A COMPREHENSIVE REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM

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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. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. 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 bloodstream. Delivery of drugs through the skin has been always a challenging area for research due to barrier properties exhibit by the outermost layer of skin stratum corneum. In the last two decades, the transdermal drug delivery system has become a proven technology that offers significant clinical benefits over other dosage forms. Because transdermal drug delivery offers controlled as well as predetermined rate of release of the drug into the patient, it able to maintain steady state blood concentration. It’s a desirable form of drug delivery because of the obvious advantages e.g. Convenient and pain-free self-administration for patients, avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs over other routes of delivery. The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS.

KEYWORDS: Convenient, First pass metabolism, Patches, Steady state, Stratum corneum, Transdermal drug delivery systems.
INTRODUCTION
Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. 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. Transdermal delivery provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first pass metabolism respectively.[1] 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. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Trans mucosal delivery systems etc. emerged. 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, Transdermal-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea. 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.[2]

DEFINITION: A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. Today the most common transdermal system present in the market mainly based on semipermeable membranes which were called as patches.[3]

ANATOMY AND PHYSIOLOGY OF SKIN
Human skin comprises of 3 distinct but mutually dependent tissues
A) The stratified, vascular, cellular epidermis
B) Underlying dermis of connective tissues and
C) Hypodermis.
A. **EPIDERMIS**: The multilayered epidermis varies in thickness, depending on 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. It consists outer stratum corneum and viable epidermis.

a) **Stratum corneum**: This is the outermost layer of skin also called as horny layer. It is approximately 10µm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar.” The lipids are arranged in multiple bilayers. There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form.

b) Viable epidermis: 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 basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

B. **DERMIS**: 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. The blood supply thus keeps the dermal concentration of a permeant very low and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation.

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.\(^\text{[4]}\)

FUNDAMENTALS OF SKIN PERMEATION

Until the last century the skin was supposed to be impermeable with exception to gases. However, in the current century the study indicated the permeability to lipid soluble drugs. Also it was recognized that various layers of skin are not equally permeable i.e. epidermis is less permeable than dermis. After a large controversy, all doubts about stratum corneum permeability were removed and using isotopic tracers, it was suggested that stratum corneum greatly hamper permeation.

A. Stratum corneum as skin permeation barrier.

The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per square centimeter. Especially water-soluble substances pass faster through these ducts; still these ducts don’t contribute much for skin permeation. Therefore most neutral molecules pass through stratum corneum by passive diffusion.

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.

B. 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.\(^\text{[5]}\)

C. Permeation pathways.
Percutaneous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route.

1. **Appendageal route:** Appendageal route comprises transport via sweat glands and hair follicles with their associated sebaceous glands. These routes circumvent penetration through the stratum corneum and are therefore known as “shunt” routes. This route is considered to be of minor importance because of its relatively small area, approximately 0.1 % of the total skin area.

2. **Epidermal route:** For drugs, which mainly cross-intact horny layer, two potential micro routes of entry exists, the transcellular (intracellular) and intercellular pathways.

   i) **Transcellular:** Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds and endocytosis and transcytosis of macro molecules.

   ii) **Paracellular:** Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient (log k). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs. [6]

**SKIN AS A SITE FOR DRUG INFUSION**

The skin is the largest organ of the body. The skin an average adult body is about 20 square feet and it received about one third of total available blood. The skin is multi layered organ composed of three histological tissues.

1. The outermost layer of skin, epidermis is which provides a waterproof barrier and creates our skin tone.

2. Dermis, beneath epidermis, contains tough connective tissue, hair follicles, and sweat glands and

3. Deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue. [7]
There are main three pathways through which foreign particles diffused or penetrate into skin.

1. Transcellular/Intracellular permeation through the stratum corneum.
2. Intercellular permeation through the stratum corneum.
3. Trans appendageal permeation via the hair follicles, sweat and sebaceous gland.\(^8\)

**Mechanism of transdermal permeation**

Transdermal permeation of a drug moiety involves the following steps.

