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### A REVIEW: THE NOVEL DRUG DELIVERY BY TRANSDERMAL PATCHES

PANKAJ SINGH NEGI<sup>1</sup>, G. GANANARAJAN<sup>1</sup>, ASHUTOSH BADOLA<sup>2</sup>, PREETI KOTHIYAL<sup>1</sup>

Department of Pharmaceutics, Shri Guru Ram Rai Institute of Technology & Sciences, Dehradun, (248001) Uttarakhand, India

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**Abstract:** Now a day about 74% of drugs are taken orally and which are not as effective as desired. To overcome such problems transdermal drug delivery system (TDDS) was developed. Delivery of a drug through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from conventional topical drug delivery. Transdermal drug delivery system (TDDS) are dosage forms involves drug transport to viable epidermal and/or dermal tissues of the skin for local therapeutic effect while a very major fraction of a drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system (TDDS) is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Many important advantages of transdermal drug delivery (TDDS) are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and the maintenance of steady plasma level of the drug. Thus, this article provides an overview of types of transdermal patches, methods of preparation and its physicochemical methods of evaluation.

**Keywords:** Transdermal drug delivery system (TDDS), Topical drug delivery, Systemic blood circulation.



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Corresponding Author: MR. PANKAJ SINGH NEGI

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## INTRODUCTION

Two important layers in skin: Epidermis and Dermis. The outermost layer, the epidermis, is 100-150 micrometer thick, with no blood flow that includes a layer most important to transdermal delivery which is known as stratum corneum, and its composition allow it to keep water within the body and foreign substances out <sup>[1]</sup>. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is capable to penetrate the stratum corneum, it might be capable to enter into the blood stream, this process is known as passive diffusion, which occurs too slowly, is the only way to transfer normal drugs be both water-soluble and lipid soluble. Transdermal drug delivery generally refers to topical application of drug to intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin. A transdermal drug delivery device, which can be of an active or a passive design, provides an alternative route for administering medicament and allow pharmaceutical to be delivered across the skin barrier <sup>[2]</sup>. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. By a diffusion process, the drug is entered in the blood stream directly through the skin <sup>[3]</sup>. There is a high concentration on the patch and low concentration in the blood for a long period of time, by maintaining the constant concentration of drug in the blood flow. The best mixture is approx. 50% of the drug being each hydrophilic and lipophilic. This is because "lipid-soluble substances readily pass through the intercellular lipid bi-layer of the cell membranes whereas water-soluble drugs are able to pass limiting steps in transdermal drug delivery system. The only path of entry by Sweat ducts and hair follicles, but they are considered rather insignificants <sup>[4, 5]</sup>.

### Need of study

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). Drug that can dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets.

The other strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with

poorly soluble drugs. In this type of formulation there is one potential problem that is the drug may favor a more thermodynamically stable state that can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.

### BASIC COMPONENTS OF TDDS

#### 1. Polymer Matrix<sup>[6,7,8]</sup>:-

The release of the drug from the device is controlled by the polymer.

- a) **Natural Polymers**:-Cellulose derivative, Shellac, Starch, Waxes, Proteins, Gums and their derivatives, Gelatin, Natural rubber, Zein etc.
- b) **Synthetic Elastomers**:-Hydrin rubber, Polysiloxane, Silicone rubber, Acrylonitrile, Butyl rubber, Polybutadiene, Styrenebutadiene rubber, Neoprene etc.
- c) **Synthetic Polymers**:-Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyamide, Polyvinylpyrrolidone, Polymethacrylate, Epoxy, Polyurea etc.

#### 2. Drug<sup>[6,8]</sup>:-

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

- Physicochemical properties
  - a) The molecular weight of the drug should be >1000 daltons<sup>[8,9]</sup>.
  - b) The drug should have affinity for both- lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin<sup>[10]</sup>.
  - c) The melting point of the drug should be low.

Along with these properties the drug should be potent, having short half life and should be non irritating<sup>[11]</sup>.

#### 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 heading:

**a) Solvents<sup>[6,12]</sup>:-**

These are compounds that increase the penetration possibly by swallowing the polar pathway and/or by fluidizing lipids.

**Examples**

Water Alcohol	Ethanol and Methanol.
Alkyl methyl Sulfoxide	Dimethyl Sulfoxide
Alkyl Homologs	Methyl sulfoxidedimeurthylacet amide
Pyrrolidones	2pyrrolidone

**Mechanism of permeation enhancer:**

- These are the chemical compounds that increase the permeability of stratum corneum, so as to attain greater therapeutic level of drug.
- Permeation enhancer interacts with structural components of stratum corneum that is proteins and lipids.
- They alter protein and lipid packaging of stratum corneum thus chemically modifying barrier function leading to increased permeability.

