Abstract:

Transdermal drug delivery system is topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. It was realized & later demonstrated that the benefits of a infusion could be closely duplicated without its hamless by using the skin as the port of entry of drugs. This is known as transdermal administration & the drug delivery systems are known as transdermal patches. Transdermal medications delivers a steady infusion of a drug over an extended period of time & improved patient compliance & reduced inter & intra patient’s variability. The future may see improved technologies methods to produce better & cost efficient transdermal system, Iontophoresis may play a key role in this regards. Eg. Nitroglycerine it have the very short half-life when administrated as transdermal patches, release medicaments at a constant rate for a time period.

Key words: Components, Kinetics, Types, Evaluation and TDDS.

Introduction

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise spatial and temporal placement within the
body thereby reducing both the size and number of doses. New drug delivery systems are also essential for the
delivery of novel, genetically engineered pharmaceuticals (i.e., peptides, proteins) to their site of action, without incurring significant immunogenicity or biological inactivation. Apart from these advantages, the pharmaceutical companies recognize the possibility of repattening successful drugs by applying the concepts and techniques of controlled drug delivery systems coupled with the increased expense in bringing new drug moieties to the market. One of the methods most often utilized has been transdermal very-meaning transport of therapeutic substances through the skin for systemic effect. Closely related is percutaneous delivery, which is transport into target tissues, with an attempt to AVOID systemic effects. There are two important layers in skin: the dermis and the epidermis. The outermost layer, the epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum. This is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, it can enter the bloodstream. A process known as passive diffusion, which occurs too slowly for practical use, is the only means to transfer normal drugs across this layer. The method to circumvent this is to engineer the drugs be both water-soluble and lipid soluble. The best mixture is about fifty percent of the drug being each. This is because “Lipid-soluble substances readily pass through the intercellular lipid bi-layers of the cell membranes whereas water-soluble drugs are able to pass through the skin because of hydrated intracellular proteins”. Using drugs engineered in this manner, much more rapid and useful drug delivery is possible.
The stratum corneum develops a thin, tough, relatively impermeable membrane which usually provides the rate limiting step in transdermal drug delivery systems. Sweat ducts and hair follicles are also paths of entry, but they are considered rather insignificant.

Transdermal Drug Delivery System

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering
medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. In theory, transdermal patches work very simply\(^4\). 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. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

This approach to drug delivery offers many advantages over traditional methods. As a substitute for the oral route, transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosage due to the shortened destabilization pathway of the transdermal route versus the gastrointestinal pathway. The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications. Multi-day therapy with a single application, rapid notification of medication in the event of emergency, as well as the capacity to terminate drug effects rapidly via patch removal, are all further advantages of this route\(^5\).

However this system has its own limitations in which the drug that require high blood levels cannot be administered and may even cause irritation or sensitization of the skin. The adhesives may not adhere well to all types of skin and may be uncomfortable to wear. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product\(^4\).

**Properties That Influence Transdermal Delivery**

- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response.

**Kinetics of Transdermal Permeation**

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems\(^6\). Transdermal permeation of a drug involves the following steps:
1. Sorption by stratum corneum.

2. Penetration of drug through viable epidermis.

3. Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physiochemical properties.

The rate of permeation across the skin is given by:

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

Where \(C_d\) and \(C_r\) are the concentration of the skin penetrate in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. \(P_s\) is the overall permeability coefficient of the skin tissue to the penetrate. This permeability coefficient is given by the relationship:

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

And the rate of skin permeation is constant provided the magnitude of \(C_d\) remains fairly constant throughout the course of skin permeation\(^6\). For keeping \(C_d\) constant the drug should be released from the device at a rate \(R_t\) i.e. either constant or greater than the rate of skin uptake \(R_a\) i.e. \(R_t >> R_a\). Since \(R_t >> R_a\), the drug concentration on the skin surface \(C_d\) is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum \(C_s\) i.e. \(C_d >> C_s\). Therefore a maximum rate of skin permeation is obtained and is given by the equation:

\[
\left(\frac{dQ}{dt}\right)_m = P_s C_s
\]
From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient $P_s$ and is equilibrium solubility in the stratum corneum $C_s$. Thus skin permeation appears to be stratum corneum limited.

**Basic Components of Transdermal Drug Delivery Systems**

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:

   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 none irritating.

3. Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrates. 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, Decodecylmethyl sulphoxide etc.

Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.

Bile Salts: e.g. Sodium 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.

c) Miscellaneous chemicals: These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently
been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.

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.

Desirable features for transdermal patches

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is (typically) zero order.
Delivery is efficient.

TYPES OF TRANSDERMAL PATCHES

Four Major Transdermal Systems

1. **Single-layer Drug-in-Adhesive**

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. The intrinsic rate of drug release from this type of drug delivery system is defined by

\[
\frac{dQ}{dT} = \frac{Cr}{1/P_m + 1/P_a}
\]

Where Cr is the drug concentration in the reservoir compartment and Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane. Pm is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. Pm and Pa, respectively, are defined as follows.

\[
P_m = \frac{K_{m/t} \cdot D_m}{h_m}
\]

\[
P_a = \frac{K_{a/m} \cdot D_a}{h_a}
\]
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where $K_{m/r}$ and $K_{a/r}$ are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively; $D_m$ and $D_a$ are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and $h_m$ and $h_a$ are the thicknesses of the rate controlling membrane and adhesive layer, respectively.\(^8\)

2. Multi-layer Drug-in-Adhesive

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 multiple drug-in-adhesive layers under a single backing film.