1. Sorption by stratum corneum
2. Permeation of drug through viable epidermis
3. Uptake of the drug moiety by the capillary network in the dermal papillary layer.
4. The drug must possess some physicochemical properties to reach target site via systemically through stratum corneum. The rate of permeation of drug moiety across the skin is governed by following equation.

\[
\frac{dQ}{dT} = P_s (C_d - C_r)
\]

Where, \(C_d\) = concentration of penetrate in the donor phase (on the surfaced of skin); 
\(C_r\) = concentration of penetrate in the receptor phase (body); and

\(P_s\) is the overall permeability coefficient of the skin which is defined as

\[
P_s = \frac{K_s}{h_s} D_{ss}
\]

Where, \(K\) = Partition coefficient of the penetrant; 
\(D_{ss}\) = Apparent diffusivity of penetrant; 
\(h_s\) = Thickness of skin.
A constant rate of drug permeation achieved, if \( C_d > C_S \) the equation reduced as.

\[
\frac{dQ}{dt} = P_S C_d
\]

the rate of skin permeation (dQ/dt) becomes a constant, if the C value remains fairly constant throughout the course of skin permeation To maintain the \( C_d \) at a constant value, it is critical to make the drug to be released at a rate (\( R_r \)) which is always greater than the rate of skin uptake (\( R_a \)), i.e., \( R_r >> R_a \).

Schematic representation of the relationship between the rate of drug release (\( R_r \)) from a transdermal system and the rate of release of absorption (\( R_a \)) by the skin\(^{[11]}\)

By doing so, the drug concentration on the skin surface (\( C_d \)) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum...
corneum ($C_{se}$), i.e., $C_d > C_e$; and maximum rate of skin permeation ($dQ/dt)_m$ as expressed by equation.

$$\frac{dQ}{dt}_m = P_s C_{se}$$

Apparently, the magnitude of $(dQ/dt)_m$ is determined by the skin permeability coefficient ($P_s$) of the drug and its equilibrium solubility in the stratum corneum ($C_{se}$).[9]

**BENEFITS**

**LIMITATIONS**

1. The drug moiety must possess some physicochemical properties for penetration through skin and if dose of drug is large i.e. more than 10-25mg/day transdermal delivery is very difficult.
2. Local irritation at the site of administration such as itching, erythema and local edema may be caused by drug or the excipients used in the formulations.
3. The barrier function of the skin changes from one site to another, from person to person and with age. Poor skin permeability limits the number of drugs that can be delivered in this manner.
4. A high drug level cannot achieve by this system.
5. Transdermal drug delivery is unable to deliver ionic drugs.
6. Transdermal drug delivery system is restricted to potent drug.[14]
7. Tolerance inducing drugs or those (e.g., hormones) requiring chrono pharmacological management is not suitable candidates.
8. Drug molecule having large molecular size (>1000Dalton) cannot developed for transdermal delivery.
9. Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea. 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.[15]

**Polymer matrix or matrices**

Polymers are the foundation of transdermal system. The selection of polymer and design are of prime importance.

Considerations for polymer selection in transdermal delivery system.

- Should be stable and non-reactive with the drug moiety.
- Easily available, fabricated and manufactured in to desired formulations.
- The properties of polymer e.g. molecular weight glass transition temp. Melting point and chemical functionality etc. should be such that drug can easily diffused through it and with other components of system.
- Mechanical properties should not change if large amount of drug incorporate.
- Should provide consistent release of drug throughout the life of system.[16]

The polymers used in transdermal system are.

**Natural Polymers**: e.g. Zein, gelatin cellulose derivatives, gums, natural rubber, shellac, waxes and chitosan etc.

**Synthetic Elastomers**: e.g., Hydrin rubber, poly isobutylene, poly butadiene, silicon rubber, nitrile, neoprene, butyl rubber, acrylonitrile etc.

