Transdermal Patches: A Complete Review on Transdermal Drug Delivery System

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ABSTRACT

Today about 70% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy and differs from traditional topical drug delivery. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs by means of skin. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. This review article covers a brief outline of the principles of transdermal permeation, various components of transdermal patch, approaches of transdermal patch, evaluation of transdermal system, its application with its limitation.

KEYWORDS

Transdermal delivery, Patch, Microneedle, Method of preparation, Evaluation parameter

INTRODUCTION

Transdermal drugs are self contained, discrete dosage form. Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs by the mean of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. Delivering medicine to the general circulation the skin is seen as a desirable alternative to taking it by mouth or by oral route. By passing through the gastrointestinal tract would obviate the GI irritation that frequently occurs and avoid first pass in activation by liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms.

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FDA approved the first transdermal patch product in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of motion sickness while nitroglycerine for the prevention of angina pectoris associated with coronary artery disease. More recently, such dosage forms have been developed and modified in order to enhance the driving force of drug diffusion and to increase the permeability of the skin. These approaches include the use of penetration enhancers, supersaturated systems, prodrugs, liposomes and other vesicles. The highest selling transdermal patch in United States was the nicotine patch which release nicotine to help with cessation of tobacco smoking. The nicotine patch releases nicotine over sixteen hours, continuously suppressing the smoker’s craving for a cigarette. 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. Current transdermal drug delivery (TDD) relies primarily upon occlusive patches, and is now considered to be a mature technology. This method is capable of delivering drugs, the use of which would be limited due to poor oral bioavailability, side effects associated with high peaks or poor compliance due to the need for frequent administration. However, the negatives of TDDs have been skin irritation, relatively high manufacturing costs and less-than-ideal cosmetic appearance.

**ADVANTAGES**

- Avoidance of first pass metabolism
- Avoidance of gastrointestinal incompatibility
- Predictable and extended duration of activity
- Provides utilization of drugs with short biological half lives
- Narrow therapeutic window
- Improving physiological and pharmacological response
- Avoiding the fluctuation in drug levels
- Inter and intra patient variations
- Maintain plasma concentration of potent drugs
- Termination of therapy is easy at any point of time
- Greater patient compliance due to elimination of multiple dosing profile
- Ability to deliver drug more selectively to a specific site
- Provide suitability for self administration
- Enhance therapeutic efficacy

**DISADVANTAGES**

- The drug must have some desirable physicochemical properties for penetration through stratum corneum.
- The transdermal delivery will be very difficult, if the drug dose required is more than 10 mg/day for their therapeutic application.
- Only relatively potent drugs are suitable candidates for TDDS.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

**THE SKIN**

The skin (cutis) is not just the largest human organ but also an excellent biological barrier. Despite being normally less than ≤2mm thin, the skin contributes around 4% to a body weight and is 102–104 times less permeable than a blood capillary wall. The outer skin part (epidermis) is in humans generally 0.02–0.2 mm thin. Gender and body site also affect skin surface PH. The region below epidermis is called dermis. It consists of the outer papillary and the inner reticular dermis, which taken together are usually 5–20-times thicker than epidermis. This multilayered organ has an essential function of protecting the body from the surrounding environment, thus being an efficient permeation obstacle for exogenous molecules. The barrier properties of the skin lie mainly within its uppermost strata, the stratum corneum (SC). This highly hydrophobic layer is composed of differentiated non-nucleated cells, corneocytes, which are filled with keratins and embedded in the lipid domain. Its effective elastic modulus is in the 107–108Pa range but decreases with temperature and hydration. The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. The skin appendages occupy only 0.1% of the total human skin surface. Even though, the foreign agents may be able to penetrate into the skin via these skin appendages at a rate which is faster than the stratum...
corneum. The extent of skin permeation of a compound may depend on the route of absorption. There are three pathways which can be involved in the transdermal permeation of chemicals:

1. Through the intercellular lipid domains in SC;
2. Through the skin appendages; and
3. Through the keratin bundles in SC.

**Figure: 1 Drug Permeation Mechanism through the Skin**

**FACTORS AFFECTING TRANSDERMAL PERMEATION:**

**Physicochemical Properties of the Penetrant Molecules:**

**Partition coefficient**
- A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.
- It may be altered by chemical modification without affecting the pharmacological activity of the drug.

