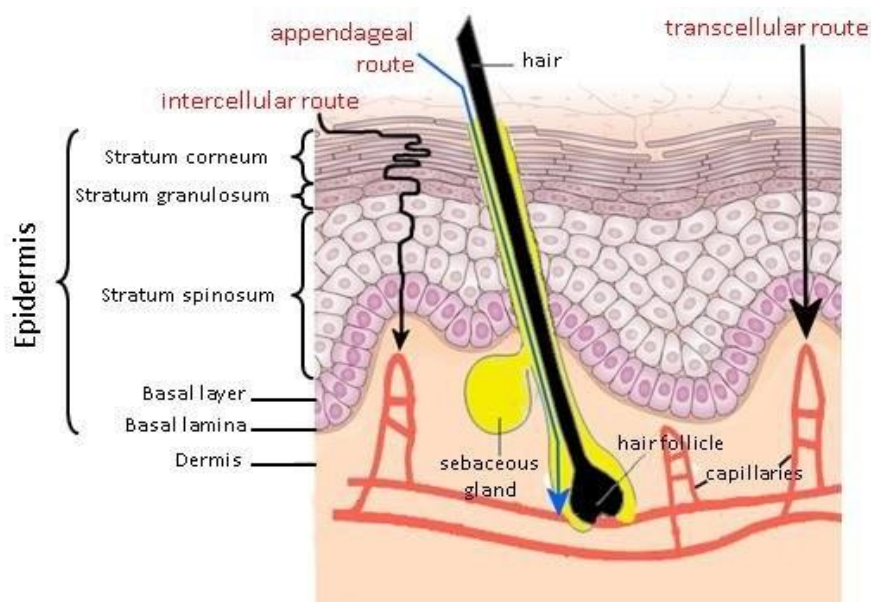


Fig. 1: Anatomical and physiological structure of the skin.

Routes of Penetration^[9-11]

A transdermal drug delivery system could be the most suitable system for long-term treatment or for a multi-dose treatment because different transdermal patches are prepared for an extended period during a suitable dose providing treatment from daily to even up for seven days. To permeate a molecule in the normal human intact skin there are two diffusion pathways: the appendageal and the transepidermal pathway. The appendageal route is for ions and large polar molecules, and also the transepidermal route is for the unionized molecules which may cross the intact layer. A molecule should have sufficient lipophilicity and optimum molecular weight to penetrate the intact skin. Hydrophilic drugs partitioned via intracellular domains, whereas lipophilic permeants (octanol/water $\log K > 2$) partitioned the subcutaneous (SC) through the intercellular route. Most of the molecules travel to the stratum corneum by both routes. The transport of various drug molecules through the skin, directly restricted by the barrier properties of the epidermis. To avert these difficulties in permeation through SC, carrier vesicles will be used as penetration enhancers for avoiding the SC barrier.

Laws for Development of the Transdermal Drug System^[12]

Based on a profile that is "S-curve" follows the basic law of establishing and developing (the plot of the major index of the system performance versus time). All methods are transdermal with four parts that are necessary, a subsystem that transmits system energy to those positions where it is needed for overall performance, a control system that regulates and controls system performance, parts that actually perform the main function of the system, and also an

energy source. These four crucial parts are very essential to complete a TDDS system to function at a rate that is high. Many important factors associated with the development this is certainly more of drug delivery systems will likely to be advancements in exactly how effectively energy is transmitted throughout the systems. The relationship between transdermal drug delivery systems along with other present and new systems are defined by various laws. The Next-generation transdermal drug delivery systems will show an improved degree of coordination among several parts of the system, and intentional dis-coordination among other parts of the system. The purpose of this dis-coordination or coordination by-design is always to achieve significant breakthroughs in system overall performance.