**Synthetic Polymers**: e.g. polyvinylchloride, polyethylene, polyvinyl alcohol, polypropylene, polyamide, poly acrylate, poly urea, polyvinyl pyrrolidone, poly methyl methacrylate etc.[17]

<table>
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<tr>
<th>Natural Polymers</th>
<th>Synthetic Elastomers</th>
<th>Synthetic Polymers</th>
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<tbody>
<tr>
<td>Cellulose derivatives, Zein, Gelatin, Waxes, Proteins, Gums, Natural rubber, Starch</td>
<td>Poly butadiene, Neoprene, Hydrin rubber, Butyl rubber, Poly siloxane, Acrylonitrile, Silicon rubber, Styrene butadiene,</td>
<td>Polyethylene, Polypropylene, poly acrylate, polyamide, Poly methyl methacrylate, Epoxy, polyvinyl pyrrolidone, Poly urea.</td>
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**Polymers used in transdermal system in versatile manner such as.**

1. **Rate controlling membrane**: It control the release of drug by disperse through an inert polymer matrix. The polymer powder blended with drug moiety by physical manner and then moulded in to desired shape with required thickness and surface area.

2. **Adhesive**: make an intimate contact between the skin and transdermal system. It carries the drug which is dissolved or dispersed in solution or suspension form. The quality of drug diffused in to skin depending on the holding power..

3. **Pressure sensitive adhesive**: Hitherto the rapidity of transdermal system can be done by pressure sensitive adhesive. The three most commonly used adhesives are poly isobutylene, poly acrylate and silicones in TDD devices.

4. **Release liners**: The patch is covered by protective liner during storage until it is used. The release liner removed and discarded just before the application of patch over the skin since release liner is in intimate contact with the transdermal system hence it should be physically as well as chemically inert. The release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. poly ethylene,
polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used as release liner in transdermal patches include polyester foil and metalized laminate.

5. **Backing laminate:** While design the backing layer following points must be in consideration.
   - Must be flexible and Non irritant.
   - Having low water vapour transmission rate so as to promote skin hydration and thus greater skin permeability of drug.
   - Should be compatible with transdermal system as remain in use while applying.
   - Should be chemical resistance.
   - Having good tensile strength.

Examples of backings laminate are polyethylene film, poly ester film, and polyolefin film, and aluminum vapour coated layer.

6. **Drug:** Various physicochemical, pharmacokinetic and pharmacological properties of the drug should be considered for transdermal system development. Because of the limited permeability of the skin, drugs have to be transdermally delivered by passive diffusion through the skin, and are limited by several substantial constraints. The drug moiety for transdermal system should be potent (dose in mg), having molecular weight \( \leq 1000 \text{ Da} \), adequate solubility in the vehicle, \( \log P \) value of \(< 5\), melting point of \(200^{\circ}\text{C}\) and appropriate lipophilicity, undergo extensive presystemic metabolism, non-ionic and non-irritant are considered as suitable candidates for delivery via this route.

7. **Penetration enhancers:** Compounds which promote the penetration of topically applied drugs are commonly referred as absorption promoters, accelerants, or penetration enhancers. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus allow the drug to penetrate to the viable tissues and enter the systemic circulation.

8. **Desired properties for penetration enhancers.**
   - It should be non-irritant, non-sensitizing, non phototoxic, and non-comedogenic.
   - Onset of action should be rapid and duration of activity should be predictable & reproducible.
   - Have no pharmacological activity in the body i.e. should not bind to the receptor site.
   - The barrier function of the skin should reduce in one direction only.
The accelerants should be chemically and physically compatible with all drugs and adjuvants to be formulated in topical preparations and devices.

- It should be inexpensive, tasteless and colourless,
- It should have a desired solubility parameter that approximates that of skin.
- It should adhere and spread well on the skin with a suitable skin feel.
- Some of the examples of the widely used classical enhancers involve various classes that include water, hydrocarbons alcohols, acids amines, amides, esters, surfactant terpenes, terpenoid sand essential oil, sulfoxides, lipids and miscellaneous such as cyclodextrin derivatives, chitosan etc.

Other excipients

**Plasticizers:** Plasticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Along with the brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other surfaces or membranes and improvement in strength of film. Some of its examples are glycerol or sorbitol, at 15%,w/w, dry basis, phosphate, phthalate esters, fatty acid esters and glycol derivatives such as PEG 200, and PEG 400.

