



# Transdermal Drug Delivery: A Novel Approach for Intended Drug Action

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## ABSTRACT

*From decades application of the medicaments topically has been rampant to attain a particular therapeutic response and Transdermal Drug Delivery System (TDDS) has been a boon for topical administration of therapeutic substances. These are self-contained, discrete dosage forms offering painless and desired pharmacokinetics. The drugs which are not suitable for administration through oral route due to various inefficiencies can be administered via transdermal route. These are the preparations that vary in sizes, containing the active ingredient to be applied on the unbroken skin to deliver the active pharmaceutical ingredient into the systemic circulation through diffusion process thus avoiding the first pass metabolism. The present review describes about the Anatomy of skin, Components, Types, Merits, Demerits and Evaluation of Transdermal Drug Delivery System.*

**Keywords:** *Transdermal Drug Delivery, Skin Anatomy, Components, Evaluation.*

## 1. INTRODUCTION

There are different types of route of administration and most common route of administration is oral route. Though oral route of administration has many advantages but also has disadvantages like first pass metabolism and tendency of producing rapid blood level spikes that leads to frequent dosing. To overcome these drawbacks the need for controlled and continuous delivery of drugs, transdermal drug delivery system has become one of the most innovative system where drug is administered through skin into systemic circulation. The drug must be able to penetrate through the skin easily and reaches the targeted site. [1-4]

These transdermal patches are now used for various disorders and among those it is mostly used for controlling obesity as it reduces the access body weight. Some of the natural weight loss patches are zinc pyruvate, flax seed oil, lecithin, l-carnitine etc. Transdermal patches are the pharmaceutically formulated patches that contain one or more ingredients that can easily penetrate through the skin. The transdermal drug delivery patches are to be applied on unbroken skin so that the drug enters into the systemic circulation passing through the skin barriers. In 1979, Transderm-SCOP (scopolamine) which is the first transdermal system was approved by FDA for the prevention of motion sickness and vomiting. In India Nicotine patch was the first transdermal patch. These transdermal drug delivery patches can produce systemic as well as local effects. Some of the important uses are it is used for preventing gastro intestinal mucosal damages, gastro intestinal toxicity and gastric irritation. These are also used for maintaining the health of the skin and for preventing infection of skin as well as mucous membrane. [5-8]

Transdermal patches consists of high dose of the drug inside it. This patch is applied on the skin for a long period of time. Slowly the drug enters into the systemic circulation as the drug enters into the blood stream directly through the skin through diffusion process. Due to the difference in the concentration of drug in the patch which is applied and in the blood, the drug diffuses into the blood as the concentration of the drug in the blood is less. Thus, maintaining a constant drug concentration in blood. The concentration of drug that is absorbed in the blood can be determined by measuring the blood levels of the drug, presence or excretion of drug and its metabolites in the urine. And also through clinical response of the patient to the therapy. [9-11]

### Anatomy of Skin:

Skin is made up of three layers i.e., epidermis, dermis and hypodermis. Epidermis is the outer most layer of the skin and with epithelium it covers maximum surface of the body. Epithelium is stratified squamous keratinized epithelium. Division of the cells takes place in lowest cellular layers-stratum spinosum and stratum mucosa. After each cell division one daughter cell migrates towards the surface and the other starts dividing again. The cells become cornified and form into granules as they migrate towards

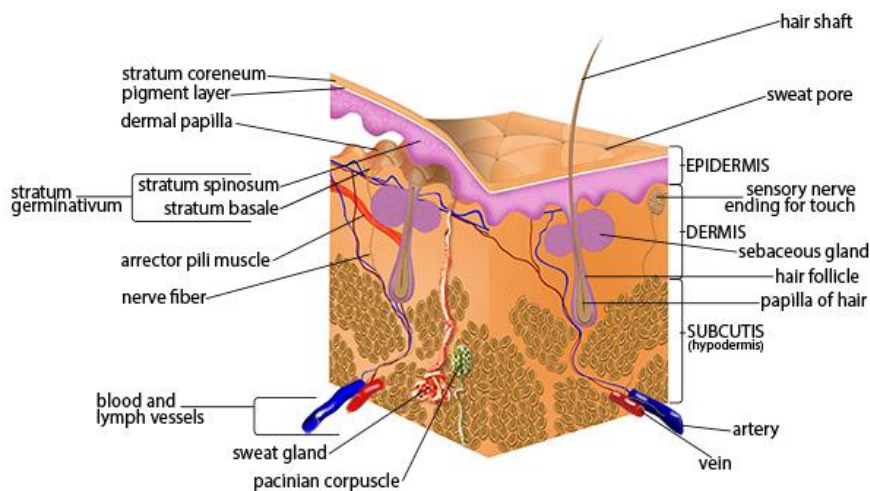
the surface giving rise to stratum granulosum. Stratum corneum the upper layer of the epidermis consists of keratinized, flattened relics of previously divided epidermal cells. It is hygroscopic but impermeable to water and is a flexible and tough membrane.[12-24]

