TRANSDERMAL DRUG DELIVERY SYSTEM: A TOOL FOR NOVEL DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Transdermal drug delivery system is a formulation that is applied to the body surface and is designed to deliver the active drug across the skin, into the systemic circulation. The advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Skin is an effective medium for absorption of the drug takes place and enters the circulatory system. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product.

Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Enhancement via modification of the stratum corneum by hydration, chemical enhancers acting on the structure of the stratum corneum lipids and keratin, partitioning and solubility effects are also discussed. Thus the aim of this review work is to focus on the recent innovations in Transdermal Drug Delivery Systems which can be a platform for the research and development of Pharmaceutical drug dosage form for Transdermal Drug Delivery. The main disadvantage to Transdermal delivery systems stems from the fact that the skin is a very effective barrier as a result, only medications those molecules are small enough to penetrate the skin can be delivered in this method.

Keywords: - TDDS, Transdermal patches, Permeation enhancers.
INTRODUCTION
The new idea several Transdermal drug delivery systems have recently been developed, aiming to achieve the objectives of systemic medications through topical applications to the intact skin surface \[^{[1]}\]. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered \[^{[2]}\]. The skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis, and into the blood circulation. The skin behaves as a passive barrier to the penetrate molecule \[^{[3]}\]. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption. Penetration enhancers are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea \[^{[4]}\]. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy. Transdermal delivery systems are topically administered medicaments in the form of patches (or semisolids) that deliver drugs for systemic effects at a predetermined and controlled rate. \[^{[5]}\]

**Merits** \[^{[5, 6]}\]
- It avoid first pass metabolism presystemic and systemic.
- It is removed can be quickly terminated by removal of the patch from the skin.
- It provides ease of rapid identification of medication in emergencies non-responsive patients, unconscious or comatose patients.
- It provides steady permeation of drug across the skin, allowing consistent serum drug level.
- It permits self-administration
- It has fewer side effects
- It increases the therapeutic value of many drugs via avoiding specific problems associated with the drug. E.g. GI irritation, lower absorption, decomposition due to ‘hepatic first pass’ effect.
- It is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if e.g. the drug is given orally.
- It improved patient compliance and reduced inter and intra-patient variability
- It provides stable and controlled blood level.
- Long duration of action ranging from a few hours to one week.
- These dosage form is suitable for administration of drugs having-
  i. Very short half life, e.g. Nitroglycerine.
  ii. Narrow therapeutic window.
  iii. Poor oral availability.

**Demerits** [5, 6]
- It causes skin irritation and allergic response.
- Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.
- Heavy drugs molecules (>500 Daltons) usually difficult to penetrate the stratum corneum.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- Drugs that are highly melting can be given by this route due to their low solubility both in water and fat.
- Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy.
- This route is unsuitable when
  i. Drug dose is large.
  ii. Drug is skin sensitizing and irritating.
  iii. Drug is metabolized in skin.
  iv. Drug undergoes protein binding in skin.
  v. Drug is highly lipophilic or hydrophilic.
STRUCTURE OF SKIN \[3, 7, 8\]

![Fig.1: Structure of Skin](image)

The skin can be considered to have four distinct layers of tissue shown in fig [1].

**Non-viable epidermis (stratum corneum):** Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. The stratum corneum of the multilayered epidermis varies in thickness, ranging from about 0.8 mm on the palms and soles to 0.006 mm on the eyelids. Each cell is a flat, plate-like structure - 34-44 µm long, 25-36 µm wide, 0.5 to 0.20 µm thick - with a surface area of 750 to 1200 µm stocked up to each other in brick like fashion. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

**Viable epidermis:** This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50- 100 µm. The structure of the cells in the viable epidermis is physiochemical similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%. Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histological in normal tissue. Dermis (corium) thickness range from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous tissue (collagen, elastin and reticulin) that are embedded in an amorphous ground substance of mucopolysaccharide.
Subcutaneous connective tissue: The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

Penetration into skin $^{[9,10]}$
Molecules moving from the environment must penetrate the stratum corneum and any material of endogenous or exogenous origin on its surface. They must then penetrate the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, where upon they are removed from the skin by flow of blood or lymph. To move across the skin membrane is obviously a complex phenomenon and challenge in analysis.