**Solvents:** Various solvents such as methanol, chloroform, acetone, isopropanol and dichloromethane etc. are used to prepare drug reservoir. \[^{18}\]

**TYPES OF TRANSDERMAL PATCHES**

**Single-layer drug-in-adhesive**

In this system drug and excipients is inclusive with skin adhesive which serve as formulation foundation as a single breaking layer. The rate of release of drug through diffusion phenomenon.

\[
\frac{dQ}{dT} = \frac{C_r}{P_m P_a} \tag{1}
\]

Where \(C_r\) = drug concentration in reservoir compartment;
\(P_a\) = Permeability coefficient of adhesive layer;

\[
P_m = \frac{1}{\sqrt{\Delta T}}
\]
$P_m = \text{Permeability coefficient of rate controlling membrane}$

**Multi-layer drug-in-adhesive**

In this system drug and excipients incorporated with adhesive but both layer of adhesive separated by single layer membrane. The released of drug occurred through diffusion phenomenon.

Multi-layer drug in adhesive patch and its different component

The rate of release of drug is governed by following equation

$$\frac{dQ}{dt} = \frac{K_a D_a}{h_a} C_r$$

Where $K_a/r = \text{partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.}$

**Drug reservoir-in-adhesive**

In the reservoir system, inclusion of liquid compartment containing drug solution/suspension between baking layer and semipermeable membrane followed by adhesive layer and release liner.

Drug reservoir in adhesive patch and its different component

The rate of drug release from this drug reservoir system is given by

$$\frac{dQ}{dt} = \frac{K_a D_a}{h_a(t)} A (h_a)$$

Where $h_a = \text{thickness of adhesive layer;}$

$A = \text{thickness of diffusional path}$
Drug matrix-in-adhesive.
This system is designed by inclusion of semisolid matrix having drug in solution or suspension form which is in direct contact with the release liner.

![Diagram of Drug Matrix-Adhesive System]

Single layer drug in adhesive patch with its different component

The rate of release of drug is governed by following equation.

\[
\frac{dQ}{dT} = \frac{AC_pD_{p}^{1/2}}{2t}
\]

Where
- \(A\) = the initial drug loading dose dispersed in the polymer matrix;
- \(C_p\) = solubility of the drug;
- \(D\) = diffusivity of the drug in the polymer\(^{[19]}\)

TDDS Classification Based On Their Technical Sophistication.

These are classified into 4 types.

They are.

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

A) Rate Pre Programmed Drug Delivery System

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

1. Polymer membrane permeation controlled drug delivery system- It involves the system in which the drug is enclosed within a drug reservoir. This is covered by the semipermeable membrane of polymer that regulates the intestinal targeted controlled release gastrointestinal device and gel diffusion controlled drug delivery system.\(^{[20]}\)

2. Polymer matrix diffusion controlled drug delivery system- It is developed by dispersing drug particles in carrier matrix (in a homogenous manner) that is rate controlling i.e.
NitroDur. It is designed for application onto intact skin for 24 hrs that provide consistence transdermal infusion of nitroglycerine.\(^{[21]}\)

3. Microreservoir partitioned controlled drug delivery system - It involves dispersion of micro particles of suspension of drug (aqueous in nature) in a polymer using high energy dispersion. e.g. Syncromate implant. Engineered to deliver subdermal administration of norgestomet.

B) Activation Modulated Drug Delivery System
This type of delivery system can be achieved by.

1-Physical means
- Osmotic pressure activated drug delivery system.
- Hydrodynamic pressure controlled drug delivery system.
- Vapour pressure activated drug delivery system.
- Mechanically activated drug delivery system.
- Magnetically activated drug delivery system
- Electrically activated drug delivery system.
- Ultrasound activated drug delivery system.
- Hydration activated drug delivery system.