**pH conditions**
- Applications of solutions whose pH values are very high or very low can be destructive to the skin.
- With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

**Penetrate concentration**
- Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.
- At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

**Physicochemical Properties of the Drug Delivery System:**

**Release characteristics**
- Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:
  - Whether the drug molecules are dissolved or suspended in the delivery systems.
  - The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
  - pH of the vehicle

**Composition of the drug delivery systems**
- The composition of the drug delivery systems(boundary layers, thickness, polymers, vehicles)not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., Benzocaine permeation decreases with PEG of low molecular weight.

**Enhancement of transdermal permeation**
- Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy.
- In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the DDS.
Skin Structure Related:
- Stratum corneum layer of the skin
- Anatomic site of application
- Skin metabolism
- Desquamation (peeling or flaking of the surface of the skin)
- Skin irritation and sensitization
- Physical chemistry of transport

Formulation Related:
- Vehicles and membrane used
- Penetration enhancers used
- Method of application
- Device used
- Partition coefficient of 1 or greater is required
- Age of the patient

**TYPES OF TRANSDERMAL PATCHES**

There is a Four Major Types Of Transdermal Patch:

**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.

**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.

**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.

**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.

**BASIC COMPONENTS OF TRANSDERMAL PATCH:**

**Polymer Matrix / Drug Reservoir:**

Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers:

An outer impervious backing layer that prevents the loss of drug through the backing surface, and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane.

The polymers utilized for TDDS can be classified as:

<table>
<thead>
<tr>
<th>Natural Polymers</th>
<th>Cellulose Derivatives, Zein, Gelatin, Shellac, Waxes, Gums, Natural Rubber and Chitosan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Elastomers</td>
<td>Polybutadiene, Hydrin Rubber, Polyisobutylene, Silicon Rubber, Nitrile, Acrylonitrile, Neoprene, Butylrubber</td>
</tr>
<tr>
<td>Synthetic Polymers</td>
<td>Polyvinyl Alcohol, Polyvinylchloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone</td>
</tr>
</tbody>
</table>

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinyl pyrrolidone and hydroxyl propyl methyl cellulose are used as matrix formers for TDDS. Other polymers like ethylene vinyl acetate (EVA), silicon rubber and polyurethane are used as rate controlling membrane.

**Drug**

The best drug candidates for passive adhesive transdermal patches should comply following criteria:

- Should be Non ionic
- Should have Low molecular weight (less than 500 Daltons)
- Should have adequate solubility in oil and water (log P in the range of 1-3)
- Should have low melting point (less than 200°C)
- Should be potent (dose in mg per day).

Drugs like rivastigmine for alzheimer’s and Parkinson dementia, rotigotine for parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

**Permeation Enhancers**

To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug penetration enhancers interact with structural components of stratum corneum *i.e.*, proteins or lipids. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for transepidermal and transfollicular penetration.

**CLASSIFICATION OF PENETRATION ENHANCERS**

<table>
<thead>
<tr>
<th>Terpenes</th>
<th>Nerodilol, menthol, 1 8 cineol,limonene, Carvone</th>
</tr>
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<tbody>
<tr>
<td>Pyrrolidones</td>
<td>N-methyl-2-pyrrolidone(NMP), azone</td>
</tr>
<tr>
<td>Fatty acids and esters</td>
<td>Oleic acid, linoleic acid, lauric acid, capric acid.</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Sulfoxides and similar compounds</th>
<th>Dimethyl sulfoxide (DMSO), N,Ndimethyl Formamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohols, Glycols, and Glycerides</td>
<td>Ethanol, Propylene glycol, Octyl alcohol</td>
</tr>
<tr>
<td>Micellaneous Enhancers</td>
<td>Phospholipids, Cyclodextrins, Amino acid derivatives, enzymes</td>
</tr>
</tbody>
</table>

**Chemical Enhancers**
- Increasing the drug permeability through the skin by causing reversible damage to the SC.
- Increasing (and optimizing) thermodynamic activity of the drug when functioning as co-solvent.
- Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin.
- Conditioning the SC to promote drug diffusion.
- Promoting penetration and establish drug reservoir in the SC.