**Epidermis:**

It can be divided into:

- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinulosum
- Stratum basale
- Stratum germinativum

Stratum corneum also known as horny layer is a tightly packed scale like cells. Stratum lucidum consists of small cells and this layer is a clear layer as it consists of small transparent cells. Stratum granulosum consists of cells that appear like granules. These are the cells that die in stratum corneum. Followed layer is stratum spinulosum which is also known as prickly layer or prickle cell layer. The cells present in this layer undergo mitosis and the cells are pushed upward direction. Stratum mucosa is basal layer and consists of lowest row of cells to make the basal zone. The last layer of epidermis is stratum germinativum and is composed of single layer of cells .The cells undergo mitosis and replaces the older cells that are shed. Melanocytes that are responsible for the pigmentation of the skin are formed in this layer. It takes 28 days for the formation of melanocytes.



**Fig-1: Anatomy of Skin**

**Dermis:**

Epidermis is followed by dermis and dermis consists of collagen and elastin fibers which provide strength and flexibility to the skin. Dermis consists of network of nerves, blood and lymph vessels.

Dermis is divided into two layers:

- Papillary layer
- Reticular layer

Papillary layer is made up of areolar tissue and small capillaries, lymphatic and sensory neurons.

Reticular layer consists of collagen and elastin fibers and is made up of dense irregular tissue.

**Hypodermis:**

Hypodermis which is also known as subcutaneous layer and consists of adipose and connective tissue. It is present in the bottom of the skin and as it is a fatty layer it functions as a shock absorbing layer for outer skin.

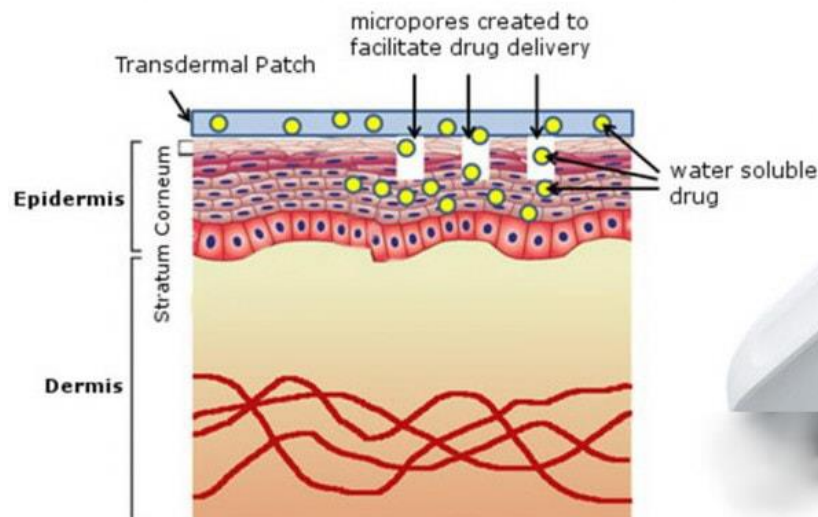


Fig-2: Representation of mechanism of a TDDS patch

## 2. BASIC COMPONENTS OF TDDS

- Polymer matrix
- Drug
- Release liners
- Permeation enhancers
- Pressure sensitive adhesive
- Backing laminate

The above components are described briefly below: [25-50]

**1) Polymer matrix:** Polymer matrix is the most important component of TDDS as it plays an important role in controlled drug delivery.

There are many types of polymers used such as:

- Natural polymers-e.g.: cellulose derivatives, natural rubber, waxes, zein, gelatin, shellac, gums etc.
- Synthetic polymers-e.g.: polyvinyl chloride, polypropylene, polyethylene, polyacrylate, polyvinyl alcohol, polyamide, polyurea, polyvinylpyrrolidone, epoxy etc.
- Synthetic elastomers-e.g.: hydrin rubber, silicon acrylonitrile, polybutadiene, polyisobutylene, butyl rubber etc.

