TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW ON ITS TYPES, BASIC COMPONENTS, PREPARATION METHODS AND RECENT ADVANCES

Lalita Chauhan*, Prerna Thakur1 and Sheetal Sharma2

1,2School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Village Makhnumajra Baddi District Solan, Tehsil Nalagarh, H.P-173205.

*Corresponding Author: Lalita Chauhan
School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Village Makhnumajra Baddi District Solan, Tehsil Nalagarh, H.P-173205.

ABSTRACT
This review focuses on the recent advances in Transdermal drug delivery system which can be a used for the research and development of pharmaceutical dosage form for transdermal drug delivery. TDDS (transdermal drug delivery system) is the novel drug delivery system that offers a variety of significant clinical benefits over other dosage forms such as tablets, capsules and injections. TDDS overcome the problems that are encountered with oral route. Transdermal route is non-invasive that includes lack of first pass metabolism effect, high bioavailability and steady drug plasma concentration. A Transdermal Patch is the discrete dosage form that is placed on the skin to deliver specific dose of the medicine (drug) into the bloodstream over a period of time. Transdermal patch is a medicated adhesive pad, after application to the skin it releases the active ingredient at a constant rate over a period of several hours to days. Skin is the major site of application for both local and systemic effects. However, stratum corneum is the main barrier for the penetration of drug through the skin. Here in this article, we mainly highlights on main ingredients, preparation methods, advantages, disadvantages, types of TDDS, evaluation parameters, modern techniques of TDDS.

KEYWORDS: TDDS, skin, evaluation, polymers.

INTRODUCTION
Transdermal drug delivery systems (TDDSs) can be defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s) through the skin portal at a predetermined and reproducible rate into the systemic circulation over a prolonged period.3 Today the most common transdermal system present in the market mainly based on semi permeable membranes which were called as patches. Transdermal drug delivery system4-5 (TDDS) is topically administered medicaments in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined & controlled rate. Transdermal drug delivery system has many advantages over conventional modes of drug administration, it provides a controlled rate release of medications, it avoids hepatic metabolism, ease of termination and long duration of action. The Transdermal drug delivery system has gained popularity over the fast decades the major penetration pathway of drug molecules through the stratum corneum of impact human skin is by diffusing through lipid envelopes of the skin cell.5 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. Transdermal therapeutic systems are also defined as a self contained, discrete dosage 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.

PHYSIOLOGY OF HUMAN SKIN
The skin is the largest single organ in the body. An average human skin is known to contain, on an average 40-70 hair follicles and 200-250 sweat ducts per every square centimeter of the skin.9 These skin appendages, however actually occupy grossly only 0.1% of total stratum corneum surface henceforth the transappendageal route of percutaneous absorption has provided only a very limited contribution to the overall mm kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecule at steady can thus be considered as primarily diffusion through the intact stratum corneum in the interfollicular region. So, for fundamental understanding of TDD
Chauhan et al. European Journal of Biomedical and Pharmaceutical Sciences

(Transdermal drug delivery), the structure should be understood. The skin can be divided in to two layers.
1. Epidermis - It is superficial layer of stratified epithelium which is of ectodermal origin.
2. Dermis or Corium - It is foundation of firm connective tissue upon which epidermis is laid and is of mesoderm origin.

The total thickness of skin has got considerable regional variation, ranging in human body from less than 1/10 of millimeter tip to 3 or even 4 millimeters.

**Fig. 1: Cross sectional view of skin.**

**Fig. 2 Drug in adhesive type**

**Fig. 3 Multi laminate type**

**TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM**
There are mainly four types of basic transdermal patches in the market.  
1. **Drug in adhesive type**  
In this type drug is loaded in adhesive itself and stratum corneum acts as rate controlling barrier. This is most old type of transdermal patch design. This type of transdermal drug delivery system is best illustrated by the development and marketing of a nitroglycerin releasing system named as deponit by PharmaSchwartz/Lohmann in Europe. Basic construction includes backing membrane, adhesive loaded with drug and release liner.

2. **Multi laminate type**  
This is most complicated type of design for transdermal patches. Basic construction includes backing membrane, drug in adhesive, rate controlling membrane, then again adhesive (loaded with drug) on to it. This shows that there are two adhesive layers. First layer that is in contact with the release liner is actually delivering drug and second layer of adhesive (after membrane) acts as depot of drug. The example is Scopolamine releasing TDDS named as Transderm-scop by Ciba and clonidine releasing TDDS named as CataPress-TTS by Boehringer Ingelheim.