**Physical Enhancers**
- The iontophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents.

**Pressure Sensitive Adhesives (PSA)**
A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. For example polyacrylates, polyisobutylene and silicon based adhesives. PSA should be physicochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device (as in reservoir system) or in the back of the device and extending peripherally (as in case of matrix system).

**Backing Laminate**
While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipients compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusive to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films.

**Release Liner**
During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metalized laminates.

**Other Excipients**
Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

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**METHOD OF PREPARATION**

**Asymmetric Tpx ((poly (4-methyl-1-pentene))) Membrane Method**

A prototype patch can be prepared by using a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter 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.

**Circular Teflon Mould Method**

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug and Enhancers in different concentrations are dissolved in the organic solvent. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. 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.

**By Using “Ipm (Isopropyl Myristate) 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. The formed gel will be incorporated in the IPM membrane.

**By Using “Evac (ethylene vinyl acetate copolymer) Membranes” Method**

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. 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.

**Aluminium Backed Adhesive Film Method**

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. For preparation of same, the drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

**Preparation of TDDS by Using Proliposomes**

The proteoliposomes are prepared by carrier method using film deposition technique. The proteoliposomes 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 proteoliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proteoliposomes) 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.

**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 dry film will be separated out and stored between the sheets of wax paper in a desiccator until use.
Membrane Permeation – Controlled Systems
In this type of system, drug reservoir is encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate – controlling polymeric membrane.

Adhesive Dispersion – Type Systems
The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.

Matrix Diffusion- Controlled Systems
In this approach, the drug reservoir can be formed by dissolving the drug and the polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. This drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing membrane. The polymer is spread along the circumference of the patch to form an adhesive rim around the medicated disc. e.g. Nitro-Dur: Delivers nitroglycerin for the treatment of angina pectoris.

Micro Reservoir Type or Micro Sealed Dissolution
The drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer (e.g. Polyethylene glycol) and then dispersing the drug suspension homogenously in lipophillic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable micro spheres of drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim. E.g. Nitroglycerin: Releasing transdermal therapeutic system for once – a day treatment of angina pectoris. Treatment with Protocatechuic acid produced a significant decrease in the serum level of lipids in atherogenic diet induced hyperlipidemia in rats. Hence by considering the effects observed in this model, the possible mechanism of Protocatechuic acid may involve increase of HDL-cholesterol, which is attributed to the mobilization of cholesterol from peripheral cells to the liver by the action of Lecithin Cholesterol O-acyltransferase (LCAT) enzyme. LCAT enzyme is involved in the transesterification of cholesterol, the maturation of HDL and the flux of cholesterol from cell membranes into HDL. Thus from the above results we can conclude that Protocatechuic acid has hypolipidemic activity.

ENHANCEMENT IN PERMIATION CAN BE ACHIEVED VIA SYNERGISTIC ACTION OF FOLLOWING CHEMICALS

Water
Increased hydration of the stratum corneum enhances transdermal flux of a variety of drugs.

Hydrocarbons
Several hydrocarbons including alkanes, alkenes, halogenated alkanes, squalane,squalene and mineral oil have been used as vehicles or penetration enhancers to increase permeation of a variety of drugs across the skin. These permeation enhancers generally work by partitioning into the stratum corneum and disrupting the ordered lipid bilayer structure. The alkanes with 9–10 carbon atoms showed highest skin permeation enhancement of propranolol and diazepam while shorter alkanes (5–6 carbon atoms) showed highest permeation enhancement of caffeine.
Acids
These chemicals enhance transport of drug molecules across the skin by a variety of mechanisms such as partitioning into the lipid bilayers and disrupting their ordered domains, improving drug partitioning into the stratum corneum and forming lipophilic complexes with drugs.

Amides
Azone, the first synthetic permeation enhancer and its analogues along with pyrrolidones are the most extensively studied amides.

Esters
Isopropyl myristate is the most widely studied ester along with several other esters of fatty acids. These chemicals generally work by partitioning themselves in the ordered lipid domains of the stratum corneum.

Surfactant
Surfactants are usually used with a vehicle or solvent system and their activity depends upon the hydrophilic to lipophilic balance, charge and lipid tail length. Anionic and non-ionic surfactants are relatively more widely studied compared to others within this category.

Sulfoxides
Dimethyl sulfoxide was the first chemical to be studied in depth as a permeation enhancer.

