ABSTRACT:

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. The relative impermeability of skin is well known, and this is associated with its functions as a dual protective barrier against invasion by micro-organisms and the prevention of the loss of physiologically essential substances such as water. Elucidation of factors that contribute to this impermeability has made the use of skin as a route for controlled systemic drug delivery possible. Basically, four systems are available that allow for effective absorption of drugs across the skin. The microsealed system is a partition-controlled delivery system that contains a drug reservoir with a saturated suspension of drug in a water-miscible solvent homogeneously dispersed in a silicone elastomer matrix. A second system is the matrix-diffusion controlled system. The third and most widely used system for transdermal drug delivery is the membrane-permeation controlled system. A fourth system, recently made available, is the gradient-charged system. Additionally, advanced transdermal carriers include systems such as iontophoretic and sonophoretic systems, thermosetting gels, prodrugs, and liposomes. Many drugs have been formulated in transdermal systems, and others are being examined for the feasibility of their delivery in this manner (e.g., nicotine antihistamines, beta-blockers, calcium channel blockers, non-steroidal anti-inflammatory drugs, contraceptives, anti-arrhythmic drugs, insulin, antivirals, hormones, alpha-interferon, and cancer chemotherapeutic agents). Research also continues on various chemical penetration enhancers that may allow delivery of therapeutic substances. For example, penetration enhancers such as Azone may allow delivery of larger-sized molecules such as proteins and polypeptides.

KEYWORDS: Transdermal, elastomer, iontophoretic, sonophoretic.

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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 (site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery system are also essential for the delivery of novel, genetically engineered pharmaceuticals (ie 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 system coupled with the increased expense in bringing new drug moiety to the market. One of the methods most often utilized has been transdermal delivery - 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 blood stream. 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 system. Sweat ducts and hair follicles are also paths of entry, but they are considered rather insignificant.

DEFINATION

Transdermal drug delivery system are topically administered medicament 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. 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.

Advantage:

1. Avoids gastrointestinal tract difficulties during absorption caused by enzymes, drug interactions with food, etc.

2. Suitable in instances like vomiting/diarrhoea where oral route is not desirable.

3. Avoids first pass i.e. the initial passage of a drug substance through the systemic and portal circulation.

4. Provides the capacity for multi day therapy with a single application thereby improving patient compliance. Extends the activity of drugs having short half-life through the reservoir of drug present in the delivery system and its controlled release characteristics.

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
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.

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.
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 acetal and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N-methyl, 2-purrolidone; 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 sulphonyl oxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc. Bile Salts: e.g. Sodium m-taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

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\[8\].

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.

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.\textsuperscript{[9]}

TYPES OF TRANSDERMAL PATCHES

Four Major Transdermal Systems


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\textsuperscript{[11]}.

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\textsuperscript{[11]}.

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\textsuperscript{[11]}. 

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. \textsuperscript{[11]}

RECENT TRANSDERMAL PATCHES REVISITED ADVANCES

The number of medications and the ways in which they can be administered have expanded dramatically over the years. One such advance has been the development of transdermal patch delivery systems. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems. This review article covers a brief outline of various components of transdermal patch, applications of transdermal patch, their advantages, disadvantages, when the transdermal patch are used and when their use should be avoid and some of the recent development in the field along with the latest patents in this field.
## Marketed Products of Transdermal Patches