Transdermal Patches^[13-18]

A transdermal patch is also identified by the name of skin patch that is used to deliver the specific amount of dose through skin and it directly goes into the bloodstream (Fig. 2). The transdermal drug delivery route an advantage on different types like oral, intravenous, topical, etc provides a controlled release of the drug into the patient. a wide variety of medicaments are delivered by transdermal patches. a new crystal reservoir technology has come out with success with the advancement in TDDS which manufacture comparable smaller patches with a more controlled and sustained release. The success of a transdermal patch depends on a variety of biological physiological, biochemical, and biophysical factors as well as the following:

- Direct application on the body
- Composition, integrity & thickness of the corneum
- Structure & size of the molecule that is an indicator of diffusivity
- Porosity of the membrane within the transdermal drug delivery system
- State of skin hydration pH scale and different physiochemical drug properties
- Drug metabolism/first-pass metabolism
- lipid solubility/lipophilicity
- Degree of the partitioning of drug and associated components
- Depot of the drug in skin
- Alteration of drug flow within the skin by additives and body temperature
- Interactions between molecules and molecules

Components of a Transdermal Patch^[19-20]

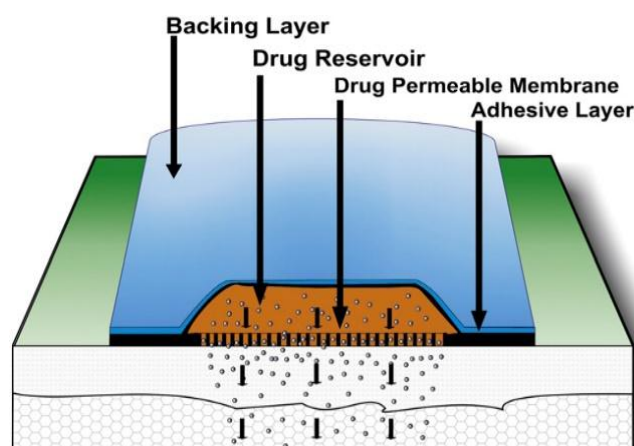


Fig. 2: Transdermal patch.

The transdermal patch consists of the following components:

- **Liner** - It protect the patch when we stored it for a long period of time. Before use the transdermal patch liner is removed Ex: Polyester film.
- **Drug**-Drug solution is in direct contact with the release liner Ex: nicotine and estrogen.
- **Adhesive** – It is a material that helps adhere to the components of the patch and also the patch to the skin Ex: Acrylates, polyisobutylene, silicones.
- **Membrane** - control the release of drugs from the reservoir and multilayer patches.
- **Backing** -It is a process by which we will save the patch from the outer environment. Ex: cellulose derivatives, polyvinyl alcohol, polypropylene silicon rubber.
- **Permeation enhancers** - The controlled amount of drug is released by the use of permeation enhancers Ex: alcohol, ethanol, terpenes, pyrrolidone, surfactants like sodium lauryl sulphate, Pluronic f127 etc.

Types of Transdermal Patches^[21-29]

Single-layer Drug-in-adhesive

In this type, the adhesive layer consists of the drug and it not only serves to adhere the various layers collectively however with the whole system to the skin but is additionally responsible for the releasing of the drug. On the outer side of the adhesive layer, there is a lining of the temporary liner and a backing layer (Fig.3d).

Multi-layer Drug-in-Adhesive

It is comparable to the single layer system in respect that each adhesive layer also responsible for the release of the drug. The multilayer system is different it provides another layer of

drug-in-adhesive, normally separated through a membrane (but not in all cases). This patch also surrounded via a temporary liner-layer and a permanent backing (Fig. 3c).

Reservoir System

In a reservoir system, the drug reservoir is enclosed between an impenetrable backing layer and a rate-controlling membrane. The rate-controlling membrane is microporous or nonporous which can release the drug. Within the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel. The hypoallergenic adhesive polymer can be utilized as an outer surface polymeric membrane that is compatible with the drug. This patch is backed via the backing layer (fig. 3b). Zero-order kinetics is followed through this system.

