REVIEW ON TRANSDERMAL PATCH

Rajni*, Kuamr Rohit, Bharti Nitan and Bhandari Neeraj

Sri Sai College of Pharmacy, Badhani, Pathankot.

ABSTRACT

A Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream. The transdermal drug delivery system is one of novel drug delivery system which overcomes arise from the conventional dosage from. Transdermal patches are pharmaceutical preparation of varying sizes, containing one or more active ingredient to the systemic circulations. The review gives valuable information about the transdermal patch like its advantage, disadvantage, mechanism of action, types of transdermal patch, factors basic components, methods and evaluation, application of transdermal patch. A wide variety of pharmaceuticals are now available in transdermal patch form.

KEYWORDS: transdermal patch, factors basic components, methods and evaluation.

INTRODUCTION

Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver the drug via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. For effective Transdermal drug delivery system, the drug are easily able to penetrate the skin and easily reach the target site. TDDS increase the patient compliance and reduces the load as compared to oral route. FDA approved the first Transdermal system Transderm-SCOP in 1979. FDA approved this for the prevention of nausea and vomiting associated with ravel, particularly by sea. Transdermal therapeutic systems are also defined as a self contained, discrete dosage

*Corresponding Author
Rajni
Sri Sai College of Pharmacy, Badhani, Pathankot.
forms which, when applied to the intact skin, deliver the drug, through the skin at control rate to the systemic circulation. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration.\(^{[3]}\)

**ADVANTAGES\(^{[4,5,6]}\)**

- Transdermal medication delivers a steady infusion of a drug over an extended period of time.
- An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, e.g. the drug is given orally.
- Self administration is possible with these systems.
- They are easily and rapidly identified in emergencies (e.g. unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.
- They can be used for drugs with narrow therapeutic window.
- Longer duration of action resulting in a reduction in dosing frequency.
- Increased convenience to administer drugs which would otherwise require frequent dosing.
- Improved bioavailability.
- Avoid inter and intra patient variation and enhance therapeutic efficacy.
- Flexibility of terminating the drug administration by simply removing patch from the skin.

**DISADVANTAGES\(^{[7,8]}\)**

- Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.
- Only small, lipophilic drugs can be delivered currently through the skin.
- Drug molecule must be potent because patch size limits amount that can be delivered.
- Not suitable for high drug doses.
- Adhesion may vary with patch type and environmental conditions.
- Skin irritation and hypersensitivity reactions may occur.
- Drugs that require high blood levels cannot be administered.
IDEAL PROPERTIES OF TRANSDERMAL PATCH

- The shelf life of the patches up to 2 years.
- The patch should be in small size (i.e. < 40cm²)
- Should provide convenient dose frequency (i.e. once a day or once a week)
- Cosmetically acceptable (i.e. clear, white colour).

ANATOMY OF SKIN

The skin is one of the most extensive organs of the human body covering an area of about 2m² in an average human adult. This multilayered organ receives approximately one third of all blood circulating through the body. Human skin comprises of three distinct but mutually dependent tissues.

(A) The stratified, vascular, cellular epidermis
(B) Underlying dermis of connective tissues
(C) Subcutaneous layer or hypodermis

Each layer has its own function and own importance in maintaining the integrity of skin and thereby the whole body structure.

Figure no.1 Structure of human skin

(A) The stratified, vascular, cellular epidermis

The multilayered epidermis varies in thickness depending on the cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Table 1 gives thickness, water permeability and diffusivity of water through epidermis. It consists of outer stratum corneum and viable epidermis. Epidermis results
from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards the skin surface. Below this layer are the other layers of the epidermis—the stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum. Together, these other layers constitute the viable epidermis.\textsuperscript{[12]}

\textbf{a. Stratum corneum}\textsuperscript{[13]}

This is the outermost layer of skin also called ashorney layer. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called as corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horney layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid mortar.

\textbf{b. Viable epidermis}\textsuperscript{[13]}

This is situated beneath the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface.

\textbf{(B) Dermis}\textsuperscript{[13]}

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier.

\textbf{(C) Hypodermis}

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

**STRATUM CORNEUM AS SKIN PERMEATION BARRIER**

The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per square centimeter. Especially watersoluble substances pass faster through these ducts; still these ducts do not contribute much for skin permeation. Therefore most neutral molecules pass through stratum corneum by passive diffusion. permeation of drug molecule through skin showed in Figure 2.

**Series of steps in sequence**

1. Sorption of a penetrant molecule on surface layer of stratum corneum.
2. Diffusion through it and viable epidermis and finally reaches to dermis and then
3. The molecule is taken up into the microcirculation for systemic distribution.

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.\(^{[13]}\)

**Figure no.2 A multilayer skin model showing sequence of transdermal permeation**

**DRUG PENETRATION PATHWAYS\(^{[14]}\)**

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages (shunt routes); through the intercellular lipid domains; or by a transcellular route (Figure 3). A particular drug is likely to permeate by a combination of
these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule.