**b) Surfactants<sup>[6,9]</sup>:-**

Polar pathway transport is enhanced by these compounds, especially of hydrophilic drugs. The ability of surfactants to alter penetration is a function of the polar head group and the hydrocarbon chain length.

- Anionic Surfactants : Ex.- Sodium lauryl sulphate, Dioctylsulphosuccinate.
- Nonionic Surfactants : Ex.- Pluronic F68, Pluronic F127 etc.
- Bile Salt : Ex.- Sodium mstaurocholate, Sodium tauroglycocholate, Sodium deoxycholate.

**c) Miscellaneous Chemical<sup>[9,13]</sup>:-**

These include urea a hydrating and keratolytic agent; Calcium thioglycolate; N, N-dimethyl-m-toluamide; anticholinergic agents.

Some potential permeation enhancers have recently been described but the availability data on their effectiveness sparse. These include eucalyptol, di-o-methyl- $\beta$ -cyclodextrin and soyabean casein.

#### **4. Other Excipients:-**

##### **a) Adhesives<sup>[13,14]</sup>:-**

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:

- Should adhere to the skin aggressively, should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should not be irritating or sensitive the skin.

The face adhesive system should also fulfill the following criteria <sup>[3,15]</sup>.

- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- Permeation of drug should not be affected.
- The delivery of simple or blended permeation enhancers should not be affected.

##### **b) Backing Membrane<sup>[16]</sup>:-**

Backing membrane are flexible and 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 Ex. Metallic plastic laminate, plastic backing with adsorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate(aluminium foil disc) etc.

##### **Desirable features for transdermal patches<sup>[17]</sup>**

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.

- Delivery is zero order.
- Delivery is efficient.

#### **TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM**

##### **Single-layer Drug-in-adhesive<sup>[3,18]</sup>:-**

The Single-layer Drug-in-adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin.

##### **Multi-layer Drug-in-adhesive<sup>[19]</sup>:-**

The Multi-layer Drug-in-adhesive is similar to the Single-layer Drug-in-adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multi-drug-in-adhesive layers under a single backing film.

##### **Drug Reservoir-in-Adhesive<sup>[6,20]</sup>:-**

The reservoir transdermal system design is identified by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

##### **Drug Matrix-in-Adhesive<sup>[5,21]</sup>:-**

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension having a direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

#### **ADVANTAGES OF TDDS<sup>[22,23]</sup>**

1. In case of toxicity there is easy elimination of drug delivery.
2. First pass metabolism of drug is avoided.
3. Plasma concentration levels of drugs are reduced with decreased side effects.

4. Fluctuation of plasma levels of drugs is reduced, utilization of drug candidates with short half-life and low therapeutic index.
5. Delivery of a study infusion of a drug by transdermal medication over an extended period of time
6. Enhancement of patient compliance and reduction of dosing frequency.
7. There is a increased in the therapeutic value of many drugs via avoiding specific problems associated with the drug like GI. Irritation lower absorption, decomposition due to 'hepatic first pass' effect.
8. The simplified medication regimen results to improved patient compliance and reduction in inter and intra patient variability.

#### **DISADVANTAGES OF TDDS<sup>[22]</sup>**

1. In site of application there is a possibility of local irritation Erythema, itching and local edema case caused by the drug, adhesive or other excipients in the patch formulation.
2. In skin's low permeability there is the limit of the number of drugs that can be delivered in this manner. Because of the skin protective function, it inhibits compounds from crossing. Drugs with the hydrophilic structure permeate the skin too slowly to be of therapeutic benefit. Drugs having a lipophilic character, however, better suited for transdermal delivery.

#### **EVALUATION OF TDDS**

##### **Physico-Chemical Evaluation:**

##### **1. Thickness of the patch<sup>[24]</sup>:-**

Screw Gauge in mm is used to measure the thickness of the patch.

##### **2. Folding endurance<sup>[25, 26]</sup>:-**

Folding endurance measured manually for the prepared film. A strip of a film cut evenly and at the same place is folded till it breaks. Film could be folded at the number of time at the same place without breaking gives folding endurance are exact value.