Micro reservoir system

The drug delivery system is a combination of a reservoir and a matrix system in this type. The drug reservoir is produced by the drug is suspending in an aqueous solution of water-soluble polymer and at that point dispersing the solution homogeneously in a lipophilic polymer to produce lots of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized rapidly by promptly cross-linking the polymer situated by utilizing cross-linking agents.

Vapour Patch

In this type of patch, the adhesive layer serves to follow the different layers together yet in addition to discharge vapour. The vapour patches are new for the market and release essentials oils for up to 6 h. Essential oils are discharged from this patch and they are used only in cases of decongestion mainly. Controller vapour patches are available within the market that improves the quality of sleep. Vapour patches that diminish the number of cigarettes that one smoke in a month are also available in the market.



Fig.3a

Fig.3b

Fig.3c

Fig.3d

Fig.3: Types of transdermal patches.

Matrix system

- **Drug in adhesive system**

In this system, drug is dispersed in adhesive polymer to form a drug reservoir, after which the prepared adhesive by solvent casting or melting (as in form of hot melt adhesive) is applied on an Impervious backing layer. Adhesive polymer layers are mounted at the top of the reservoir for protection purposes (fig. 3a).

- **Matrix dispersion system**

The drug is distributed homogenously within the hydrophilic or lipophilic polymer matrix in that type. This polymer disk-containing drug reservoir is then placed on an occlusive base plate in a drug impermeable layer compartment. The adhesive polymer is applied across the circumference of the patch to produce a strip of the adhesive rim around the medicated patch.

Different techniques for preparation of TDDS

Asymmetric TPX membrane method^[30]

The prototype patch is made with a polyester film (type 1009, 3m) that is heat-sealable using a concave 1cm diameter used as a back membrane. Sample of the drug is administered to the concave membrane sheet, which is covered by the TPX {poly(4-methyl-1-pentene)} membrane layer and sealed by the adhesive layer.

Asymmetric TPX membrane layer preparation^[30]

They are fabricated through the use of the inversion process that is dry/wet. TPX is dissolved in a mixture of solvent (cyclohexane) and ingredients that are non-solvent additives at 60 °C to create a polymer solution. The solution of polymer is a store at 40 °C for 24 h and cast on a glass plate to a thickness that is pre-determine with a gardener knife. After that, the casting film is evaporated at 50 °C for 30 sec, and afterward, the glass plate is quickly be immersed in a coagulation bath at a temperature of 25 °C. The membrane layer is removed, air-dry in a circulation oven at 50 °C for 12 h after 10 minutes of immersion.

Circular teflon mould method^[31]

The solution containing polymers in various proportions can be used within an organic solvent. The calculated quantity of drug is dissolved in half the amount of the same organic solvent. Enhancers in different concentrations are to be dissolved into the other half of the organic solvent afterward added. Di-N-butyl-phthalate is added as being a plasticizer into drug-polymer solution. the whole material can be stirred for 12 h and after poured into a

circular teflon mould. The moulds is placed on a surface that is levelled covered with an inverted funnel to control solvent vaporization in a laminar flow, hood model with the speed of air 1/2 m/sec. The solvent is kept to evaporate for 24 h. Before evaluation, the dried films should be kept for the next 24 h at 25 ± 0.5 °C in a desiccator's silica gel is containing before to eliminate aging effects. These types of films can be evaluated within certainly one week of their preparation.

Mercury substrate method^[32]

In this method, drug is dissolved up in a polymer solution along with plasticizer. Then the above solution is to be mixed for 10-15 min to make a homogeneous dispersion and poured into a levelled mercury surface. At that point, the solution is covered with an inverted funnel to control solvent evaporation.