The rate of drug release in this system is defined by:

$$\frac{dQ}{dt} = \frac{K_{a/r} \cdot D_a}{h_a} \cdot \frac{C_r}{C_i}$$

Where $K_{a/r}$ is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

3. Drug Reservoir-in-Adhesive
The Reservoir transdermal system design is characterized 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.

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

\[
\frac{dQ}{dt} = \frac{K_{aw} \cdot Da}{h_a(t) A(h_a)}
\]

In the above equation, the thickness of the adhesive layer for drug molecules to diffuse through increases with time \( h_a(t) \). To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusion path \( A(h_a) \).

**4. Drug Matrix-in-Adhesive**

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in 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,

Where \( A \) is the initial drug loading dose dispersed in the polymer matrix and \( C_p \) and \( D_p \) are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, \( C_p \) is essentially equal to \( C_R \), where \( C_R \) is the drug concentration in the reservoir compartment.
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indication</th>
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<tr>
<td>Alora</td>
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<td>TheraTech/Protocol &amp; Gamble</td>
<td>Posmenstrual syndrome</td>
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<tr>
<td>Androderm</td>
<td>Testosterone</td>
<td>Glaxosmithkline</td>
<td>Hypogonadism in males</td>
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<td>Catapress- TTS</td>
<td>Clonidine</td>
<td>Alza/Boehinger Ingelheim</td>
<td>Hytension</td>
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<td>Climara</td>
<td>Estradiol</td>
<td>3 M Pharmaceutical/Berlex Labs</td>
<td>Postmenstrual syndrome</td>
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<td>Deponit</td>
<td>Nitroglycerin</td>
<td>Schwarz-Pharma</td>
<td>Angina pectoris</td>
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<td>Alza/Janssen Pharmaceutical</td>
<td>Moderate/ severe pain</td>
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<td>Nicotine</td>
<td>Novartis</td>
<td>Smoking cessation</td>
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<td>Ethical Holdings/Schering</td>
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<td>Prostep</td>
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<td>Smoking cessation</td>
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<tr>
<td>Testoderm TTs</td>
<td>Testostrone</td>
<td>Alza</td>
<td>Hypogonadism in males</td>
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<td>Transderm scop</td>
<td>Scopolamine</td>
<td>Novaatis</td>
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<td>Transderm Nitro</td>
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<td>Vivelle</td>
<td>Estradiol</td>
<td>Noven Pharmaceuticals</td>
<td>Postmenstrual syndrome</td>
</tr>
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Administered by this route and the common names by which they are marketed; it also gives the conditions for which the individual system is used.
Transdermal Market

The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future\textsuperscript{10}. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, active ingredients are approved for use in TDD products globally. The table 1 gives detail information of the different drugs which are

ADVANCE DEVELOPMENT IN TDDS

The pie diagram given below shows that Fentanyl and nitroglycerine are the drugs most popularly marketed using transdermal patches\textsuperscript{11}.

Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called “active”
transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.\textsuperscript{10}

**Evaluation For Transdermal Drug Delivery System**

Transdermal drug delivery system requires systemic evaluation at various stages of its development. These evaluation tests are described below\textsuperscript{12}.

1. **Evaluation of Adhesive**
2. **In-vitro drug release**
3. **In-vivo evaluation**

1. **Evaluation of Adhesive:** Pressure sensitive adhesives are evaluated for the following properties.

   A. **Peel adhesion properties:** Peel adhesion is the required to remove an adhesion coating from a test substrate. The important in transdermal devices because the adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular weight of the adhesive polymer, the type & amount of additives and polymer composition. It is tested by measuring the force required to pull a single coated tape applied to a substrate at a \(180^\circ\) angle.

   B. **Track properties:** Track is the ability of a polymer to adhere to a substrate with little contact pressure. It is important in transdermal devices which are applied with finger pressure. Track is dependent on the molecular weight and composition of polymer as well as the use of tackifying resins in the polymer. Tests for tack include\textsuperscript{11}:

   i) **Thumb tack test:**

   This is a subjective test in which evaluation is done by pressing the thumbs briefly into the adhesive experience is required for using this test.
ii) **Rolling ball tack test:**

This test involves measurement of the distances that a stainless ball travels along an upward-facing adhesive. The test tacky the adhesive the farther the ball will travel.

iii) **Quick stick (or peel-tack) test**

The peel force required to break the bond between an adhesive and substract is measured by pulling the tape away from the substrate at $90^\circ$ at a speed of 12 inch/min.

2. **In-vitro drug release evaluation:**

The design and development of transdermal drug delivery systems is greatly aided by in vitro studies. In vitro studies can help in investigating the mechanisms of skin permeation of the drug before it can be developed into a transdermal therapeutic system. In vitro studies excised skin in mounted on skin permeation cells. It is generally considered alied to use excised skin in vitro studies because the stratum corneum which is physiologically inactive tissue, is the principle barrier to the permeation of a drug and diffusion through the stratum corneum is a passive process.

Then the apparent rate of release or permeation obtained in an experiment can be corrected for the effect of hydrodynamic diffusion layer and the intrinsic rate of release or permeation can determined.

3. **In-vivo evaluation**

By using varies animal models, Human Models, Biophysical models.

**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 micro needles for administration of a wide variety of drugs in the future.

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