TRANSDERMAL DRUG DELIVERY: A TECHNICAL WRITEUP


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Received on: 21/12/11 Revised on: 14/01/12 Accepted on: 24/01/12

ABSTRACT

Transdermal drug delivery is another system which provides controlled and continuous delivery of the drug through the skin into the systemic circulation. Topical application which involves drug transport to viable epidermal and/or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. Transdermal route provides many advantages over conventional oral and invasive methods of drug delivery such as avoids first pass metabolism, improve patient compliance, maintenance steady state plasma concentration. This article provides an overview of skin permeation pathways, types of transdermal drug delivery system, methods of preparation with different methods of evaluation, and the recent advancement in transdermal drug delivery, which includes Transfersomes, Magnetophoresis, Controlled Heat Aided Drug Delivery System, Laser Radiation, Medicated Tattoos, Laser radiation.

KEY WORDS: Topical drug delivery, percutaneous permeation, adhesive, penetration enhancers, proliposomes, transfersomes, magnetophoresis.

INTRODUCTION

Conventional systems of medication require multi dose therapy to deliver the right amount of medicine at the right target site, which becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient. The design of conventional dosage form whether it is in tablet form or injection form or in a patch form, has to be delivered in an optimal manner, which becomes complicated1-2.

Optimum therapeutic outcomes required not only proper drug selection but also effective drug delivery. Innovations in drug delivery system, offer substantial clinical advantages including reduced dosage frequency; improved patient compliance & minimized fluctuation of the concentration and maintenance of drug blood level within desired range and reduced adverse effects. The creation of transdermal delivery system has been one of the most important of these innovations3.

Controlled drug release can be achieved by transdermal drug delivery system (TDDS); also known as “Patches”, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin to systemic circulation at a predetermined rate over a prolonged period of time4-8. FDA approved the first transdermal patch products in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of motion sickness (Transderm-scop, ALZA corp.) and nitroglycerine for the prevention of angina pectoris associated with coronary artery disease (Transderm-Nitro). Over the last two decades, more than 35 transdermal products have been approved generating sales of $3.2 billion in 2002, which is predicted to rise to $4.5 billion in 2008. More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the use of penetration enhancers for transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin5-8.

Advantages of transdermal drug delivery systems9

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are avoidance of first pass metabolism and gastro intestinal incompatibility, predictable and extended duration of activity, minimizing undesirable side effects, provides utilization of drugs with short biological half lives and narrow therapeutic window, Greater patient compliance due to elimination of multiple dosing profile.

Disadvantages of transdermal drug delivery systems10

Only small lipophilic drugs can be delivered currently through the skin, avoids peak and trough drug levels and longer multiday dosing interval, drug molecule must be potent because patch size limits amount that can be delivered and also not suitable for high drug doses which will show skin irritation and hypersensitivity reactions.

Since the human skin is a readily accessible surface for drug delivery. Skin of an average adult body covers a surface of approximately 2 m² and receives about one-third of the blood circulating through the body. Skin contains an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of dead cells embedded in a continuous matrix of lipid membranous sheets. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body11. Transdermal drug delivery the delivery of drugs across the skin and into systemic circulation is distinct from topical drug penetration, which targets local areas. Transdermal drug delivery provides advantage of the relative accessibility of the skin12.

Pathway of Transdermal permeation13-14

Permeation can occur by diffusion via.

a) The appendageal route

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skins surface area), thus limiting the area available for direct contact of the applied drug formulation.

b) Transcellular route

Drugs entering the skin via the transcellular route pass through corneocytes containing highly hydrate keratin provide an aqueous environment for which hydrophilic

JPSI 1 (1), JAN – FEB 2012, 5-12
drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps.

c) Intercellular route
The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons.

- Recalling the ‘bricks and mortar’ model of the stratum corneum, the interdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route.
- The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.

Skin status or conditions for Drug permeation

- **Hydration:** Hydrated skin is more permeable than dry skin.
- **Broken or irritated skin:** Drugs can more easily bypass the stratum corneum, increases permeability.
- **Temperature:** Warmer skin is more permeable.
- **Sunburn:** Initially skin is less permeable; after peeling, it becomes more permeable.
- **Eczema/ Psoriasis:** Regions exhibit increased/decreased permeability.
- **Skin peels:** Removal of the stratum corneum increases permeability.

Basic components of Transdermal Drug delivery system

a) **Drug**
For successfully developing a TDDS, the drug has to be chosen with great care. Some of the desirable properties of a drug and factors to be considered for transdermal delivery are shown in Table 1 & 2.