By using IPM membrane^[33]

In this technique, the drug is dispersed in a mixture of water and propylene glycol, carbomer-940 polymer, and stirring in a magnetic stirrer for 12 h. The dispersion will be neutralized, making it viscous by the addition of tri-ethanolamine. Buffer pH 7 can be utilized to get solution gel, in the method that drug solubility in aqueous solution is poor. The formed gel can be incorporated into the IPM membrane.

By use of EVAC membranes method^[34]

In this procedure to prepare the target therapeutic transdermal system, it is certainly 1 % carbohydrate reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not water soluble, propylene glycol is used for the preparation of the gel. The drug is dissolved in propylene glycol; the above solution is added to carbopol resin and neutralized using 5% w/w sodium hydroxide solution. The drug (in the form of a gel) is mounted on a backing layer sheet covering the specified area. The rate control Membrane should be positioned over the gel and the edges will be sealed by heat to achieve a leak-proof device.

Aluminium backed adhesive film method^[35]

Transdermal drug delivery system can produce unstable matrices with a loading dose greater than 10 mg. Chloroform can be the preference of solvent for the preparation of aluminium backed film, because most drugs, as well as adhesives, are soluble in chloroform. The drug is dissolved in chloroform and the drug solution can be added to the adhesive material and

dissolved. Former is lined with aluminium foil and the ends off with tightly cork block fitting.

Preparation of TDDS by using proliposomes^[36]

The proliposomes are prepared by a carrier method film using a deposition technique. Through the previous reference drug and lecithin within the ratio of 1:2 can be utilized being an optimized ratio. Proliposomes are prepared by taking 5 mg of mannitol powder in a 100 ml round bottom flask, which can be held at a 60-70°C temperature addition to the flask, rotated at 80-90 rpm and vacuum-dried mannitol for 30 minutes. After drying, the temperature of this water-bath is adjusted to 20-30 °C. Drug and lecithin are dissolved inside a suitable organic solvent mixture. Aliquot of 0.5 ml of organic solution is transferred to the round bottomed flask at 37°C containing mannitol after complete drying of aliquots second (0.5 ml) of the solution is added. After the final loading, the flask proliposomes which are containing connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are put in desiccators overnight and then sieved through 100 mesh. The collected powder is transferred directly into a glass container and stored in the freeze temperature until characterization.

By using free film method^[37]

Free film of cellulose acetate is produced by casting on a mercury surface. A 2 % w/w polymer solution is prepared using chloroform. Plasticizers are added at a concentration of 40% w/w of the polymer weight. 5 ml of polymer solution poured inside a glass ring which can be placed over the mercury surface in a glass petri dish. The evaporation rate of the solvent is regulated by placing the inverted funnel over the petri dish. The film formation is mentioned by observing the mercury surface after the complete evaporation of the solvent. The film, which is dry, is removed and deposited in desiccators between sheets of wax paper before it is used. Free films of different thickness could be prepared by changing the volume of the polymer solution.

Factors Influencing Transdermal Drug Delivery^[13]

An effective drug that is transdermal could be formulated by considering three factors as Drug, Skin, and also vehicles. So factors affecting may be divided into classes as biological factors and physicochemical factors.

A. Biological factors

1. Skin condition: Acids and alkalis, many solvents like chloroform, methanol damage the epidermis cells and penetration that is improved. The diseased state of the patient alters skin conditions. The intact skin is a better barrier but the above mentioned problems influence penetration.

2. Skin age: the skin that is young more permeable than older. Kids are more sensitive to skin absorption of toxins. Hence, skin age is just one of the factor penetration that is affecting TDDS.

3. Blood supply: alterations in peripheral circulation can affect transdermal absorption.

4. Regional skin site: The thickness of the skin, the nature of the stratum corneum, and the density of the appendages differ from site to site. These components have a particular effect on penetration.

5. Skin metabolism: Skin metabolizes steroids, bodily hormones, chemical carcinogens, and some medications. So skin metabolism determines the effectiveness of drugs permeated through the skin.