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinell</td>
<td>Nicotine</td>
<td>Novartis</td>
<td>Pharmacological smoking cessation</td>
</tr>
<tr>
<td>Matrifen</td>
<td>Fentanyl</td>
<td>Nycomed</td>
<td>Pain relief patch</td>
</tr>
<tr>
<td>Ortho Evra</td>
<td>Norelgestromin/</td>
<td>ORTHO-McNEIL</td>
<td>Postmenstrual syndrome</td>
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<tr>
<td></td>
<td>Ethinyl Estradiol</td>
<td></td>
<td></td>
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<tr>
<td>NuPatch</td>
<td>Diclofenac</td>
<td>Zydus Cadila</td>
<td>Anti Inflammatory</td>
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<td>100</td>
<td>diethylamine</td>
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<tr>
<td>Neupro</td>
<td>Rigotine</td>
<td>UCB and Schwarz Pharma</td>
<td>early-stage idiopathic Parkinson’s disease</td>
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<tr>
<td>Alora</td>
<td>Estradiol</td>
<td>TheraTech/Proctol and Gamble</td>
<td>Postmenstrual syndrome</td>
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<tr>
<td>Nicoderm</td>
<td>Nicotine</td>
<td>Alza/GlaxoSmithKline</td>
<td>Smoking cessation</td>
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<tr>
<td>Estraderm</td>
<td>Estradiol</td>
<td>Alza/Norvatis</td>
<td>Postmenstrual syndrome</td>
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<tr>
<td>Climara</td>
<td>Estradiol</td>
<td>3M Pharmaceuticals/Berlex Labs</td>
<td>Postmenstrual syndrome</td>
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<tr>
<td>Androderm</td>
<td>Testosterone</td>
<td>TheraTech/GlaxoSmithKline</td>
<td>Hypogonadism in</td>
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<td>Drug</td>
<td>Active Ingredient</td>
<td>Manufacturer</td>
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<tr>
<td>Nitrodisc</td>
<td>Nitroglycerin</td>
<td>Roberts Pharmaceuticals</td>
<td>Angina pectoris</td>
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<tr>
<td>Nuvelle TS</td>
<td>Estrogen/Progestrone</td>
<td>Ethical Holdings/Schering</td>
<td>Hormone replacement therapy</td>
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<td>Schwarz-Pharma</td>
<td>Angina pectoris</td>
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<td>Catapres TTS&lt;sup&gt;R&lt;/sup&gt;</td>
<td>Clonidine</td>
<td>Alza/Boehinger Ingelheim</td>
<td>Hypertension</td>
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<td>Parke-Davis</td>
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<tr>
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<td>Angina pectoris</td>
</tr>
<tr>
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<td>Estradiol</td>
<td>Ethical Holdings/Wyeth-Ayerest</td>
<td>Postmenstrual syndrome</td>
</tr>
<tr>
<td>Duragesic&lt;sup&gt;R&lt;/sup&gt;</td>
<td>Fentanyl</td>
<td>Alza/Janssen Pharmaceutical</td>
<td>Moderate/severe pain</td>
</tr>
<tr>
<td>Product</td>
<td>Active Ingredient</td>
<td>Company/Supplier</td>
<td>Condition</td>
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<td>Estraderm</td>
<td>Estradiol</td>
<td>Alza/Norvatis</td>
<td>Postmenstrual syndrome</td>
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<tr>
<td>Fematrix</td>
<td>Estrogen</td>
<td>Ethical Holdings/Solvay</td>
<td>Postmenstrual syndrome</td>
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<td>Healthcare Ltd.</td>
<td></td>
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<tr>
<td>Transderm-Nitro&lt;sup&gt;R&lt;/sup&gt;</td>
<td>Nitroglycerin</td>
<td>Alza/Norvatis</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Testoderm TTS&lt;sup&gt;R&lt;/sup&gt;</td>
<td>Testosterone</td>
<td>Alza</td>
<td>Hypogonadism in males</td>
</tr>
<tr>
<td>Oxytrol&lt;sup&gt;R&lt;/sup&gt;</td>
<td>oxybutynin</td>
<td>Watson Pharma</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>Prostep</td>
<td>Nicotine</td>
<td>Elan Corp./Lederle Labs</td>
<td>Smoking cessation</td>
</tr>
</tbody>
</table>

**FACTORS AFFECTING TRANSDERMAL BIOAVAIBILITY<sup>[4,16]</sup>**

Two major factors affect the bioavailability of the drug via transdermal routes:

1. Physiological factors
2. Formulation factors

**Physiological factors include<sup>[4,16]</sup>**:

1. Stratum corneum layer of the skin
2. Anatomic site of application on the body
3. Skin condition and disease
4. Age of the patient
5. Skin metabolism
6. Desquamation (peeling or flaking of the surface of the skin)
7. Skin irritation and sensitization
8. Race

**Formulation factors include<sup>[4,16]</sup>**:
(1) Physical chemistry of transport (2) Vehicles and membrane used (3) Penetration enhancers used (4) Method of application (5) Device used

Care taken while applying transdermal patch[17]

(1) The part of the skin where the patch is to be applied should be properly cleaned. (2) Patch should not be cut because cutting the patch destroys the drug delivery system. (3) Before applying a new patch it should be made sure that the old patch is removed from the site. (4) Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch. (5) The patch should be applied accurately to the site of administration.

MECHANISM OF ACTION OF TRANSDERMAL PATCH

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

1. Iontophoresis[18, 19]

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

2. Electroporation[18, 20, 21, 22, 23]

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

3. Application by ultrasound[18, 24]

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

4. Use of microscopic projection[18]

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in
rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.

Various other methods are also used for the application of the transdermal patches like thermal poration, magnetophoresis, and photomechanical waves. However, these methods are in their early stage of development and required further detail studying.

**RECENT RESEARCH DONE IN THE FIELD**

Many research works have been and are few are going on in this field. Few of the latest research done in the field of transdermal patches are stated below:

Pain-free diabetic monitoring using transdermal patches[26]

Testosterone Transdermal Patch System in Young Women with Spontaneous Premature Ovarian Failure[27]. Transdermal Patch of Oxybutynin used in overactive Bladder[28, 29, 30]. Transdermal Patch (Ortho Evra™)[31]. Rotigotine transdermal patch[32].

**ADVANCE DEVELOPMENT IN TDDS**

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 ad formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch[12]. 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.[12]

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.

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