These are some examples of drugs which are suitable for TDDS like Nicardipine hydrochloride, Captopril, Atenolol, Metoprolol tartrate, Clonidine, Indapamide, Propranolol hydrochloride, Carvedilol, Verapamil hydrochloride and Nitrendipine etc.

b) **Release liner**
During storage the patch is covered by a protective liner that is removed and discarded 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. Liner should be chemically inert and permeable 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.

c) **Polymer matrix / drug reservoir**
Polymers are the backbone of a TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have both good stability as well as compatibility with the drug and other components of the system and they should provide effective release of a drug throughout the device with safe status.

Various Techniques which are employed to modify the Polymer properties and thus Drug Release Rates

Techniques of matrix

- **Cross linked polymers:** The higher the degree of cross linking, the denser the polymer and slower the diffusion of drug molecules through the matrix.
- **Polymer blends:** Polymers have been blended on varying ratios to combine the advantages of the individual polymers. Advantages of polymer blends include easy fabrication of devices, manipulation of drug loading and other devices properties such as hydration, degradation rate and mechanical strength.
- **Plasticizers:** Plasticizers have been known to reduce the stiffness of the polymer backbone, thereby increasing the diffusion characteristics of the drug. Commonly used plasticizers are polyethylene glycol, propylene glycol, glycerol, dibutyl phthalate.

The polymers used for TDDS can be classified as in Table 3.

- **The polymers like polyethylene glycol:** Eudragit, ethyl cellulose, polyvinylpyrrolidone and hydroxypropyl methylcellulose are used as matrix type TDDS.
- **The polymers like EVA:** silicon rubber and polyurethane are used as rate controlling TDDS.

d) **Permeation enhancers**
One long-standing approach for improving transdermal drug delivery by using penetration enhancers (also called sorption promoters or accelerants) which penetrate into skin to increase permeability of stratum corneum by interacting with structural components of stratum corneum i.e. proteins or lipids to attain higher therapeutic levels of the drug. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability.

Some of the more desirable properties for penetration enhancers acting within skin have been given

- They should be non-toxic, non-irritating and non-allergenic.
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body, i.e. should not bind to receptor sites.
- The penetration enhancers should work unidirectionally.
- When removed from the skin, barrier properties should return both rapidly and fully.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.

Some example are Dimethyl sulfoxide (DMSO), Glycol (Propylene glycol), 2-Pyrrolidone, Isopropyl myristate, Laurcapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Pluronic, Cardamom oil, Caraway oil, Lemon oil, Menthol, dlimonene, Linoleic acid.

e) **Pressure sensitive adhesives**
An approach to explain the adhesive properties of pressure sensitive adhesives (PSAs) is based on the belief that the PSA will adhere to a skin, because of inter atomic and intramolecular attractive forces established at the interface, provided that intimate contact is achieved. To obtain this degree of contact, the material must be able to deform under slight pressure, giving rise to the term “pressure sensitive.”
Adhesion involves a liquid-like flow resulting in wetting of the skin surface upon the application of pressure, and when pressure is removed, the adhesive sets in that state. PSA/skin bond can be built by stronger interactions (e.g. hydrogen bonding), which will depend on skin characteristics and other parameters. The PSA should be compatible with the drug and excipients since their presence can modify the mechanical characteristics of the PSA and the drug delivery rate. PSAs used in commercially available Transdermal systems include polyacrylate, polysisobutylene, and polysiloxane.

f) Backing laminate

Backinc materials must be flexible while possessing good tensile strength. Commonly used materials are poloylefins, polyesters, and elastomers in clear, pigmented, or metalted form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing exhibits lowest modulus or flexibility and is ideal for clinical application. Good oxygen transmission and high moisture vapour transmission rate are desirable.

Examples of some backing materials are vinyl, polyester films, polyester-polypopylene films, Polypropylene resin, Polystyrene resin, Polyurethene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate.

g) Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutyl phosphate, triethyl citrate, polyethylene glycol and propylene glycol are added to provide plasticity to the Transdermal patch.

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM

I) Reservoir systems

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate-controlling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied.

II) Matrix systems

a) Drug-in-adhesive system

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) onto an impervious backing layer. On top of the reservoir, layers of unmedicated adhesive polymer are applied.

b) Matrix-dispersion system

The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim.

III) Microreservoir systems

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs.

The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross-linking agents.