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

B. Physicochemical factors

1. Skin hydration: in touch with water the permeability of skin increases significantly. Hydration is the most factor that is very important in the permeation of skin. So the use of humectants is performed in transdermal delivery.

2. Temperature and pH: The permeation of the drug increases tenfold with temperature difference. The diffusion coefficient reduces as the temperature falls. Weak bases and weak acids dissociate depending on the pH and pKa or pKb values. The proportion of unionized drugs determines the drug concentration in the skin. Therefore, temperature and pH are important facets of drug penetration that is affecting.

3. Diffusion coefficient: Penetration of drugs depends on the diffusion coefficient of drug. The diffusion coefficient of a drug relies on properties of drug, diffusion medium, and interaction among them in a constant temperature.

4. Drug concentration: The flux is proportional to your concentration gradient across the concentration gradient and barriers are greater in the concentration of the drug will likely be more across the barrier.

5. Partition coefficient: The K that is optimal coefficient is needed for good action. Drugs with high K are not prepared to leave the lipid portion. Also, drugs with low K will not permeate.

6. Molecular size and form: Drug absorption is inversely associated with molecular weight. Small molecules penetrate quicker than large ones. The effect of molecular size is not known because of partition coefficient domination.

Evaluation Parameters

Interaction studies^[5-43]

The integral part of practically all pharmaceutical dosage forms is the excipients. The stability of the formulation between various factors depends on the compatibility of the drug with the excipients. The drug and excipients should be compatible to produce a stable product, and hence it is required to identify any possible physical and chemical interaction as it can influence the bioavailability and stability of the drug. Interaction studies are usually carried out in thermal analysis, FT-IR, UV, and chromatographic techniques by comparing their physiochemical characters, for example, assay, melting points, characteristic wave numbers, and absorption maxima, and so on.

Thickness of the patch^[44]

The thickness of the drug-loaded patch is measured at various points by utilizing a digital micrometre and decides the average thickness and standard deviation for the equivalent to ensure the thickness of the prepared patch.

Weight uniformity^[44]

The prepared patches are dried at 60 °C for 4h prior to testing. A specific region of the patch is cut into various parts and weighed in the digital balance. The average weight and standard deviation values are to be calculated by the individual weights.

Folding endurance^[44]

A strip of specific dimensions is cut equally and more than once folded at a similar spot till it broke. Without breaking, the number of times the film could be folded at a similar spot and gave the value of the folding endurance.

Percentage moisture content^[44]

The films being prepared are individually weighted and placed in desiccators containing fused CaCl₂ at room temperature for 24 hours. Then after 24h the films are reweighed and determine the percentage moisture content from the below formula is discussed.

$$\text{Percentage Moisture Content} = [\text{Initial Weight} - \text{Final Weight}/\text{Final Weight}] \times 100$$

Percentage moisture uptake^[44]

The weighed films are placed in desiccators at room temperature for 24 h containing a saturated solution of KCl in order to maintain 84% RH. The films are to be reweighed after 24 h and determine the percentage of moisture uptake by using the following formula.

$$\text{Percentage Moisture Uptake} = [\text{Final Weight} - \text{Initial Weight}/\text{Initial Weight}] \times 100$$

Water vapour permeability (WVP) evaluation^[44]

Water vapour permeability is determined with a foam dressing technique. The WVP maybe determined by the formula that is following

$$\text{WVP} = W/A$$

Where WVP is expressed in gm/m² per 24 hours.

W is the level of vapour permeated through the patch indicated in gm/24 h and A is the surface area of these exposure samples expressed in m².

Drug content^[45]

A specified area of patch is usually to be mixed in a suitable solvent in a specific volume. Then the solution would be filtered through a filter medium and the medication content is analysed using the suitable method (UV or HPLC technique). Each value should represent the average of three different samples.