2-Chemical means
- pH activated drug delivery system
- Ion activated drug delivery system
- Hydrolysis activated drug delivery system

3-Biochemical means
- Enzymes activated drug delivery system\(^{[22]}\)

C) Feedback Regulated Drug Delivery System
The release of the drug molecules from the transdermal system is facilitated by an agent that triggers the release of drug, such as bio chemicals in the body and also regulated by its concentration through some feedback mechanism.
- Bio-erosion regulated drug delivery system.
- Bio responsive drug delivery system.
- Self-regulated drug delivery system.
D) Carrier Based Drug Delivery System

Colloidal particulates carrier system: This involves vesicular system like hydrogels, liposomes, niosomes, nanocapsules, nanoparticles, polymeric complexes, microspheres, nanoerythrosomes, transferosomes, dendrimers, aquasomes, etc. [23]

VARIOUS METHODS FOR PREPARATION TDDS

a. Asymmetric TPX membrane method: A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly(4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

b. Circular teflon mould method: Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation. [24]

c. Mercury substrate method: In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation. [25]

d. By using IPM membranes method: In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane. [26]

e. By using EVAC membranes method: In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not
soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.[27]

f. Aluminium backed adhesive film method: Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved.[28]

g. Preparation of TDDS by using Proliposomes: The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.[29]

h. By using free film method: Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.[30]
RECENT TECHNIQUES FOR ENHANCING TDDS

A) STRUCTURE-BASED ENHANCEMENT TECHNIQUES

1. Transdermal Patches: A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation. The adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the stickyness of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied again and again.[31]

Components of Transdermal Patch

Liner - Protects the patch during storage. The liner should be removed before its use.

Drug - Drug solution is in direct contact with release liner.

Adhesive - It serves to adhere the components of the patch together along with adhering the patch to the skin. E.g.- Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications. For applications in which the adhesive, the drug, and perhaps enhancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).

Membrane - It controls the release of the drug from the reservoir and multi-layer patches.

Backing - The film protects the patch from the outer environment.

Requirements for pressure sensitive adhesives (PSAs)

Several classes of PSAs are used for skin contact application include acrylics, polyisobutylene and silicone polymers. The functional properties of PSAs such as tackyness, adhesive property, release force, and cohesive strength as well as adhesive formulations having attributes such as enhanced drug flux and skin friendliness. A PSA must be able to performance effectively under a wide range of temperatures, humidity levels, and application frequency.[33]

2. Micro fabricated Microneedles: These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the membrane. The systems consists of a drug reservoir and a some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug. Microneedles are tiny and very sleek
devices that are manufactured by the silicon etching technology and micro-mechanical system manufacturing (MEMS) technique, which do not penetrate deep enough into the skin to reach up to the nerve endings and thus there is no pain sensation during the microneedles insertion into the skin. There are number of delivery approaches that have been employed to use the microneedles for TDDS. These includes.

**Poke with patch approach** - Involves piercing into the skin followed by application of the drug patch at the site of treatment.

**Coat and poke approach** - Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

**Biodegradable microneedles** - Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

**Hollow microneedles** - Involves injecting the drug through the needle with a hollow bore.[34]

3. **Macroflux:** These are devices having an area of around 8cm as well as 300 micro projections per cm² with the length of individual micro projection less than 200μm. Three types of Macroflux have been designed. They include, Dry-Coated Macro flux system—this is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.

4. **Metered-Dose Transdermal Spray (Mdt)**: It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come nonvolatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin.[35]

**B) ELECTRICALLY-BASED ENHANCEMENT TECHNIQUES**

1. **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. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia.[36]
2. Ultrasound
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.

3. 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.

4. Electroporation
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.

5. 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.

C). VELOCITY BASED ENHANCEMENT TECHNIQUES
1. Needle-Free Injections
   - Intraject
   - Implantject
   - Jet Syringe
   - Iject
   - Mini-ject

2. Powderject 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.
D) OTHER ENHANCEMENT TECHNIQUES

1. Transfersomes
This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

2. Medicated Tattoos
Med-Tats is a modification of temporary tattoo which contains an active drug substance for tranadermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

3. Skin Abrasion- This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules is generally known as Micro scissuining.

4. Controlled Heat Aided Drug Delivery (CHADD) System
It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

5. Laser Radiation
This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. Removal of the stratum cornea by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

6. Magnetophoresis
The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.[37]

EVALUATION OF TRANSDERMAL SYSTEM

Interaction studies: The drug and polymer compatibility was characterized by means of FTIR spectroscopy. The compatibility was checked by making physical mixture of drug and polymer (1:1) and then the FTIR analysis of the mixture was done. The peaks should not be
changed in FTIR spectra of mixtures, and it should be similar to the pure drug and polymer FTIR spectra.