VARIOUS METHODS OF PREPARATION OF TDDS

a) Circular teflon mould method

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution stirred for 12 hrs. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5 °C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

b) Mercury substrate method

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

c) By using “EVAC membranes” method

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopel resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (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.

d) Aluminium backed adhesive film method

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custommade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

e) Preparation of TDDS by using Proliposomes

The proliposomes are prepared by carrier method using film deposition technique. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70 °C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30 °C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5 mL aliquot of the organic solution is introduced into the round bottomed flask at 37 °C, after complete drying second aliquots (0.5 mL) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through
100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

f) 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. 5 mL of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petridish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

EVALUATION OF TDSS
1. Physicochemical Evaluation
A) Interaction studies
The drug and the excipients must be compatible with each other to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, and absorption maxima.

B) Thickness of the patch
The thickness of the drug loaded patch is measured by using a digital micrometer at different point of patch and determines the average thickness and also the standard deviation for the same to ensure the thickness of the prepared patch.

C) Weight uniformity
The prepared patches are to be dried at 60 °C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

D) 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 gives the value of the folding endurance.

E) Percentage Moisture content
The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

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

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

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

G) Water vapour permeability (WVP) evaluation
Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula.

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

Where, WVP is expressed in gm/m² per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m².

H) Drug content
A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Then the average of three different samples is taken.

I) Uniformity of dosage unit test
An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. Suitable analytical technique (UV or HPLC) and the drug content for each piece are to be calculated.

J) Polaroscope examination
This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or in amorphous form in the patch.

K) Shear Adhesion test
Shear adhesion strength is determined by measuring the time taken to pull the adhesive coated tape off a stainless steel plate. The longer the time for removal, greater is the shear strength.

L) Peel Adhesion test
In this test, a single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removal is measured.

M) Thumb tack test
It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

N) Flatness test
Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

O) Percentage elongation break test
The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

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

Where, L1 is the final length of each strip and L2 is the initial length of each strip.
Evaluation of TDDS

Drug release studies

It is one chambered (vertical) type cell. Most widely used for in-vitro testing of TDDS. Many modifications have been made in the Franz diffusion cell design according to the requirement. Here skin is mounted on the plate above O ring. 20-70 ml phosphate buffer of pH 7.4 (physiological pH) is filled in reservoir compartment. Transdermal patch is applied on upper layer of skin. Diffusion medium in reservoir is stirred at particular rpm. Sampling is done at particular interval from reservoir compartment i.e. specified volume of fluid is withdrawn and is replaced by equivalent amount of the same fluid. In vitro drug release studies

2. In vitro Evaluation of TDDS

a. In vitro drug release studies

It is one chambered (vertical) type cell. Most widely used for in-vitro testing of TDDS. Many modifications have been made in the Franz diffusion cell design according to the requirement. Here skin is mounted on the plate above O ring. 20-70 ml phosphate buffer of pH 7.4 (physiological pH) is filled in reservoir compartment. Transdermal patch is applied on upper layer of skin. Diffusion medium in reservoir is stirred at particular rpm. Sampling is done at particular interval from reservoir compartment i.e. specified volume of fluid is withdrawn and is replaced by equivalent amount of the same fluid.

b. In vitro skin permeation studies

In vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. The temperature of the cell was maintained at 32 ± 0.5 °C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or H LC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated mg cm⁻² vs time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load mg cm².

3 In vivo Evaluation

A) In vivo evaluations are the true depiction of the drug performance. 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: 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. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.

• 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. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions.

• Skin Irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits and guinea pigs (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.

RECENT ADVANCEMENT IN TDDS

The way of releasing a medicament effectively has taken up a great advancement based on the oversaturation of an adhesive polymer with medication, thus propel the drug from reservoir by a partial crystallization of the drug. The presence of both molecular solute and solid crystal Transdermal drug absorption markedly alters drug kinetics. The toxic effect of the drug and problem in limiting drug uptake are major considerable potential for transdermal delivery systems, especially in children because skin thickness and blood flow in the skin usually vary with age. The increased blood supply in the skin along with thinner skin has significant effects on the pharmacokinetics of transdermal delivery for children. In some situations this may be an advantageous, while in others systemic toxicity may occur. This was observed after using scopolamine patches that are used to prevent motion sickness, a eutectic mixture of local anesthetics (EMLA) cream used to minimize the pain, corticosteroid cream applied for its local effect on skin maladies. Episodes of systemic toxic effects, including some fatalities in children, have been documented with each of these, often secondary to accidental absorption through mucous membranes.