Uniformity of dosage unit test^[46]

In this test, an accurately weighed portion of the patch will be cut into small pieces and transferred to a volumetric flask dissolve within a suitable solvent and sonicate for total extraction of the drug through the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was then diluted to provide the desired concentration with the required solvent. The solution was filtered using a membrane filter this is certainly 0.2µm and examined by suitable analytical technique (UV or HPLC) plus the drug content per piece should be calculated.

Polariscope examination^[47]

This test will be performed to examine the drug crystals from the patch by polariscope. A certain surface area of the film must be kept on the slide of the object, and the drug crystals must be observed to distinguish whether the drug appears as a crystalline or amorphous form in the patch.

Shear adhesion test^[46]

This test is carried out to measurement of the cohesive strength of an adhesive polymer. It could be influenced by the molecular weight, the amount of crosslinking, and the composition of polymer, type, and the level of tackifier added. The adhesive-coated tape is applied on a stainless-steel plate than specified weight is hanging from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time to pull the tape removed from the plate. The longer the time required for removal, the greater the shear strength.

Peel adhesion test^[46]

In this test, the force required to remove an adhesive layer from the test substrate is known as peel adhesion. The molecular weight of adhesive polymer, the amount and type of ingredients are the variables that determined the peel adhesion properties. A single tape is applied to the stainless steel dish or back membrane and then the tape is pulled through the surface at an angle of 180° and the force required to remove the tape will be measured.

Thumb tack test^[46]

The thumb is simply pressed onto adhesive and the related tack property is detected which is a qualitative test.

Flatness test^[47]

Three longitudinal strips are cut from each film at different areas like one through the centre, other one through the left side, and one from the right side. The length of each strip was measured and the difference in length as a result of the non-uniformity in flatness was calculated by the determination of percent constriction, with zero constriction equivalent to 100% flatness.

Percentage elongation break test^[47]

The portion elongation break is determined by noting the length right before the breakpoint, the percentage elongation may be determined from the below formula^[47]

$$\text{Elongation percentage} = \frac{L_1 - L_2}{L_2} \times 100$$

Where L_1 is the final length of each strip and L_2 could be the initial length of each strip.

Rolling ball tack test^[48]

The softness is calculated by this test of a polymer that relates to tack. In this test, a stainless-steel ball of 7/16 inches in diameter is introduced on a track this is certainly inclined that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the glue gives the measurement of the tack, which will be expressed in inches.

Quick stick (peel-tack) test^[49]

The tape is pulled from the substrate at 90 °C at a speed of 12inches/min. to Break the bond between substrate and adhesive. The peel force needed is assessed and recorded as tack worth, and expresses in ounces or grams per inch width.

Probe tack test^[48]

The tip of the clean probe with definite surface roughness is brought into contact with adhesive, so when a bond is formed between adhesive and probe. It is mechanically broken by the subsequent removal of the probe. The force required to pull the probe away through the adhesive at a fixed rate is recorded as a tack and represented in grams.

In vitro drug release studies^[46]

The paddle over disc technique (USP apparatus V) is used to determine the release of the drug through the patch that is prepared. Dry films of known thickness will be cut into a definite shape and weighed, then fixed over a glass plate with an adhesive. Then glass plate was placed in 500 ml of the dissolution medium or buffer phosphate pH 7.4), and the apparatus was equilibrated to 37±0.5 °C. The paddle was then set a distance of 2.5 cm through the glass plate and operated at a speed of 50 rpm. samples can be withdrawn at proper time intervals up to 24 h and reviewed by Ultraviolet spectrophotometer or HPLC method. The experiment is to be performed in triplicate as well as the value that is mean be calculated.