Lipid
In the form of self-assembled structures such as vesicles or micelles, they can fuse with the lipid bilayers of the stratum corneum thereby enhancing partitioning of encapsulated drug as well as disruption of the ordered bilayers structure.

The mechanisms by which such systems increase transdermal flux may include:
(a) Change in the thermodynamic activity (e.g., by increasing the degree of saturation in the solvent and, hence, increasing the escaping tendency)
(b) Specific interaction with the stratum corneum, either by increasing the drug solubility in the stratum corneum (i.e., facilitate partitioning of drug from the vehicle into the skin) or by altering the various transport pathways (i.e., the polar and nonpolar pathways) in the stratum corneum.

A NEW APPROACH OF NANO PARTICLES AND MICRO-SCALE DEVICE USED IN TDDS

NANOPARTICLES
Nanoparticles for pharmaceutical applications range from the size and shape of a (spherical) micelle through to 1 μm. In a suspension they are always much longer lived than micelles. This can be a consequence of polymeric conjugation (e.g. in polymeric nanoparticles, such as latex, or in the special purpose polymer particles); poor solubility of the components that form nanoparticles core is the other common reason (e.g. in the solid ordered phase) lipid particles sized between 50 nm and 1000 nm. Rare cutaneous shunts excluding, normal stratum corneum only contains pores with 10 nm diameter, the majority of which are smaller than 5 nm. If this were not the case, skin would soon be infected by pathogens from its surface. It consequently stands to reason that a nanosized aggregate useful for drug delivery across skin barrier must either widen an epidermal pathway to the size of the aggregate, but not much more, or else improve transdermal transport indirectly, by acting as skin permeation enhancer.

Mechanisms of Transdermal Drug Delivery with Nanosized Particulates
First, measure the rate of transbarrier transport for the different nominal pore/penetrant size ratios focusing on the values N1, since the particles with a lower value should have no
problem diffusing through a semipermeable membrane; if the first test excluded substantive sieving for the relative size ratios $\geq 1.5$, in the second test recheck the penetrants size after barrier crossing, and in case of doubt scrutinize the outcome of different driving forces creating various transport rates to clarify the situation; if the average (extrapolated) penetrants size remained more or less the same after pores passage, in the third test series vary the penetrants number density or concentration, or else the penetrant/pore density ratio to assess the extent of simple permeation; fourth, gauge the proportionality between transport rate and penetration driving force to verify the results conformity with comparing the results of an occlusive and a non-occlusive application can identify hydration gradient as the main source of transport driving force.

Example of Nanoparticles in TDDS

Ketoprofen applied epidermally in a conventional gel diffuses readily across the skin, as this NSAID is both suitably small (MW=254.3) and soluble in lipids (log PN=3.3; log PI=1; log Dapparent~2). However, the drug is then rapidly cleared from underlying subcutaneous tissue. Its half-life in pigs ($t_{1/2}$~2 h) is consequently similar for a topical drug application and an intramuscular drug injection. The drug half-life in the plasma is also practically the same in healthy young volunteers taking oral, rapidly absorbed, drug (Oruvail®; Sanofi-Aventis information). Ketoprofen bioavailability from several conventional gels in pigs is $\leq 7\%$, consistent with the results of in vitro human skin permeation measurements with ketoprofen and with independently measured data.

MICRO SCALE INJECTOR DEVICE USED IN TDDS

Such device can maximize the delivery efficiency and can minimize the undesirable reactions. So, over the last decade, great progress has been made with the advent of devices which have at least one working parameter in micrometer range and are collectively referred to as micro-scale devices. Operation at micron scale is important because micron-sized breaches in the stratum corneum barrier are large enough to let most drugs through, since most drugs are of nanometer dimensions. At the same time, they are small enough that they appear to be safe, well tolerated by patients and allow rapid skin recovery post-administration. Such micro-scale devices include liquid jet injectors, solid powder injectors, microneedles.

Liquid Jet Injector

These are single-dose jet injectors, known as DCJIs (disposable cartridge jet injectors) and MUNJIs (multi-use-nozzle jet injectors). Some DCJIs are only partly disposable while others are fully disposable. MUNJIs did not have any disposable parts and were introduced for rapid mass immunization. Their use, however, was discontinued in the wake of reports of spread of hepatitis B in the 1980s due to their use.