The polymer used in transdermal patches should contain the following criteria:

- Molecular weight and chemical functionality of the polymer should be in such a way that the drug diffuses properly.
- The polymer used should be non-toxic.
- The polymer should be stable and should not react with the drug.
- The polymer used should be inexpensive and large amount of active ingredient can be incorporated in it.
- The polymer should be manufactured easily.

**2) Drug:** The ideal properties of the drug that are to be considered during preparation of TDDS are:

- Molecular weight of the drug should be less than 1000 Daltons
- The drug should have low melting point
- The drug should have affinity towards both lipophilic and hydrophilic phases

Some of the biological properties of the drug used for TDDS are

- Half-life should be 10 hrs. or less
- Dose should be <20mg/day
- Drug should be non-sensitizing and non-irritating to skin
- Permeability coefficient of skin should be  $<0.5 \times 10^{-3}$ cm/h.
- Oral bioavailability and therapeutic index should be low.

**3) Release liners:** Release liners are the covering of the transdermal patch and are important in maintaining the properties and characteristics of transdermal patch. These liners are important in maintaining the stability of the patch during storage. Before the application of the patch on the skin the liner is first removed. A great care must be taken in choosing release liners as incorrect release liners will not permit the easy release of the drug in the patch and can reduce its shelf life by reacting with the active ingredients. Polyethylene and polyvinyl chloride are used in preparation of liners.

**4) Permeation enhancers:** These are the chemical substances that enhance the permeation rate of the active ingredients through the skin by several times. These enhancers increase the feasibility of the system as most of the active ingredients cannot enter the skin

in a relatively small area in the required dosage form. The permeation enhancers increase the diffusivity of the drug into the stratum corneum by denaturing the skin protein.

These are divided into two types:

#### **Chemical enhancers:**

These are the enhancers that are important for penetration of the drug topically as well as transdermally. These are important in increasing the partition coefficient of the drug which promotes the drug diffusion and increasing the penetration of the drug.

#### **Physical enhancers:**

These enhancers also help in the penetration and permeability of the drug material through the skin. Methods such as iontophoresis and ultra sound methods are used in the enhancement of percutaneous penetration and absorption.

#### **5. Pressure sensitive adhesives:**

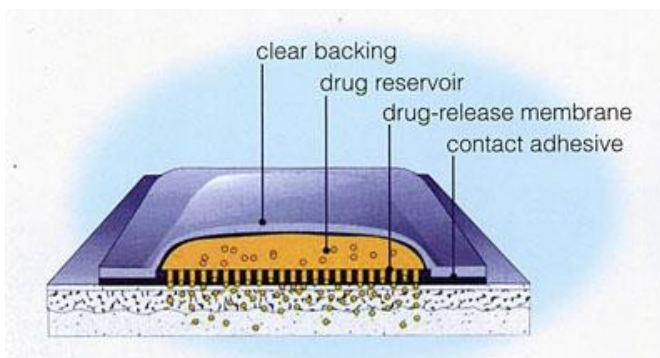
Pressure sensitive adhesives play an important role by making the patch stick to the skin. These provide matrix that carries additives and permeation enhancers. These adhesives should give strong adhering force, should adhere with finger pressure and should be able to be removed easily without leaving any residue.

Mostly used adhesives are polyacrylates, polyisobutylene and silicon based adhesives.

#### **6. Backing laminate:**

Backing laminate is an impermeable substance that prevents the drug from leaking or leaving from the top and protects the product during the usage on the skin.

to avoid the incompatibility it must be fully inert to the drug, additives, enhancers and other excipients.



**Fig-3: Representation of a typical transdermal drug delivery patch**

### **3. TYPES OF TDDS**

The various types of Transdermal Drug Delivery Systems are: [51-57]

**1. Single layer drug in adhesive:** In this type the adhesive layer contains the drug and is responsible for the release of the drug into systemic circulation through the skin. It adheres various layers together along with the entire system to the skin. The adhesive layer is surrounded by a temporary liner and backing.