3. **Reservoir type**  
In this type the drug is incorporated in reservoir which is lined with membrane. The adhesive is coated on to this membrane. This membrane can be rate controlling. Basic construction includes backing membrane, drug in reservoir, membrane, adhesive and release liner. Example of this type of TDDS is Nitro-glycerine releasing system named as Nitrodisc by Searle.
4. Matrix type
In this type, the drug is incorporated in the matrix of polymer which itself releases drug in zero order. The adhesive layer is just at the periphery and little inside the periphery of the patch. Basic construction includes backing membrane, adhesive, and drug in matrix and release liner. The example of matrix type transdermal patch in nitroglycerine releasing TDDS named as Nitrofur by Key.[8]

![CTS OF TDDS](image1)

Fig. 4 Reservoir type

**BASIC COMPONENTS OF TDDS**

1) Polymer matrix / Drug reservoir
Polymers are the heart of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base.[10]

![Fig. 5 Matrix type](image2)


Some commonly used polymer for TDDS are shown in Table 1.

<table>
<thead>
<tr>
<th>Natural Polymers</th>
<th>Synthetic Elastomers</th>
<th>Synthetic Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose derivatives</td>
<td>Polybutadiene</td>
<td>Polymethylalcohol</td>
</tr>
<tr>
<td>Arabino Galactan</td>
<td>Hydrocork</td>
<td>Polyethylene</td>
</tr>
<tr>
<td>Zein</td>
<td>Polysiloxane</td>
<td>Polyvinyl Chloride</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Acrylonitrile</td>
<td>Polycrlylates</td>
</tr>
<tr>
<td>Proteins</td>
<td>Neoprene</td>
<td>Polyamide</td>
</tr>
<tr>
<td>Shellac</td>
<td>Chloroprene</td>
<td>Acetal copolymer</td>
</tr>
<tr>
<td>Strach</td>
<td>Silicon rubber</td>
<td>Polystyrene</td>
</tr>
</tbody>
</table>

2) Drug
i. Drug should be very potent, i.e. it should be effective in few mg/day
ii. The drug should have short biological half life.
iii. The drug should not be irritant and non-allergic to human skin.
iv. The drug should be stable when contact with the skin.
v. They should not stimulate an immune reaction to the skin.
vi. Tolerance to the drug must not develop under near zero order release profile of transdermal delivery.

3) Permeation enhancers
These compounds are useful to increase permeability of stratum corneum by interacting with structural components of stratum corneum i.e., proteins or lipids to attain higher therapeutic levels of the drug.[20] Some example are Dimethyl sulfoxide, Propylene glycol, 2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Phuronic, Cardamom oil, Caraway oil, Lemon oil, Menthol, limonene, Linoleic acid.

4) Pressure sensitive adhesives
The pressure-sensitive adhesive (PSA) affixes the Transdermal drug delivery system firmly to the skin. Adhesives must be skin-compatible, causing minimal irritation or sensitization, and removable without inflicting physical trauma or leaving residue. In addition, they must be able to dissolve drug and excipient in quantities sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability. PSAs used in commercially available Transdermal systems include polycrlylate, polysisobutylene, and polysiloxane.[21]

5) Backing laminate
Backings materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin’s, polyesters, and elastomers in clear, pigmented, or metallized form. In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen...
transmission and a high moisture vapour transmission rate.\textsuperscript{[22]}\textsuperscript{[23]}

Examples of some backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate.

6) Release Liner
During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates.\textsuperscript{[24]}\textsuperscript{[25]}

7) Other excipients
Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.\textsuperscript{[26]}\textsuperscript{[27]}

VARIOUS METHODS FOR PREPARATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Asymmetric TPX membrane method
A prototype patch can be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX (poly (4-methyl-l-pentene)) asymmetric membrane, and sealed by an adhesive.\textsuperscript{[28]}

2. These Asymmetric TPX membrane preparation
These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexanone) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardener knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.\textsuperscript{[29]}

3. Circular teflon mould method\textsuperscript{[30]}
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 h and then poured into a circular teflon mould. The moulds are placed on a leveled surface and covered with an inverted funnel to control solvent vaporization in a laminar flow hood model with speed of air 1/2 m /sec. The solvent is allowed to evaporate for 24 h. Before evaluation the dried films are to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before to eliminate aging effects. These types of films are to be evaluated within one week of their preparation.\textsuperscript{[29]}