**Physical evaluation of transdermal system**

**Film thickness:** The thickness of film is measured by using micro meter, electronic vernier callipers, with a least count of 0.01mm, dial gauge, or screw gauge. Thickness is measured at five different points on the film and average of five readings is taken.

**Percentage flatness:** Film is cut in to strips, two from either end or one from the center. The length of these strips is measured to the nearest centimetre without applying any additional pressure. The percentage flatness of the strips is selected as the average per cent of length calculated from the 7 cm strips. Zero percent constriction is equivalent to 100 percent flatness.

\[
\text{% constriction} = \frac{(\text{initial length}-\text{final length})}{\text{initial length}} \times 100
\]

**Tensile strength:** The tensile strength can be determined by using a modified pulley system. Weight is gradually increased so as to increase the pulling force till the patch breaks. The force required to break the film is considered as tensile strength and it is calculated as kg/cm2.

\[
\text{Tensile strength} = \frac{\text{Tensile load}}{\text{cross section}} \times \text{area}
\]

**Patch thickness:** Patch thickness can be measured by using digital micrometer screw gauge at three different points and the mean value is calculated.

**Elongation break test:** The elongation break is to be determined by noting the length just before the break point.

**The elongation break can be determined by the formula**

\[
\text{Elongation break} = \frac{(\text{Final length}-\text{Initial length})}{\text{Initial length}}
\]

**Weight uniformity:** weight uniformity is studied by randomly selected patches about 10 in number. A specified area of patch is to be cut in different parts of the patch and weighed in a digital balance. Calculate average weight and standard deviation value from the individual weights. Such determination is performed for each formulation.
**Drug content:** A film of required area (1 x 1 cm / 2 x 2 cm etc.) is cut, put this small piece of film in to 100 ml buffer (pH7.4 or 6.8 or as prescribed) and shaken continuously for 24 hours. Then the whole solution is ultra sonicated for 15 minute. After filtration, the drug is estimated spectro photometrically and the drug content is determined.

**Percentage of moisture content:** The films are weight individually and left in a desiccator containing anhydrous calcium chloride or activated silica at room temperature for 24 hours. Individually films are weighed repeatedly until they showed a constant weight. Calculation of % of moisture content is done as the difference between initial and final weight with respect to the final weight.

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

**Percentage of moisture uptake:** A weight film kept in a desiccator at room temperature for 24 hours is taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccator until a constant weight for the film is obtained. The percentage of moisture uptake is calculated as the difference between the final and initial weight with respect to initial weight.

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

**Water vapour transmission rate:** Glass vials approx. 5 ml capacity of equal diameter were taken for transmission study. All vials washed thoroughly and dried in an oven completely. Weigh about 1 gm of anhydrous/ fused calcium chloride and kept in respective vials. Fix the films on the brim of vials and weigh individually then kept in closed dessicator containing saturated solution of potassium chloride to maintain humidity approx. 84%. The vials were weighed in 6, 12, 24, 36, 48, and 72 hours respectively.

\[
\text{Transmission rate} = \frac{\text{final weight} - \text{initial weight}}{\text{area x time}} \times 100
\]

**Content uniformity test:** Select 10 patches but content is determined for individual patches. If 9 out of 10 showed content between 85-115% of the specified value and no one has shown 75-125% of the specified value, it means the test has been passed but if 3 patches shown the
content between 75-125% then taken 20 additional patches and further test performed. If these 20 patches shown content between 85-115%, then the patches passed the test.

**Uniformity of dosage unit test**: A patch of accurately weigh is cutted in to small pieces and transferred to volumetric flash containing specific volume of suitable solvent for dissolution of drug and then sonicated for a limited period of time for complete extraction of drug from pieces and then mark the volume with the same solvent. The solution obtained kept untouched for 1 hour to settle down then supernatant diluted as required. The dilute solution was filtered by membrane having pore size 0.2μm and analyzed with suitable analytical (HPLC / UV) technique and the calculation was done for drug content.