**2. Multi-layer drug in adhesive:** This type of adhesive layer is similar to single layer drug in adhesive and both the adhesive layers are responsible for the drug release. One will be the immediate drug release layer and the other will be controlled release layer along with the adhesive layer which is responsible for the releasing of the drug. This patch is also covered by temporary layer and permanent backing.

**3. Reservoir:** Reservoir transdermal system unlike single and multi-layer drug in adhesive, has a separate drug layer which is a liquid compartment containing drug solution and suspension which is separated by the adhesive layer. The drug releases through micro porous or non-porous membrane. Hypoallergenic adhesive layer can be applied as the outer surface polymeric membrane and should be compatible with the drug.

**4. Matrix:** In this patch the adhesive layer surrounds the drug layer partially overlaying it. This system the drug layer has semi solid matrix and contains drug solution or suspension with direct contact with release liner.

**5. Vapour patch:** In this type of patch the adhesive layer adheres various layers together as well as releases vapour. These patches release essential oils up to 6 hours. These types of patches are mainly used in cases of decongestion. Some are used for improving the quality of sleep and some vapour patches are used to reduce the addiction to cigarettes that one smokes in mouth.

#### **Various methods of preparation of TDDS:**

Few methods of preparation of Transdermal Drug Delivery Systems are:[58-70]

#### **Asymmetric TPX membrane method:**

In asymmetric TPX membrane method a prototype patch is fabricated by using a heat sealable polyester film. It is of type 1009, 3m. It consists of a concave which is of 1cm diameter as backing membrane which consists of drug later total system is covered by TPX membrane.

#### **Circular Teflon Mould method:**

In this method polymeric solution in various ratios are used in an organic solvent. The amount of drug is calculated and then added to the half the quantity of the same organic solvent. The other half quantity of the organic solvent consists of different concentrations of enhancers dissolved in it and then two halves are mixed together.

Plasticizer such as Di-N-Butylphthalate is added to the drug polymer solution. The total contents are stirred for 12 hours and then poured into a circular Teflon mould. These moulds are placed on a leveled surface and should be covered with inverted funnel to control the solvent vaporization. This is done in a laminar flow hood model with an air speed of 0.5m/s. Evaporation of solvent is done for 24 hours. The dried films are stored for another 24 hours at 25 degree celsius in dessicators containing silica gel before evaluation to eliminate aging effects. These are to be evaluated before one week after preparation.

#### **Mercury substrate method:**

In this method both the drug and plasticizer are dissolved in polymer solution. All the components are stirred for 10-15 minutes to obtain a homogenous dispersion. This homogenous dispersion is poured into a leveled mercury surface. This is then covered with inverted funnel to control the solvent evaporation.

#### **IPM membrane method:**

In this method the drug is dispersed in a mixture of water and propylene glycol and also containing carbomer 940 polymer. This mixture along with the dispersed drug is stirred in magnetic stirrer for 12 hours and neutralized. The neutralized dispersion is made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain a solution gel if the drug solubility is very poor in aqueous solution. The so formed gel will be incorporated in the IPM gel.

#### **EVAC membranes method:**

In this method ethylene vinyl acetate copolymer membranes are used as rate controlling membranes and it also consists of 1% of carbopol reservoir gel and polyethylene (PE). Propylene glycol is used in the preparation of the gel if the drug is not soluble in water. Drug is dissolved in propylene glycol, carbopol and resin is added to the above solution then by using 5% w/w sodium hydroxide solution, which is neutralized. The drug is placed on a sheet of backing layer covering the specific area and the drug is in gel form. A rate controlling membrane is placed over the gel and the edges are sealed with heat to obtain a leak proof device.

#### **Advantages of TDDS:**

The advantages are: [72-77]

- They can be used as a substitute for oral administration of medicament in case of vomiting and diarrhea.
- These transdermal systems are used in avoiding gastrointestinal drug absorption. and also difficulties that are caused by gastrointestinal pH, enzymatic activity and interaction of drug with food, drink, and also by other orally administered drug.
- The therapeutic value of many drugs is increased by avoiding decomposition due to hepatic first pass effect, formation of metabolites that causes side effects etc.
- These are non-invasive thus avoiding the inconvenience of parenteral therapy.
- They provide extended therapy with a single application which improves the compliance over other dosage forms which require more frequent dose administration.
- This type of simplified medication improves patient compliance and reduce inter and intra patient variability.
- Application and removal of transdermal patch produces the optimal sequence of the pharmacological effect.
- Self-administration is possible with transdermal drug delivery systems.
- The drug therapy can be terminated at any point of time by removing transdermal patch from the skin.