4. 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 min to produce a homogeneous dispersion and poured in to a leveled mercury surface. Then the solution is covered with inverted funnel to control solvent evaporation.\textsuperscript{[29]}

5. By using “IPM membranes” method
In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940polymer 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.\textsuperscript{[30]}

6. 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.\textsuperscript{[30]}

7. 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. A custommade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.\textsuperscript{[29]}\textsuperscript{[30]}

8. 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 1:2 can be used as an optimized ratio. The proliposomes are prepared by taking
5 mg 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 min. 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. Aliquot of 0.5 ml of the organic solution is introduced into the round bottomed flask at 37 °C containing mannitol after complete drying second aliquots (0.5 ml) 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 desiccators over night and then sieved through 100 mesh. The collected powder is transferred in to a glass bottle and stored at the freeze temperature until characterization. [29]

9. By using free film method

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is prepared by using chloroform. Plasticizers are 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 petridish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. 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 desiccators until use. Free films of different thickness can be prepared by changing the volume of the polymer solution. [25]

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Avoid the risks and inconveniences of intravenous therapy and of varied conditions of absorption and metabolism associated with the oral therapy.
2. Continuity of drug administration in TDDS permits the use of a drug with short biological half-life.
3. Transdermal drug delivery improves the bioavailability that reduces the total daily dose.
4. Avoids first-pass hepatic metabolism.
5. Less chances of over or under dosing as the result of prolonged pre programmed delivery of drug at the required therapeutic rate.
6. Decrease gastrointestinal side effects.
7. Elimination drug food interactions.
8. Increased patient compliance in following manner
11. Eliminates swallowing.
12. No chances of forgetting the dose once the device is applied on skin.
13. Easy to carry a patch in wallet or ladies purse.
14. Patches offer less friability problems of wear and tear than the tablets.
15. In a multi drug regimen TDDS avoids drug interaction in GIT [31, 32]
16. It is easy to terminate the medication simply by removing the drug delivery device from the skin surface.
17. TDDS system can be taken without any aid, which makes it most suitable formulation; for instance, tablet and capsule need little water. Liquid oral preparation needs teaspoon and parenteral delivery needs specialized person whereas if a patient is told to apply TDDS patch, he/she can do it anywhere e.g. in office, in theatre, in club, in house without any aid.
18. Chance of toxicity due to additives e.g. preservatives, stabilizing agent antioxidants etc. are less as compared to other dosage forms.
19. Problem of dose dumping is least in TDDS, because stratum corneum is more resistant than the inner membranes and stratum corneum itself is a rate limiting factor.
20. Need not to be sterile, obviates processing problem. [33]

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Transdermal drug delivery system cannot deliver ionic drugs.
2. It cannot achieve high drug levels in blood.
3. It cannot develop for drugs of large molecular size.
4. It cannot deliver drugs in a pulsatile fashion.
5. It cannot develop if drug or formulation causes irritation to skin.
6. Possibility of local irritation at site of application.
7. May cause allergic reaction.
8. Sufficient aqueous and lipid solubility, a log P (octanol/ water) between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.
9. Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin’s impermeability.
10. Long time adherence is difficult. [34, 35, 36]

EVALUATION PARAMETERS
The evaluation methods for transdermal dosage form can be classified into following types:
1) Physicochemical evaluation
2) In vitro evaluation
3) In vivo evaluation [17]

1) Physicochemical Evaluation
   a) Interaction studies
The drug and the excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are taken out by Thermal analysis, FTIR, UV and chromatographic techniques by...
comparing their physicochemical properties like assay, melting point, wave numbers, absorption maxima.\textsuperscript{[37],[38]}

**Thickness of the patch**

The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.\textsuperscript{[39]}

**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.\textsuperscript{[40]}

**Folding endurance**

A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance.\textsuperscript{[41]}

**Percentage moisture content**

The prepared patches are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 hrs the films are to be reweighed and determine the percentage moisture content by below formula. \textsuperscript{[42]}

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

**Percentage moisture uptake**

The prepared patches are to be weighed individually and to be kept in a desiccator 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 by below formula. \textsuperscript{[43]}