##### **3. Percentage(%) of moisture absorbed<sup>[27]</sup>:-**

Checking the physical stability of the film in high humidity conditions, film that are accurately weighted were placed in a desiccators containing saturated aluminium chloride

solution 79.5%RH for 3 days. The films were re-weighed and the percentage moisture absorption was calculated using the formula.

$$\text{Percentage(\%)} \text{ moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight} \times 100}{\text{Initial weight}}$$

#### 4. Percentage(%) of moisture lost<sup>[28]</sup>:-

In order to check the extent of moisture loss from freshly prepared film, the accurately weighed film are placed in a desiccators containing fused anhydrous calcium chloride for 72hrs, After 72hrs films were re-weighed percentage moisture is calculated using by the following formula

$$\text{Percentage (\%)} \text{ moisture lost} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{Initial weight}}$$

#### 5. Drug content uniformity<sup>[29]</sup>:-

By cutting a patch into pieces and put in dissolution of 100 ml or diffusion medium is used respectively and stirred continuously using a mechanical stirrer and after the ends of 3hrs the sample is withdrawn the drug content to be determined spectrophotometrically at 275 nm.

#### 6. Skin irritation test<sup>[30]</sup>:-

The test of skin irritation is done on a healthy rabbit weighing between 2-3kg. Drug loading a polymeric film of 3,14cm<sup>2</sup> was placed on the left of the dorsal surface of the rabbit. After 24hrs the patch was removed with the help of alcohol swab. The skin was examined for erythema/oedema.

#### 7. *In-vitro* Diffusion Study:-

The study of *in-vitro* diffusion is carried out by using Franz Diffusion Cell (Ponmani and Co, Coimbatore)<sup>[31, 32]</sup>. Egg membrane is used the purpose of semi-permeable membrane for diffusion. Franz diffusion cell has a receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14cm<sup>2</sup>.

#### 8. Stability studies<sup>[33]</sup>:-

In two different hot air oven all the film were exposed to two selected item of 37°C and 45°C. For a period of four weeks transdermal film were kept in the oven. At the end of every week the films were analyzed for the drug content. The averages of triplicate readings were taken.

## METHODS FOR PREPARATION OF TDDS

### 1. Asymmetric TPX membrane method<sup>[34]</sup>:-

A prototype patch can be fabricated for this a heat sealable polyester film with a concave of 1cm diameter will be used as the backing membrane. Sample of a drug is then dispensed into the concave membrane, which is covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and then sealed by an adhesive.

### 2. Circular Teflon mould method<sup>[35]</sup>:-

Solutions containing polymers in a different ratio in organic solvent are used. Drug in a calculated amount 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-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12hrs 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 0.5m/s. The solvent is then allowed to evaporate for 24hrs. The dried films are too stored for another 24hrs 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.

### 3. Mercury substrate method<sup>[36]</sup>:-

In this method drug along with plasticizer is dissolved in polymer solution. The solution above is to be stirred for 10-15min in a order to produce a homogenous dispersion and poured in to a leveled mercury surface, which is covered with inverted funnel to control solvent evaporation.

### 4. By using IPM membranes method<sup>[37]</sup>:-

In this method drug is then dispersed in a mixture of propylene glycol and water containing carbomer940 polymers and stirred for 12hrs in magnetic stirrer. The dispersion is to be neutralizer and it is made viscous by the addition of triethanolamine. In a order to obtain solution gel buffer pH 7.4 can be used, if the solubility of the drug in aqueous solution is very poor. The gel formed will be incorporated in the IPM membrane.

### 5. By using EVAC membrane method<sup>[38]</sup>:-

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; 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 then placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and to obtain a leak proof device the edges is then sealed by heat.

#### **6. Aluminium backed adhesive film method<sup>[39]</sup>:-**

Transdermal drug delivery system (TDDS) can produce unstable matrices if the loading dose is greater than 10mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, choice of solvent is chloroform, 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 custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

#### **7. Preparation of TDDS by using Proliposomes<sup>[40-41]</sup>:-**

Using film deposition technique the proliposomes are prepared by carrier method. 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 100ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90rpm and dried the mannitol at vacuum for 30min. After drying, the water bath temperature is adjusted to 20-10°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 desiccators over night and then sieved through 100mesh. The powder that is collected is transferred into a glass bottle and stored at the freeze temperature until characterization.

#### **8. By using free film method<sup>[42]</sup>:-**

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. Polymer solution of 5ml 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 film that is dry will be separated out and stored between the sheets of wax paper in desiccators until use. Changing the volume of the volume of the polymer solution free films of different thickness can be prepared.

## **CONCLUSION**

Good controlled release properties are should by a transdermal patch. This article provides an valuable information regarding the transdermal drug delivery system and its evaluation process details. The article shows that 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 interaction, and polymer are required TDDS a realistic practical application as the next generation of drug delivery system. The transdermal drug delivery system holds a promising future in effective transdermal delivery of bioactive agents and having a opportunities for clinicians to experiment with various drugs to study their systemic and local effects.

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