#### **Disadvantages of TDDS:**

The disadvantages include: [78-83]

- These types of delivery systems also have disadvantages as only potent drugs are suitable for transdermal patch. This is because of the natural limits of drug entry imposed by skin's impermeability.
- At the site of application some patients develop contact dermatitis from system components and developing the necessary of discontinuation.
- The transdermal delivery will be very difficult if the drug dose for therapeutic value is more than 10mg/day, and the drug must have desirable physicochemical properties for penetration through stratum corneum.
- Long time adhesion of the patch is difficult.
- The barrier function of the skin is different in different individuals and it also changes from one site to another on the same person and with age.

#### **Evaluation of TDDS:**

The evaluation parameters of Transdermal Drug Delivery Systems are discussed below: [84-96]

**1) Interaction studies:** The compatibility of the drug with the excipients is very important as the stability of a formulation amongst others factors depends on the compatibility of drug and excipients. Thus it is mandatory to detect any possible physical or chemical interaction as it can affect the stability and bioavailability of the drug. The compatibility studies play an important role in formulation development if the excipients are new and have not been used in formulations containing the active substance. By comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc., interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques.

**2) Thickness of the drug patch:** By using the digital micrometer the thickness of the drug loaded patch is measured at different points. It determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

**3) Weight uniformity:** The patches that are prepared are to be dried at 60°C for 4 hours before testing for weight uniformity, and a specified area of the patch is cut in different parts and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

**4) Folding Endurance:** Specific area of a patch is cut evenly and is folded at the same place repeatedly till the patch breaks. The value of folding endurance is given by the number of times the film can be folded at the same place without breaking.

**5) Percentage moisture content and percentage moisture uptake:** The prepared films are weighed individually. After weighing these are kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. The films are reweighed after 24 hrs. and the percentage moisture content is determined from the below mentioned formula.

$$\text{Percentage moisture content} = \left[ \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \right] \times 100.$$

For percentage moisture uptake the weighed films are kept in a desiccator at room temperature for 24 hrs. containing saturated solution of potassium chloride in order to maintain 84% RH. The films are reweighed after 24 hrs. and the percentage of moisture uptake can be determined from the below mentioned formula.

$$\text{Percentage moisture uptake} = \left[ \frac{\text{Final weight} - \text{Initial weight}}{\text{initial weight}} \right] \times 100.$$

**6) Water vapour permeability (WVP) evaluation:** Foam dressing method is the method used for WVP evaluation. The natural air circulation oven is used in this method. The WVP can be determined by the following formula:

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

Where, WVP is expressed in gm/m<sup>2</sup> per 24hrs,

W-Amount of vapour permeated through the patch. It is expressed in gm/24hrs

A-surface area of the exposure samples expressed in m<sup>2</sup>.

**7) Drug content:** In a specific volume of suitable solvent a specified area of patch is dissolved. Then the solution is filtered through a filter medium and the drug content is analyzed with suitable method such as UV, HPLC etc. Each value represents average of three different samples.

**8) Uniformity of dosage unit test:** Uniformity of dosage unit test is done by taking an accurately weighed portion of the patch and is cut into small pieces. These pieces are transferred to a specific volume volumetric flask, these are then dissolved in a suitable solvent and sonicated for complete extraction of drug from the patch and is made up to the mark with same. The resulting solution is allowed to settle for about an hour, and the supernatant is suitably diluted to give the desired concentration with suitable solvent. The solution is filtered using 0.2 micro m membrane filter and analyzed by suitable analytical technique such as UV or HPLC and the drug content per piece is calculated.

**9) Polariscope examination:** Polariscope is used to examine the drug crystals from patch. A specific surface area of the piece is kept on the object slide and observed for the drug's crystals to identify whether the drug is present as crystalline form or in amorphous form.

**10) Shear adhesion test:** Shear adhesion test is performed to measure the cohesive strength of an adhesive polymer. this can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate. To affect it pulling in a direction parallel to the plate a specified weight is hung from the tape. This is determined by measuring the time taken to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

**11) Peel adhesion test:** In peel adhesion test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determine the peel adhesion properties. To a stainless steel plate a single tape or a backing membrane is applied and then the tape is pulled from the substrate at an angle of 180°, and the force required for tape to remove adhesive coating form is measured.