In vitro skin permeation studies^[42]

Diffusion cell is used to carry out the permeation study on complete thickness abdominal skin of male Wistar rats evaluating 200-250g. Hair through the abdominal region becoming removed carefully by using a clipper this is certainly electric, the dermal side of the skin was completely cleaned with distilled water to remove any adhering cells or arteries, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before beginning the test and had been put on a magnetic stirrer through a tiny needle that is a magnetic uniform distribution of the diffusant. The temperature of this cell had been maintained at 32 ± 0.5 °C using a thermostatically controlled heater. The rat-skin that is isolated piece is to be attached between the compartments of the diffusion cell, with the epidermis facing up into the donor compartment. Sample value of definite volume is to be taken off the receptor compartment at regular intervals and a volume this is certainly equal to fresh medium will be replaced. Samples are to be filtered through a filtering medium and certainly will be analyzed spectrophotometrically or HPLC. Flux could be determined directly as the slope for the curve between the steady state values for the quantity of drug permeated (mg cm^{-2}) vs. time in hours and permeability coefficients had been deduced by dividing the flux by the initial drug load (mg cm^{-2}).

Skin irritation study^[42]

Healthy rabbits are widely used to perform skin sensitization and irritation testing. The dorsal surface (50 cm^2) of the rabbit is usually to be clean and the hair removed by shaving and the surface cleaned by the application of rectified spirit and the representative formulations should be applied to the epidermis. The patch will be removed after 24 h and the skin is observed and classified into five grades on the basis of the extent of skin injury.

Stability studies^[38]

Stability studies are performed based on the ICH guidelines by storing the TDDS samples at 40 ± 0.5 °C and $75\pm 5\%$ RH for 6 months. The samples became withdrawn at 0, 30th, 60th, 90th, and 120th day and analyzed suitably for the drug content.

List of marketed transdermal products**Table 1: Some marketed transdermal products.^[8]**

S.N.	Name of Product	Manufacturer	Drug	Uses
1	Deponit	Schwarz pharma	Nitroglycerine	Angina pectoris
2	Nitro-dur	Key pharmaceuticals		
3	Minitrann	3M pharmaceuticals		
4	Transderm nitro	Alza/Novartis		
5	Climara	3M Pharmaceuticals/Berlex Labs	Estradiol	Postmenstrual syndrome
6	Alora	TheraTech/proctol and Gamble		
7	Estraderm	Alza/Novartis		
8	Fempatch	Parke-davis		
9	Duragesic	Alza/ Janssen pharmaceutical	Fentanyl	Moderate /severe pain
10	Fematrix	Ethical holdings/solvay healthcare LTD	Estrogen	Post menstrual syndrome
11	Androderm	Theratech/GalxosmithKline	Testosterone	Hypogonadism In males
12	Testoderm TTS	Alza		
13	Nicoderm	Alza/glaxo smithkline	Nicotin	Smoking cessation
14	Nicotrol	Cygnus inc./Mc Neil Consumer products Ltd.		
15	Habitraol	Novartis		
16	Prostep	Elan Corp./Lederle Labs		
17	Transderm Scop	Alza/Novartis	Scopolamine	Motion sickness
18	Ortho Evra	Ortho-McNeil Pharmaceutica	Ethinyl estradiol with norelgestromin	Contraception
19	Oxytrol	Watson Pharma	Oxybutynin	Overactive bladder
20	Lidoderm	Endo Pharmaceuticals	Lidocaine	Post-herpetic neuralgia pain

CONCLUSION

Transdermal drug delivery is one of the fastest-moving areas for novel drug delivery. Because of recent technological advances and the ability to deliver the drug systemically without rupturing the skin membrane, the transdermal route is now a commonly accepted route of drug administration. The transdermal drug delivery system (TDDS) is designed to control the release of drugs through the skin into the systemic circulation, maintaining efficacy. It provides the delivery of drugs at a reduced dosage that will protect the patient from harm caused by high doses with increased bioavailability. This can be accomplished by

bypassing the hepatic metabolism. Almost all large and smaller pharmaceutical companies are developing TDDS. Potential developments in drug delivery systems include using advanced adhesive and/or enhancer technologies; and systems that exploit thermal, electrical, ultrasonic, or other sources of energy.

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