FACTORS THAT INFLUENCE TRANSDERMAL DRUG DELIVERY $^{[11,12,13]}$

Biological factors include
1. Skin condition
2. Skin age
3. Blood flow
4. Regional skin sites
5. Skin metabolism
6. Species differences

Physiological factors include
1. Skin hydration
2. Temperature and pH
3. Diffusion coefficient
4. Drug concentration
5. Partition coefficient
6. Molecular size and shape

THE COMPONENTS USED FOR THE PREPARATION OF TDDS $^{[14,15,16,17]}$

Drug
- The drug molecular weight less than approximately 1000 Daltons.
- The drug must low melting point
The shelf life of drug up to only 2 yrs.

- The drug particle size must be $<40cm^2$
- The drug molecule would require a balanced partition coefficient to penetrate the skin.
- The drug have adequate solubility in oil and water (water solubility $>1$ mg/ml and oil solubility $>1$ mg/ml)
- Drug is in direct contact with release liner. Ex: Nicotine, Methotrexate and Estrogen.

**Polymer matrix**

- The polymers control the release of the drug from the drug reservoir. Both the synthetic and natural polymers are used examples as follows
- Synthetic polymers: polyamide, polyvinyl alcohol polyethylene, Polyurea, polypropylene, polymethylmethacrylate etc.
- Synthetic Elastomers: e.g. polybutadiene, hydrid rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc.
- Natural polymers: gelatin, waxes, shellac, starch, gums, etc.

**Permeation enhancers**[^14]

- These include water, fatty acids and alcohols, azone and its derivatives, pyrolidones, alcohols and glycols, terpenes and derivatives, essential oils, sulfoxides like dimethyl sulfoximide and their derivatives, urea and surfactants.

**Mechanism:** They act by three mechanisms:

1. Reduces the resistance of stratum corneum by altering its Physicochemical properties.
2. Alteration of hydration of stratum corneum.
3. Affecting the structure of lipids and protein in inter cellular channel through solvent action or denaturation and sometimes carrier mechanism is observed.

**Adhesive**

- Serves to adhere the patch to the skin for systemic delivery of drug. Ex: Silicones, Polyisobutylene.

**Backing layer**

- Backing layer protects patch from outer environment. Ex: Cellulose derivatives, Polypropylene silicon rubber[^15, ^16].
CLASSIFICATION OF TRANSDERMAL DRUG DELIVERY SYSTEM\textsuperscript{5,14} 

Transdermal DDS

Rate programmed systems (transdermal patches)  
Physically stimuli activated system

- Drug in reservoir
- Drug in matrix
- Drug in adhesive
- Drug in microreservoir

- Structure based systems
- Velocity based systems
- Electrically based systems
  - Iontophoresis
  - Electroporesis
  - Sonophoresis
  - Photomechanical waves

Some features are common to all TDDS and these includes-

a. Release liner: a protective cover that is peeled away before applying the patch.
b. Pressure sensitive adhesive.
c. Impermeable backing layer.

![Different parts of Transdermal Patch](image)

**Fig.2: Different parts of Transdermal Patch**

All these components are compatible with each other and for successful product.

1. Reservoir System (Membrane Moderated TDDS)

The drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be microporous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can
be applied. The rate of drug release from this type of transdermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate controlling membrane. A requirement for a reservoir system is that it should permit zero order release of the drug over the delivery period.

2. **Matrix System: Matrix Dispersion System (Matrix Diffusion Controlled System)**

The drug is dispersed homogeneously in a hydrophilic or lipophillic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim.

3. **Matrix System: Drug in Adhesive System (Adhesive Diffusion Controlled TDDS)**

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive onto an impervious backing layer. The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlling drug delivery system. Such system have certain disadvantage-

i. Incorporation of other excipients, such as skin permeation enhancers, into a drug in adhesive system may alter drug release rates and adhesive properties.

ii. The physicochemical characteristics of drug and adhesive system may provide very different release rates for hydrophilic and hydrophobic.