**12) Thumb tack test:** Thumb tack test is a qualitative test applied for tack property determination of adhesive. Here the thumb is just pressed on the adhesive and the relative tack property is detected.

**13) Flatness test:** To perform this test three longitudinal strips are cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length

because of non-uniformity in flatness is measured by determining percent constriction, where 0% constriction equivalent to 100% flatness.

**14) Percentage elongation break test:** This test is determined through noting the length of patch just before the break point, the below mentioned formula is used to determine percentage elongation test.

$$\text{Elongation percentage} = \frac{L1-L2}{L2} \times 100$$

Where, L1 is the final length of each strip and L2 is the initial length of each strip.

**15) Rolling ball tack test:** Rolling ball tack test measures the softness of a polymer that relates to the tackiness of the polymer. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, and is expressed in inches.

**16) Quick stick (peel-tack) test:** In this, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force that is required to break the bond between adhesive and substrate is measured and recorded as tack value, and it is expressed in ounces or grams per inch width.

**17) Probe tack test:** In this test, tip of a clean probe which consists of defined surface roughness is brought into contact with the adhesive, and when a bond is formed between probe and adhesive, the subsequent removal of the probe mechanically breaks it. To pull the probe away from the adhesive at fixed rate the force required is recorded as tack and is expressed in grams.

**18) In vitro drug release studies:** For assessment of the release of the drug from the prepared patches the paddle over disc method (USP apparatus V) can be employed. Dry films of known thickness are cut into definite shape, and is weighed and fixed over a glass plate with an adhesive. The glass plate is then placed in the dissolution medium consisting a volume of 500ml or phosphate buffer (pH 7.4), and then the apparatus is equilibrated to a temperature of 32± 0.5°C.

The paddle is then set at a distance of 2.5 cm from the glass plate and is operated at a speed of 50 rpm. Samples each of volume 5ml aliquots are withdrawn at appropriate time intervals up to 24 h and are then analyzed by HPLC or UV spectrophotometer. The experiment is to be performed in triplicate and the mean value can be calculated.

**19) In vitro skin permeation studies:** By using a diffusion cell an in vitro permeation study can be carried out. Abdominal skin of male Wistar rats weighing from 200 to 250g is taken. Hair from the abdominal region should be removed by using an electric clipper very carefully. The dermal side of the skin should be thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, then is equilibrated for an hour in dissolution medium or phosphate buffer of pH 7.4 before starting the experiment and has to be placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The rat skin piece which has been isolated is then mounted between the diffusion cell compartments, where the epidermis faces upward into the donor compartment. Sample volume of definite volume is removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are then filtered through filtering medium and can be analyzed through spectrophotometer or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm<sup>-2</sup>) vs. time in hours and Permeability coefficients are deduced by dividing the flux by the initial drug load (mg cm<sup>-2</sup>).

**20) Skin irritation study:** Skin irritation and sensitization testing can be performed on healthy rabbits of average weight about 1.2 to 1.5 kg. The dorsal surface of the rabbit is cleaned and the hair is removed from the clean dorsal surface by shaving and then the surface is cleaned by using rectified spirit and then the testing formulations can be applied over the skin. After 24 hrs. the patch is removed and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

**21) Stability studies:** According to the ICH guidelines stability studies are conducted by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples are then withdrawn at 0, 30, 60, 90 and 180 days and are analyzed suitably for the drug content.

#### 4. CONCLUSION

Transdermal drug delivery system is a novel drug delivery system and the main intension is to achieve a delivery profile which yields high blood level of drug over a long period of time. This drug delivery system assures that an ingredient which is pharmacologically active arrives at a particular in-vivo location with minimum side effects. Transdermal drug delivery system is an efficient drug delivery system and acts as a Micro emulsion, Ethosome, Nano emulsion, Niosomes, Liposomal delivery, Transdermal Patches and Transfersomes etc. A chemically inert and free of leachable impurities material must be used for successful controlled drug delivery formulations. To optimize the scope of transdermal drug delivery system a greater knowledge about different mechanisms of biological interactions and polymer used is needed. The biotechnology has to be combined with this technology so that it helps efficiently in enormous inventions of many more innovative medications as it shows a promising future.

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