Mechanism

The basic design of commercial liquid jet injectors consists of a power source (compressed gas or spring), piston, drug-loaded compartment and a nozzle with orifice size typically ranging between 150 and 300 m. Upon triggering the actuation mechanism, the power source pushes the piston which impacts the drug-loaded compartment, thereby leading to a quick increase in pressure. This forces the drug solution through the nozzle orifice as a liquid jet with velocity ranging between 100 and 200m/s.

Applications

MUNJIs have been used for mass immunization programs for diseases including measles, smallpox, cholera, hepatitis B, influenza and polio. DCJIs have been used for delivery of several proteins. Most work has been done on delivery of insulin and growth hormones while erythropoietin and interferon have also been delivered.

Insulin administration by jet injectors led to a faster delivery into systemic circulation, possibly due to better dispersion at the injection site.
Powder Injectors

Powder jet injectors deliver vaccines or drugs in dry powdered form into superficial layers of skin. The terms biolistic injectors and gene guns have also been commonly used for these injectors, with the latter term used exclusively for DNA delivery.

Mechanism

Basic design of solid jet injectors include compressed gas as the power source, a drug compartment containing particulate drug formulation, and a nozzle to direct the flow of particles. The drug compartment is closed with diaphragms on either side, which are typically few microns thick. Upon triggering the actuation mechanism, compressed gas from a storage canister expands and pushes against the diaphragms, sequentially rupturing them. The flow of gas carries the drug particles with it.

Applications

Solid jet injectors have been studied for delivery of DNA encoding for viral and bacterial antigens using coated gold microparticles. Induction of humoral and cell mediated immune response against influenza, hepatitis B and rabies has been shown in mice. Protection against tumors has also been demonstrated by injecting DNA coated gold micro-particles and DNA encapsulated in polymeric particles.

Microneedles

Microneedles, as the name suggests, are micron-scale needles that are employed for transdermal vaccination and drug delivery. The recognition that very small needles may be sufficient for transport across the 10–20 μm-thick stratum corneum was first proposed in the 1970s. Four different types of microneedle designs have been developed, which include solid microneedles that pierce the skin to make it more permeable, solid microneedles coated with dry powder drugs or vaccines for dissolution in the skin, microneedles prepared from polymer with encapsulated vaccine for rapid or controlled release in the skin, and hollow microneedles for injections. Metals used in solid microneedles include stainless steel, titanium and nickel-iron. Polymeric needles use engineering plastics, biodegradable polymers and water-soluble polymers such as polycarbonate, polylactic-co-glycolic acid, and carboxymethylcellulose, respectively.

Mechanism

All types of microneedles are typically fabricated as an array of up to hundreds of microneedles over a base substrate. Solid microneedles can either be pressed onto the skin or scraped on the skin for creating microscopic
holes, thereby increasing skin permeability by up to four orders of magnitude. This is followed by application of drugs or vaccines from a patch or topical formulation. Residual holes after microneedle removal measure microns in size and have a lifetime of more than a day when kept under occlusion, but less than 2 h when left uncovered.

Figure: 4. Schematic of drug delivery using different designs of microneedles: (a) solid microneedles for permeabilizing skin via formation of micron-sized holes across stratum corneum. The needle patch is withdrawn followed by application of drug-containing patch, (b) solid microneedles coated with dry drugs or vaccine for rapid dissolution in the skin, (c) polymeric microneedles with encapsulated drug or vaccine for rapid or controlled release in the skin, (d) hollow microneedles for injection of drug solutions.

Applications
Microneedles have been studied in vitro, in animals and in humans for a variety of applications. Microneedle piercing has been shown to increase skin permeability by orders of magnitude to a variety of compounds ranging from low molecular weight tracers to proteins, DNA and even nanoparticles. A recent study reported on delivery of naltrexone, which is used to treat alcohol and opioid addiction, at therapeutic levels in normal human subjects using this approach. Solid microneedles have also been coated with a number of different compounds, including low molecular weight drugs, proteins, DNA, virus particles and microparticles. Human clinical trials by Zosano Pharmaceuticals (Freemont, CA, USA) had completed Phase II clinical trials for delivery of parathyroid hormone from coated microneedles. Dissolving polymer microneedles have similarly encapsulated various compounds, including erythropoietin and enzymes that were shown to retain activity after encapsulation and even after at least 2 months of storage at room temperature. Hollow microneedles have been shown to deliver insulin to rodent models and modulate blood glucose levels.