![Permeation pathways through the skin](image)

**Figure no.3 Permeation pathways through the skin.**

(A) **The appendageal route**
Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skin’s surface area), therefore limiting the area available for direct contact of the applied drug formulation.

(B) **Transcellular route**
Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes containing highly hydrate keratin provide an aqueous environment from which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps.

(C) **Intracellular route**
The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons.
- Recalling the ‘bricks and mortar’ model of the stratum corneum, the inter-digitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route.
The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.

**MECHANISM OF ACTION OF TRANSDERMAL PATCH**\(^{[15]}\)

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

1. **Iontophoresis**

Iontophoresis passes a few milliamperes 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. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

2. **Electroporation**

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

3. **Application of ultrasound**

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.
4. Use of microscopic
Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 μm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.

TYPES OF TRANSDERMAL PATCH
1. Single-layer drug-in adhesive
The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

2. Multi-layer drug-in adhesive
The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.
3. **Reservoir system**
Unlike the Single-layer and Multi-layer Drug-inadhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

![Diagram of reservoir system](image)

4. **Matrix system**
The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

![Diagram of matrix system](image)

5. **Vapour patch**
In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

**FACTOR EFFECTING OF TRANSDERMAL PATCH**[^17]

1. **Physicochemical properties of permeant**
   a. **Partition coefficient**
The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.
b. Diffusion coefficient
Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

c. Drug concentration
The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

d. Molecular size and shape
Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

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

(B) Physiological factor
a. Skin condition
Chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

b. Skin age
The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS.

c. Blood flow
Changes in peripheral circulation can affect trans dermal absorption.

d. Regional skin sites
Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.
e. Skin metabolism
Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

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

**BASIC COMPONENTS OF TRANSDERMAL PATCH**\(^{[18]}\)

1. Polymeric matrix
The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

(a) Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

(b) The polymer should be stable.

(c) The polymer should be nontoxic

(d) The polymer should be easily of manufactured

(e) The polymer should be inexpensive

(f) The polymer and its degradation product must be non toxic or non-antagonistic to the host.

(g) Large amounts of the active agent are incorporated into it.

Types of polymer

(a) Natural polymers
Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

(b) Synthetic Elastomers
Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

(c) Synthetic polymers
Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy.

2. Drug
- Drug should have higher first pass metabolism.
- Drugs having narrow therapeutic window.
- Drugs with short half life.
Drugs with frequent dosing.
Low molecular weight moieties (<1000 Dalton)
Drugs with low dose (mg/day).
Low melting point substances (<200°C)
Drugs having affinity with both lipophilic and hydrophilic phases.
Drugs without any dermatological effect are suitable for formulation as transdermal patch.

3. Permeation enhancers
The stratum corneum is the principal barrier to drug permeation across the skin. Consequently, there has been a concerted effort to investigate and develop novel strategies of maximizing the amount of permeant crossing this barrier. Innovative approaches focus on altering the drug vehicle interaction to enhance partitioning into the stratum corneum or modifying the structure of the stratum corneum to make it less resistance to drug diffusion.

4. Backing laminates
- It is used to protect the patch from outer environment.
- They must be chemically resistant.
- They won’t allow to permeation of components in the patches.
- They have optimal elasticity, flexibility and tensile strength.
- It should have low water vapour transition rate.
- If a drug incorporated into a liquid (or) gel in the formulation, the backing material should be heat stable to allow fluid tight packing of drug reservoir (form-fill seal process). E.g. vinyl, poly ethylene and poly ester film.

5. Release linear
- It is removed during application of patch on skin.
- It should be chemically inert.
- It consists of two layers, one is base layer and other is release coating layer.
- The base layer may be occlusive (E.g. poly ethylene, poly vinyl chloride).
- The release coat layer made up of silicon (or) Teflon.
- The polyester foil and metallized laminate are also used as release liner.

6. Plasticizer
- They are used to provide plasticity to transdermal patch.
- This also chemically inert and compatible will all other ingredients in the formulation. 
  E.g. PEG, PG, tri-ethyl citrate, di-butyl phthlate.
- Some of the plasticizer also act as a permeation enhancer E.g. propylene glycol.

METHODS OF TRANSDERMAL PATCH[19]

1. Asymmetric TPX membrane method

Step 1
This membrane fabricated by using dry (or) wet inversion process. The required quality of TPX is taken and it is dissolved in a mixture of solvents and non-solvent additives. The temperature is maintained at 60°C. The polymer solution will form which is kept aside for 24 hours at 40°C. Then the polymer solution is cast on glass plate and the thickness is maintained by using gardener knife. After the casting, the film is evaporated for 30 seconds at 50°C. Then the glass plates are immersed in coagulation bath in the temperature maintained at 25°C. After 10 minutes the membrane is removed and it is dried on oven at 50°C for 12 hours.

Step 2
The drug is dispersed into the heat sealable polyesters film (1009, 3m) with a concave of 4cm diameter is used a backing laminate.

Step 3
Then it is covered by a TPX [poly (4-methyl-1-pentene)] asymmetric membrane, finally it sealed by using adhesive.