4. **Micro reservoir System**

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophillic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ. A transdermal system therapeutic system thus formed as a medicated disc positioned at the centre and surrounded by an adhesive rim.
5. Electrically-based system [6, 14, 18, 19]

i. Iontophoresis

It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Parameters that affect design of an iontophoretic skin delivery system include electrode type, Current intensity, pH of the system, competitive ion effect, and permeant type.
ii. Ultrasound

Ultrasound involves the use of ultrasonic energy to enhance the Transdermal delivery of solutes either simultaneously or through pretreatment, and is frequently referred to as sonophoresis. In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

![Ultrasound Diagram]

Fig.5: Ultrasound

iii. Photomechanical Waves

Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

iv. Electroporation[14]

It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, Peptides, an oligo nucleotides). For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.
v. Electro-Osmosis
To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

6. Velocity based system
a. Needle-Free Injections
   - Intraject
   - Implaject
   - Jet Syringe
   - Iject
   - Mini-ject
b. Powder ject Device
The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.

**EVALUATION PARAMETERS** [14, 17, 20, 21]
The system is evaluated in following ways:
A. Evaluation of adhesives
Pressure sensitive adhesives forms a bond by the application of light pressure. Pressure sensitive adhesives are evaluated for the following properties.
• **Peel adhesion properties**

Peel adhesion is the force required to remove an adhesive coating from a test substrate. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. Measuring the force required to pull a single coated tape applied to a substrate at a 180º angle tests it. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular wt of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at a 1800 angle. No residue on the substrate indicates ‘adhesive failure’ which is desirable for transdermal devices.

• **Tests for tack properties**

Tack is the ability of polymer to adhere to a substrate with little contact pressure. Following are the tests for the tack properties:

i. **Thumb tack test:** It is a qualitative test applied for tack property determination of adhesive. the thumb is pressed briefly into the adhesive does evaluation.

ii. **Rolling ball tack test:** This test involves measurement of the distance. 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. This method quantifies the ability of an adhesive to quickly adhere to another surface. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

iii. **Probe Tack test**

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

iv. **Quick stick test:** The peel force required to break the bond between an adhesive and tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.
• **Shear strength properties**

Shear strength is the measurement of the cohesive strength of an adhesive polymer. It 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; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

**B. In vitro evaluation**

In vitro studies can help in investigating the mechanisms of skin permeation of the drug. It is generally considered valid to use excised skin in *In Vitro* studies because the stratum corneum which is physiologically inactive tissue is the barrier to the permeation of the drug and diffusion through the stratum corneum is a passive process. The release and skin permeation kinetics of a drug from this delivery system can be evaluated by using a 2 compartment diffusion cell assembly, under identical conditions. It is carried out by mounting individually, the full thickness abdominal skin which has been freshly excised from either human cadaver or hairless skin on diffusion cell. The drug delivery system is then applied with their drug releasing surface in intimate contact with the stratum corneum surface of the skin. The skin permeation profile of drug is followed by sampling the receptor solution at predetermined intervals and assaying the drug concentration in the samples by a sensitive analytical method, such as UV or HPLC. The examples of diffusion cells used for these studies are Franz diffusion cell or vertical diffusion cell, Kesary chein cell.

The assembly of Franz diffusion cell is given below.

![Fig.7: Franz diffusion cell](image-url)
C. **In vivo evaluation**

*In Vivo* evaluation of transdermal drug delivery system can be carried out using:

a. Animal models  

b. Human volunteers  

c. Biophysical methods.

D. **Thickness of the patch**

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

E. **Weight uniformity**

The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

F. **Folding endurance**

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

G. **Percentage Moisture content**

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula. 

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

H. **Percentage Moisture uptake**

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

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

I. **Water vapour permeability (WVP) evaluation**

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following
formula WVP=W/A Where, WVP is expressed in gm/m² per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m².

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

K. Uniformity of dosage unit test
An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from 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 suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2m membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

L. Skin Irritation study
Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm²) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

M. Stability studies
Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

APPLICATION OF TDDS

- The antihypertensive drug like clonidine and ketoprofen, the non-steroidal anti-inflammatory drug are also available in the form of transdermal patches.
Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis.

Other transdermal patches for hormone delivery include the contraceptive patch.

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

Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl and Buprenorphine.

Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

CONCLUSION
The above article on transdermal drug delivery system has great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system and Due to large benefit of the TDDS, many new researchers are going on in the development of transdermal dosage forms of newer drug via this system in the present day.

REFERENCES
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