**Polariscope examination**: The instrument polariscope used to study the crystal structure of drug in a patch. A specific area of patch is cut and kept on the slide to observe that drug present in crystalline form or amorphous.

**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.

**Flatness test**: Three longitudinal strips are to be 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 was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

**Swellability**: The patches of 3.14 cm² was weighed and put in a petri dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed. The degree of swelling (S) was calculated using the formula,

\[ S (%) = \frac{W_t - W_0}{W_0} \times 100 \]
Where $S$ is percent swelling $W_t$ is the weight of patch at time $t$ and $W_0$ is the weight of patch at time zero.

**Adhesive studies**

**Shear adhesion test:** The cohesive strength of an adhesive polymer is determined by this test. The value of strength can be affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers added. An adhesive coated patch is stacked on plate made of stainless steel and specified weight hung from the patch parallel to this plat. The time taken to pull off the patch from the plate determines the cohesive strength. More the time taken, greater is the shear strength.

**Peel adhesion test:** The measure of patch strength between an adhesive and a substrate is defined as adhesion. The force required removing adhesive coating from the steel used as test substrate. The type and amount of polymer $t_m$ molecular weight and the composition of polymers determine the adhesive properties. The single patch is adhere to test substrate (Steel) and it pulled from the substrate at 1800 angle. No residue on the test substrate indicate failure of adhesion.

**Tack properties:** Tack is the ability of polymer to adhere to a substrate with little finger pressure It’s important in transdermal systems which are applied with little figure pressure. Tack is dependent on molecular weight as well as composition of polymer and tackifying resins used in the polymer.

**Tests for tack include**

**Thumb tack test:** This is subjective test in which evaluation is done by pressing the thumb in to the adhesive. Experience is required for using the test.

**Rolling ball tack test:** This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. The diameter of ball is $7/16$ inches and it released on inclined track having angle 22.50. More the distance travelled, less the tacky polymer. Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive polymer.

**Peel tack or quick stick test:** The peel force is the force required to break the bond between the adhesive and the test substrate. The patch is pulled away from the substrate at 900 with speed 12 inches/minute. The value of force is expressed in grams/inch or ounces/inch.
**Probe tack test:** In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive an probe, removal of probe at a fixed rate away from the adhesive which break the bond. The force required to break the bond is recorded as tack and it is expressed in grams.

**Skin irritancy studies:** The skin irritancy can be performed on healthy rabbits / mice albino / rats and potential of transdermal system can be evaluated by modified Draize test. The dorsal surface of given test animal is to be cleaned and remove the hair from the clean surface then applied rectified sprit. Applied the transdermal formulation over the clean surface for 24 hour. After this period, remove the formulation and observed the status of skin. The score are given from 0 to 4 depending the degree of erythema as follows: zero point given for no erythema, 1 point for slight erythema -( barely perceptible-light pink), 2 point for moderate erythema( dark pink),3 points for moderate to severe erythema( dark pink) and 4 points for severe erythema ( extreme redness).

**Stability studies:** The stability of active component is a major criterion in determining acceptance or rejection of transdermal system. The stability studies were performed as according to ICH guidelines as at different temperature and relative humidity 25-30°C (60% relative humidity) and 45-50°C (75% relative humidity) over a period of 60 days. The samples were withdrawn at 0, 3, 6, and 9 weeks respectively and were analyzed for their physical appearance, drug content and in-vitro diffusion studies.

**In-vitro skin permeation and release kinetics studies**

The design and development of transdermal patch is greatly influenced by in vitro studies. In-vitro studies greatly help in investigating the route of skin permeation and the rate of transfer through skin by which drug entered in to systemic circulation. These studies can easily performed and methodology used allowed flexibility in adapting the model in addressing different aspects involved in preliminary or feasibility studies in the development of transdermal patch.

**Franz Diffusion Cell:** The in-vitro skin permeation of transdermal patches can be studied using Franz diffusion cell (most commonly used) with an effective permeation area of 1.0 cm² and receptor cell volume of 10 ml. The temperature is maintained at 32°C ± 1°C. The receptor compartment is filled with 10 ml PBS and is constantly stirred in a magnetic stirrer at 100rpm. The skin is mounted on a receptor compartment with the stratum corneum side
facing upward in to the donor compartment. Samples are withdrawn through the sampling port of the diffusion cell at predetermined time interval over 24 hours and are analysed. The receptor phase is immediately replenished with equal volume of fresh diffusion buffer.