Circular Teflon method
The polymer solution is prepared by simple dissolving the polymers in organic solvents. Calculated amount of drug is dispersed (or) dissolved in the half the volume of same organic solvents which is used to prepare polymer solution. The other half of the organic solvents holds the enhancer. Then the polymer solution, drug solution and the enhancer mixture are added together and the Di-Nbutylphthalate is added to this mixture as a plastisizer.

The above mixture is stirred for 12 hours and it is poured in to circular Teflon mould which placed on a levelled surface and covers the funnel in invert position over the mould to control the vaporisation of solvent in laminar flow (hood model). The air speed is maintained at 0.5
m/s For 24 hours. Then the dry films are stored for another 24 hours in desiccators contain silic gel at 25+ 0.5°C. This type of film are evaluated which in one week of their formulation.

2. Mercury substrate method
In this method the drug is simply dissolved in polymer solution which is also contains plasticizer and other components. Then the solution mixture is stirred for 10-15 minutes which forms a homogenous dispersion and poured into a levelled mercury surface. The rate of evaporation is controlled by placing a funnel in an invert position over the surface.

3. By using IPM membrane method
The drug is dispersed in a mixture of solvents such as water and propylene glycol which already contains carboxer 940 polymers and stirred for 12 hours by using magnetic stirrer. Then add triethanolamine to above mixture causes the neutralisation and viscous solution (gel) the formed gel will be incorporated on the IPM membrane.

4. By using EVAC membrane method
It is majorly used to formulate the target transdermal drug delivery system. Other than ethylene vinyl acetate co polymer (EVAC) membrane, the poly ethylene (PE) membrane, 1% carbopol reservoir gel membrane gel membrane are also used for target transdermal drug delivery system. If the drug is water soluble, the water is used as solvent otherwise the propylene glycol is used for the formulation of gel. The drug is dissolved in solvent and carbopol resin is added to above solution which is neutralised by 5% sodium hydroxide solution. Then the gel is placed in the sheet of backing laminate. And finally the rate controlling EVAC membrane is placed over the gel. The leak proof device is obtained by sealing of the patch on its edges by using thermal energy.

5. By using free film method
The free film of the cellulose acetate is prepared by casting on the mercury surface. 2% w/w polymer solution is prepared by using chloroform. plasticizer is accurately weighed (40%w/w of polymer weight) and added to polymer solution. 5ml of polymer solution placed on mercury sulphate in a glass petridish. After the evaporation of solvent the free film formulation on mercury surface was observed. The dry film is collected and it is stored between the sheets of wax paper in a desiccators. Free films can be developed with different thickness by changing the volume of polymer solution.
EVALUATION OF TRANSDERMAL PATCH\textsuperscript{[20,21,22]}

1. Physicochemical evaluation

a. Thickness of patch

The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

b. Drug content analysis

An accurately weighed portion of formulated patches is dissolved in a suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 hours by using shaker incubator. Then the solution is sonicated and it is filtered. Then the filtrate is analysed by using suitable techniques such as UV (or) HPLC etc., with proper dilution.

c. Percentage moisture content

The formulated patches are weighed individually and kept in a desiccators containing anhydrous calcium chloride at room temperature for 24 hours. After the 24 hours the patches are weighed at a specific time interval until the constant weight is obtained. The percentage moisture loss is calculated by using following formulae.

\[
\text{Percentage moisture loss} = \left(\frac{\text{Initial wt} - \text{final wt}}{\text{initial wt}}\right) \times 100
\]

d. Uniformity of weight

Before done the weight uniformity test the formulated patches were dried at 60\(^{0}\)c for 4 hours. A specified area of the patch is to be cut in different parts of patch and it is weighed in digital balance. The average weight and standard deviation values are to be calculated from individual weights.

e. Folding endurance

A specific area of the patch is cut evenly and folds it repeatedly at the same place till it broke. The number of folding is noted before the breaking of patch. It will give the folding endurance.

f. Fatness

A transdermal patch should possess a smooth surface which not constrict with time. It can be studied by flatness test. In this test, one strip is cut from centre and two strips are cutted from right and left sides. The length of each strip is measured. The variation in length is measured by percentage constriction. If the percentage constriction is 0\%, it indicates 100\% flatness.
% construction = (initial length - final length)/initial length x 100

g. **Probe tack test**
The measurement of the force which is required to pull the probe away from the adhesive lower at fixed rate. It is expressed in grams.

2. **In vitro evaluation**[^23][^24]
The *in-vitro* permeation study of fabricated transdermal patches of was carried out by using excised rat abdominal skin and franz diffusion cell. The skin was sandwiched between donor and receptor compartments of the diffusion cell. A 2.2 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 5°C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24 h, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. Then the samples were analyzed spectrophotometrically at 258 nm.

3. **In vivo evaluation**[^25]
In vivo evaluation study are 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
- Human volunteers

The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc.

**APPLICATION OF TRANSDERMAL PATCH**[^26]
- Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Nitroglycerine patches are also sometimes prescribed for the treatment of Angina.
Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflammatory drug are also available in the form of transdermal patches.

Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.

Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD)

REFERENCES