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

**Water vapour permeability (WVP) evaluation**

Water vapour permeability can be determined by a natural air circulation oven. The WVP can be determined by the following formula

\[
\text{WVP} = \frac{W}{A} \times \frac{t}{\text{difference in weight}}
\]

Where, WVP is expressed in gm/m² per 24 hrs
where W is the amount of vapour permeated through the patch expressed in gm/24 hrs
A is the surface area of the exposure samples expressed in m².\textsuperscript{[44]}

**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). Then take the average of three different samples.\textsuperscript{[41]}

**Content uniformity test**

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content In the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.\textsuperscript{[7],[42]}

**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 0.2μm membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.\textsuperscript{[43]}

**Flattness 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. \textsuperscript{[44]}

\[
\%\text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100
\]

where, \(I_1\) = Initial length of each strip.
\(I_2\) = final length of each strip.

**Polariscopic examination**

A specific surface area of the piece is to be kept on the object slide of Polariscopic and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.\textsuperscript{[45]}

**Shear Adhesion test**

This test is to be performed for 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.\textsuperscript{[46]}

**Adhesive studied**

Peel Adhesion test: In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are
the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180°C a force required for tape removed is measured.\textsuperscript{[47]}

\textbf{Fig. 6 Peel Adhesion test.}

**Thumb tack test:** It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.\textsuperscript{[42]}

**Tack properties:** It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.\textsuperscript{[47]}

**Percentage elongation break test**
The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below formula:\textsuperscript{[43]}

\[
\text{Elongation percentages} = \frac{L_1 - L_2}{100} \times L_2
\]

Where, \(L_1\) = the final length of each strip.
\(L_2\) = the initial length of each strip.

**Rolling ball tack test**
This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provide the measurement of tack, which is expressed in inch 40.

\textbf{Fig. 7: Rolling ball tack test.}

**Quick stick (peel-tack) test**
In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.\textsuperscript{[48]}

\textbf{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.\textsuperscript{[48]}

\textbf{Fig. 8 Probe Tack test.}

**Shear strength properties or creep resistance**
Shear strength is the measurement of the cohesive strength of an adhesive polymer \textit{i.e.}, device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.\textsuperscript{[46]}

\textbf{Fig. 9 Shear strength test.}

**Stability studies**
Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C. 

www.ejbps.com
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.\[47\]

2) In vitro Evaluation of TDDS

2.1 In vitro drug release studies
The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.\[44\][45]

2.2 In vitro skin permeation studies
An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250 gm. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm\(^{-2}\)) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm\(^{-2}\)).\[46\]

3) In vivo Evaluation

In vivo evaluations 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.

Animal models: Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. 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.\[47\]

Human models: The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in a large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

RECENT ADVANCES IN THE FIELD OF TRANSDERMAL PATCHES

A number of therapeutically active substances are delivered transdermally including large proteins, testosterone, oxybutynin and patches for the relief of pain.

1. Patch technology for protein delivery

Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. TransPharma uses its unique printed patch technology for transdermal delivery of proteins thereby complementing its ViaDerm delivery technology. Such printed patches contain accurate doses of proteins in a dry state. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-Micro Channels, forming a highly concentrated protein solution in-situ. The delivery of the dissolved molecules is then carried out, via the RF-Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient.\[48\] [49]

2. Pain free diabetic monitoring using transdermal patches

The patch (about 1cm\(^2\)) is made using polymers and thin metallic films. The metallic interconnections and sampling array can be clearly seen. Utilizing micro-heating elements integrated into the structural layer of the patch closest to the skin surface, a high-temperature heat pulse can be applied locally, breaching the stratum corneum. During this ablation process, the skin surface experiences temperatures of 130°C for 30 minutes duration. The temperature diminishes rapidly from the skin surface and neither the living tissue nor the nerve endings are affected. This painless and bloodless process results in disruption of a 40–50 μm diameter region in the dead skin layer, approximately the size of a hair
follie, allowing the interstitial fluid to interact with the patch's electrode sites.\[50]\n
3. Testosterone transdermal patch in young women with spontaneous premature ovarian failure
In premenopausal women, the daily testosterone production is approximately 300 μg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone. The addition of TTP to cyclic E2/MPA therapy in women with sPOF produced mean free testosterone levels that approximate the upper limit of normal. \[51]\n
4. Transdermal Patch of Oxybutynin used in overactive Bladder (OAB)
The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe under the brand name of Kentera. Oxytrol is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three to four day interval. Oxytrol offers OAB patient’s continuous effective bladder control with some of the side effects, such as dry mouth and constipation encountered with and oral formulation. In most patients these side effects however are not a troublesome.\[52][53]\n
5. Pain relief
Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch,\[54]\ Several others are available in the market. Lidoderm, a lidocaine patch (5%), which is used for post herpetic neuralgic.\[55]\ This credit card size patch is an active delivery device that has a self-contained battery that delivers pulses of Fentanyl HCl, a strong narcotic. This mimics the use of intravenous self-controlled analgesic systems that are very expensive, cumbersome, and require considerable nursing care.