**Horizontal-type skin permeation system:** Next to the Franz diffusion cell, this is most commonly used for permeation study. In this both receptor and donor compartment has capacity of 3.5 ml of PBS and constantly rotated by matched set of star head magnets at 600rpm and membrane area is about 0.64cm². The temperature is controlled by their most at water through water jacket surrounding the both compartment.

**Flow Diffusion Cell:** This diffusion cells has the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell is fully automated and connected directly to HPLC. They have large capacity donor chamber to allow appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

**IN-VIVO STUDIES**
These studies are the true depiction of formulation performance. The variables which were not considered during in-vitro study taken in to account now. In-vivo studies of transdermal system can be done by using following model
1. Animal Models
2. Human volunteers
3. Biophysical Model

**Animal Models**
For in-vivo studies animals are generally preferred at small scale because of easily availability and economically view. In human, considerable time and resources are required for study. The animal species used in in-vivo study are: rat guinea pig, hairless mouse, hairless rat, hairless dog, cat horse, goat, rhesus monkey, miniature pig, squirrel, chimpanzee, etc. The most preferred animal used in in-vivo study is rhesus monkey. Various experiments have been carried out to determine which of the animal models provide the best prediction of the behaviour of the device, being tested, in humans.
Human volunteers
The ultimate stage during clinical phases in development of transdermal devices is collection of all pharmacokinetic and pharmacodynamic data from human volunteers which were required to evaluate any toxic effects generate during application of formulations. The determination of percutaneous absorption in human can be done by labelling of drug by C14 radioisotope and measuring the radioactivity in excreta but it required very attention as to know how much amount reside in body and how much excrete by other routes not defined. The method is give approx. absolute result however it has some limitations. To overcome these limitations, other methods developed which were defined as.

Biophysical Models
Also known as physiologically based pharmacokinetic models. These Models are based on known anatomical and physiological datas thus present an accurate picture of drug disposition in various organs and tissues. All these models were based on steady state mass balance equation, solution of fick’s second law of diffusion.\(^{[38]}\)

Transdermal Market Product
An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. Over the past 5 years (2003–2007), that rate has more than tripled to a new transdermal delivery system every 8 months. It is assumed that more than one billion transdermal patches are currently produced every year.

Transdermal drugs approved by the US FDA.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Indication</th>
<th>Product Name</th>
<th>Marketing company</th>
</tr>
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<tbody>
<tr>
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<td>Scopolamine</td>
<td>Motion sickness</td>
<td>Transderm-Scop</td>
<td>Novartis</td>
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<tr>
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<td>Angina pectoris</td>
<td>Transderm-Nitro</td>
<td>Novartis</td>
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<td>1984</td>
<td>Clonidine</td>
<td>Hypertension</td>
<td>Catapres-TTS</td>
<td>Boehringer Ingelheim</td>
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<tr>
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<td>Estradiol</td>
<td>Menopausal symptoms</td>
<td>Estraderm</td>
<td>Janssen Pharmaceutica</td>
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<tr>
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<td>Fentanyl</td>
<td>Chronic pain</td>
<td>Duragesic</td>
<td>Janssen Pharmaceutica</td>
</tr>
<tr>
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<td>Nicotine</td>
<td>Smoking cessation</td>
<td>Nicoderm</td>
<td>GlaxoSmithKline</td>
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<tr>
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<td>Menopausal symptoms</td>
<td>Cobipath</td>
<td>Novartis</td>
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<td>Oxytrol</td>
<td>Watson pharma</td>
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<td>Local derma anesthesia</td>
<td>Sonoprep</td>
<td>Endo therapeutics</td>
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<td>Parkinson’s disease</td>
<td>Neupro</td>
<td>Schwarz pharma</td>
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<tr>
<td>2007</td>
<td>Rivastigmine</td>
<td>dementia</td>
<td>Exelon</td>
<td>Novartis</td>
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REFERENCES


