TRANSDERMAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH

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ABSTRACT
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 outlook for continued growth of the TDD market is very optimistic. Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. This review emphasizes the three generations of transdermal drug delivery which start a new era of delivery of drug.

Key words: Barrier, blood concentration, pain-free, self-administration, hypodermic injections.

INTRODUCTION[1,2]
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 injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not
only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs through the skin. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. Skin is the important site of drug application for both the local and systemic effects.

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.

**MERITS OF TDDS** [2, 3]

- Improved bioavailability and longer duration of action resulting in a reduction in dosing frequency
- Steady permeation of drug across the skin, allowing consistent serum drug level; often a goal of therapy
- Reduced side effects and in addition, if toxicity develops from a drug administered transdermally, the effects could be moderated by removing the patch
- Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug degradation effects
- Topical patches are a painless, noninvasive way to deliver substances directly into body
- This is an effective route to deliver drugs that are broken down by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver
- Transdermal patches are alternative to oral route for people who cannot, or prefer not to take medications or supplements orally. It is of great advantage in patients who are nauseated or unconscious.
- Topical patches are cost-effective, convenient; especially notable parameter in some patches is that it requires only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.

**DEMERITS AND LIMITATIONS OF TDDS** [2, 3]

- Many drugs especially those with hydrophilic structures permeating the skin too slowly, may not achieve therapeutic level
- The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age
- TDDS cannot deliver ionic drugs
- TDDS cannot achieve high drug levels in blood/plasma
- TDDS cannot be developed for drugs of large molecular size
- TDDS cannot deliver drugs in a pulsatile fashion
- TDDS cannot be developed if drug or formulation causes irritation to skin.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelf life</td>
<td>Up to 2 years</td>
</tr>
<tr>
<td>Patch size</td>
<td>&lt; 40 cm²</td>
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<tr>
<td>Dose frequency</td>
<td>Once a daily to once a week</td>
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<tr>
<td>Aesthetic appeal</td>
<td>Clear, tan or white color</td>
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<tr>
<td>Packaging</td>
<td>Easy removal of release liner and minimum number of steps required to apply</td>
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<tr>
<td>Skin reaction</td>
<td>Non irritating and non-sensitizing</td>
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<tr>
<td>Release</td>
<td>Consistent pharmacokinetic and pharmacodynamic profiles</td>
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<td>Dose</td>
<td>Should be low</td>
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<tr>
<td>Half life (h)</td>
<td>10 or less</td>
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<tr>
<td>Molecular weight</td>
<td>&lt; 400</td>
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<tr>
<td>Skin reaction</td>
<td>Non irritating and non sensitizer</td>
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<tr>
<td>Oral bioavailability</td>
<td>Low</td>
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<tr>
<td>Therapeutic index</td>
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i. Properties Of TDDS

<table>
<thead>
<tr>
<th>Phytochemical</th>
<th>Pharmacokinetic</th>
<th>Biological</th>
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<tbody>
<tr>
<td>Solubility</td>
<td>Half life</td>
<td>Skin toxicity</td>
</tr>
<tr>
<td>Crystallinity</td>
<td>Volume of distribution</td>
<td>Site of application</td>
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<tr>
<td>Molecular Weight</td>
<td>Total body clearance</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Polarity</td>
<td>Therapeutic plasma concentration</td>
<td>Skin metabolism</td>
</tr>
<tr>
<td>Melting Point</td>
<td>Bioavailable factor</td>
<td>Skin permeability</td>
</tr>
</tbody>
</table>

ii. Factors Effecting TDDS
BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS: [4, 5]

The components of transdermal devices include:

1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Other excipients

1. Polymer Matrix

The Polymer controls the release of the drug from the device.

Possible useful polymers for transdermal devices are:

a) Natural Polymers
e.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers[27]
e.g. Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadiene rubber, Neoprene etc.

c) Synthetic Polymers
e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

2. Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 daltons.
2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
3. The drug should have low melting point.

Along with these properties the drug should be potent, having short half life and be non irritating.
3. Permeation Enhancers
These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

These may conveniently be classified under the following main headings

a) Solvents
These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N-methyl, 2-pyrrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

b) Surfactants
These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decadecylmethyl sulphasoxide etc.

Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
Biary system: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways.e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

4. Other Excipients
a) Adhesives: The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria
(i) Should adhere to the skin aggressively, should be easily removed.
(ii) Should not leave an unwashable residue on the skin.
(iii) Should not irritate or sensitize the skin.
The face adhesive system should also fulfill the following criteria.
(i) Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
(ii) Permeation of drug should not be affected.
(iii) The delivery of simple or blended permeation enhancers should not be affected.

b) Backing membrane
Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM: [5, 6]
A. Single-layer Drug-in-Adhesive
The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.
B. Multi-layer Drug-in-Adhesive
The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane. This patch also has a temporary liner-layer and a permanent backing.

C. Reservoir
Unlike the single-layer and multi-layer drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

D. Matrix
The matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. It is also known as a monolithic device.

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

**VARIOUS METHODS FOR PREPARATION OF TDDS**[^7,^8]

**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. [(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) 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 gardner 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].

**b. Circular teflon mould method:**[^27] 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.

**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 withinverted funnel to control solvent evaporation.

**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.

e. By using “EVAC membranes” method: [28] In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (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.

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. A customize aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

g. Preparation of TDDS by using Proliposomes: [26] 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 over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.
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 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.

EVALUATION PARAMETERS$^{[9,10]}$

1. Interaction studies: Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can 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 commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

2. Thickness of the patch: $^{[27]}$ The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3. Weight uniformity: $^{[21]}$ 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.30

4. Folding endurance: $^{[20]}$ A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.30
5. **Percentage Moisture content:** [24] The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.30

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

6. **Percentage Moisture uptake:** [21] The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.30

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

7. **Water vapour permeability (WVP) evaluation:** [16] 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

\[
\text{WVP} = \frac{W}{A}
\]

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 m2.31

8. **Drug content:** [19] 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).

9. **Uniformity of dosage unit test:** [18] 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.32

10. **Polariscope examination:** [15] This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object
slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.32

11. **Shear Adhesion test:** [13] 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.

12. **Peel Adhesion test:** [11] 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 180º angle, and the force required for tape removed is measured.

13. **Thumb tack test:** [24] 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.

14. **Flatness test:** [16] 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.

15. **Percentage Elongation break test:** [25] 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 mentioned formula.

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

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

16. **Rolling ball tack test:** [14] 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 provides the measurement of tack, which is expressed in inch.

17. **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 to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

18. **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.

**CONCLUSION**

Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive Patches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. It promises to eliminate needles for administration of a wide variety of drugs in the future. TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS realistic practical application as the next generation of drug delivery system. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin, membrane transdermal route is effective. This article provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems. TDDS is a realistic practical application as the next generation of drug delivery system.

**REFERENCE**