6. Molecular absorption enhancement technology
Absorption enhancers are the compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives as well as certain phenols seem to improve transdermal absorption.\[56][57]\ For example, linalool, alpha terpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it to a therapeutic level.\[58]\ Limonene, menthone, and eugenol were found to enhance transdermal absorption of Tamoxifen.\[59]\ Phloretin, a polyphenol, enhanced the absorption of Lignocaine.\[60]\ The enhancement in permeation of Celecoxib through rat skin was estimated using Transcutol and oleic acid as permeation enhancers. A comparative flux pattern of formulations containing these enhancers (oleic acid and Transcutol) showed that Transcutol was less effective as a permeation enhancer than oleic acid in increasing the flux of Celecoxib.\[61]\n
Table 3: Marketed preparations.\[62][63][64]\n
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Manufacturer Name</th>
<th>API</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chimaderm</td>
<td>Ethical Holdings/Wyeth-Ayerest</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Sono prep</td>
<td>Sontra Medical corporation</td>
<td>Peptides</td>
</tr>
<tr>
<td>Chadd</td>
<td>ZarsInc</td>
<td>S-oxybutynin</td>
</tr>
<tr>
<td>Powderject</td>
<td>Powderject Pharmaceuticals</td>
<td>Insulin</td>
</tr>
<tr>
<td>Macroflux</td>
<td>Alza Corporation</td>
<td>Vaccines &amp; Therapeutic proteins</td>
</tr>
<tr>
<td>Intraject</td>
<td>Weston medical</td>
<td>Vaccines</td>
</tr>
<tr>
<td>E-Trans</td>
<td>Alza Corporation</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Testoderm</td>
<td>Alza Corporation</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Estraderm</td>
<td>Novartis</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Oxytrol</td>
<td>Watson Pharma</td>
<td>Oxybutynin</td>
</tr>
<tr>
<td>SonaPrep</td>
<td>Echo Therapeutics</td>
<td>Lidoceaine</td>
</tr>
<tr>
<td>Habitraol</td>
<td>Novartis</td>
<td>Nicotine</td>
</tr>
<tr>
<td>SonoDerm</td>
<td>Ethical Holdings/Wyeth-Ayerest Imarx</td>
<td>Insulin</td>
</tr>
<tr>
<td>Nicoderm</td>
<td>GlaxoSmithKline</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Transderm nitro</td>
<td>Novartis</td>
<td>Nitroglycerin</td>
</tr>
</tbody>
</table>

CONCLUSION
In novel drug delivery system, Transdermal drug delivery represents one of the most rapidly advanced area. TDDS are suitable for those drug candidate which shows hepatic first pass effect and unstable in GI conditions. With the help of various enhancement techniques, permeability of low permeable drugs can be increased. For the maintenance of consistent efficacy, TDDS are designed for controlled release of drug through the skin into systemic circulation. Different mechanisms of biological interactions, and polymer are required of greater understanding for the optimization of this drug delivery system. It would seem exceptionally difficult to target the skin for drug delivery, because the basic functions of the skin are protection and containment. TDDS can save the recipient from the harm
of large doses with improved bioavailability, by offering the delivery of drugs at lower dose. The transdermal rate controlled drug delivery is expected to grow day by day, and it could be one of the best novel drug delivery system in future.

ACKNOWLEDGEMENT
Authors are highly thankful to Dr. Tilak Raj Bhardwaj, Dean of School of Pharmacy and Emerging Sciences for their support and encouragement and Department of Pharmacy, Baddi University for providing library facility during literature survey.

REFERENCES
25. Foco A, Hadziabdic J, Becic F. Transdermal drug delivery systems. Med. Ar...

31. Halwai AH, Khurana S. Formulation and evaluation of transdermal patches of antihypertensive drug.