Evaluation Parameters

Thickness
The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight
Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination
An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Content uniformity test
10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20
Transdermal Patches: A Complete Review on Transdermal Drug Delivery System

patches have range from 85% to 115%, then the transdermal patches pass the test.

**Folding endurance**

A strip of specific area 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.

**Tack properties**

It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

**Rolling ball tack test**

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

**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.

**Skin Irritation study**

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm²) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

**Stability studies**

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

**In vitro drug release studies**

The paddle over disc method (USP apparatus V) can be used for determination of drug content. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32±0.5°C and operated at a speed of 50 rpm. Samples (5-mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC.

**In vitro permeation studies**

Permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophililc side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated.

**In vivo studies**

The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using Animal models, Human volunteers.
Animal models
The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc.

Human models
The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc.

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE NOT USED:
The use of transdermal patch is not suitable when:
(1) Cure for acute pain is required.
(2) Where rapid dose titration is required.
(3) Where requirement of dose is equal to or less than 30 mg/24 hrs

IDEAL REQUIREMENT OF DRUG TRANSDERMAL PATCH:
- Shelf life up to 2 years
- Dose should be low i.e <20mg/day.
- Half life should be 10 h or less.
- Molecular weight should be <400.
- Partition coeffecient should be LogP (octanol-water) between 1.0 and 4.
- Skin permeability coefficient should be <0.5 X 10-3cm/h.
- Drug should be non irritating and non sensitizing to the skin.
- Oral bioavailability should be low.
- Therapeutic index should be low.

IDEAL PRODUCT REQUIREMENTS:
- Shelf life up to 2 years
- Small size patch (i.e., less than 40 cm²)
- Convenient dose frequency (i.e., once a day to once a week)
- Cosmetically acceptable (i.e., clear, white color)
- Simple packaging (i.e., minimum number of pouches and steps required to apply the system)
- Easy removal of the release liner (i.e., for children and elderly patients)
- Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma)
- No residue i.e., —cold flow around the edge of the patch in storage or after application to skin or beneath the patch after removal)
- No unacceptable dermal reactions (i.e., contact dermatitis, skin sensitization, phototoxicity, photosensitization, erythema, itching, stinging, burning, etc.)
- Consistent biopharmaceutical performance (i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same individuals over

LIMITATIONS OF TRANSDERMAL DRUG DELIVERY SYSTEMS:
- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin
- Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitzation
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn’t possess a favourable, o/w partition coefficient.
The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

**APPLICATIONS OF TRANSDERMAL PATCHES**

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- The anti-hypertensive drug Clonidine is available in transdermal patch form.
- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

**FUTURE TECHNOLOGIES AND APPROACHES**

- Thermal poration is the formation of aqueous pathways across stratum corneum by the application of pulsed heat, this approach has been used to deliver conventional drugs and to extract intestinal fluid glucose from human subjects.
- Jet injectors are receiving increased attention now days, which is opening doors for improved device design for controlled, needle free injection of drug solutions across the skin and into deeper tissue.
- Small needle is inserted a few millimeters into skin and drug solution is flowed through the needle into the skin at controlled rates using a micro infusion pump that is contained within a large patch affixed to skin, morphine has been delivered to humans using this approach.
- During the past decade several theories have been put forward in addressing the combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound.
- TransPharma is focused on products for which our technology will provide clear benefits over existing therapies. Such benefits could include improving safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained release patch formulations, among others.
- The ViaDerm system may be applied to the delivery of local medications for topical applications in the fields of dermatology and cosmetics. The ViaDerm system may also allow enhanced immunisations, providing a nonpainful, safe and effective alternative to current intramuscular or subcutaneous vaccination methods.
- Altea Therapeutics is currently in clinical development of a transdermal patch designed to address a major unmet need by preventing ‘off’ periods and provide an improved therapeutic option for managing Parkinson’s disease.

**CONCLUSION**

The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. It also shows the important information about the use of nanoparticles in TDDS. It helps in optimization in permeability by using different
enhancer and also include future aspects about modification in injector. This review also indicate fundamental understanding of device design parameters and how they affect device interaction with skin has significantly advanced over the last decade.

REFERENCES