Pharmaceutical companies are now developing new adhesives, substances that enhance molecular absorption as well as penetration that will ultimately affect skin permeation and greatly increase the list of drugs which can be delivered transdermally. Well known technologies that are iontophoresis and phonophoresis (sonophoresis) considered to acheive significant plasma concentration levels via skin membrane. A microneedle technology is more promising for drug administered via skin. These systems use an arrangement of small needle-like structures to open pores in the stratum corneum and facilitate drug transport without any sensation of pain because these are not reachable to nerve endings. These systems are reported to greatly enhance the permeability of macromolecules across skin.
FUTURE CHALLENGES

The statical data showed a market of $ 12.7 billion in the year 2005 which is assumed to increase by $ 21.5 billion in the year 2010 and $ 31.5 billion in the year 2015. Almost all the pharmaceutical companies are developing TDDS20. Extending the patent term of older drugs by formulating them in new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increasing absorption, delivering to the target site etc. The patented innovations in transdermal drug delivery arena aim at these goals. However, the ultimate test that an innovative technique should pass relates to its successful performance in vivo. Hence, the formulator faces a challenging task of translating the patented claims to actual practice. It is important to note that none of the generic fentanyl patches awaiting approval by US FDA could be launched in 2005. Similarly, the Evra patch landed into trouble as women using it were found to be at greater risk of blood clots. The article by Batheja and Michniak (2006) gives an analysis of US patents on transdermals filed in 2005 and shall aid the formulator in his quest for making percutaneous drug delivery more effective and patient compliant21. Commercially available Transdermal Products which are given in Table 42.

CONCLUSION

Successful transdermal drug application requires the desirable physicochemical properties for penetration through stratum corneum. Bearing in mind that the basic functions of the skin are protection and containment, it would seem exceptionally difficult to target the skin for drug delivery. However, with our greater understanding of the structure and function of the skin, and how to alter these properties, more and more new drug products are being developed for transdermal delivery. The properties of the drug, the characteristics of the transdermal device, selection of in-vivo model and the status of patient’s skin are all important for safe and effective drug delivery.

ACKNOWLEDGEMENT

Authors are very much thankful to the management of Gautham College of pharmacy, for providing the necessary service in collecting the several data needed for the preparation of this article.

REFERENCES


Table 1: Ideal properties of drug for TDDS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Properties</th>
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<tbody>
<tr>
<td>Dose</td>
<td>Should be low (less than 20 mg/day)</td>
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<tr>
<td>Half-life</td>
<td>10/less (hrs)</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt; 400 Da</td>
</tr>
<tr>
<td>Partition co-efficient</td>
<td>Log P (octanol-water) between 1.0-4.0</td>
</tr>
<tr>
<td>Skin permeability</td>
<td>&gt; 0.5×10^-3 cm^2/h</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>Non irritating and no sensitizing</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>Low</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>Low</td>
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<tr>
<td>Melting Point</td>
<td>&lt; 2000F</td>
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<tr>
<td>pH</td>
<td>Between 5.0-9.0</td>
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Table 2: Factors to be considered for transdermal dose calculation

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<tr>
<th>Physicochemical</th>
<th>Pharmacokinetic</th>
<th>Biological</th>
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<tr>
<td>Solubility</td>
<td>Half-life</td>
<td>Skin toxicity</td>
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<tr>
<td>Crystallinity</td>
<td>Volume of distribution</td>
<td>Site of application</td>
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<tr>
<td>Molecular weight</td>
<td>Total body clearance</td>
<td>Allergic reaction</td>
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<tr>
<td>Polarity</td>
<td>Therapeutic plasma concentration</td>
<td>Skin metabolism</td>
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<tr>
<td>Melting point</td>
<td>Bioavailable factor</td>
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Table 3: Polymers used in transdermal devices

<table>
<thead>
<tr>
<th>Natural Polymers</th>
<th>Synthetic Elastomer</th>
<th>Synthetic Polymers</th>
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<tr>
<td>Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch, etc.</td>
<td>Polybutadiene, Hydrid rubber, Polysioxane, Silicone rubber, Nitrate, Acrylonitrile, Butyl Rubber, Styrene-butadiene rubber, Neoprene, etc.</td>
<td>Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polycrylate, Polymide, Polyurea, Polyvinyl pyrrolidone, Polymethyl methacrylate, Epoxy, Ethyl cellulose, etc.</td>
</tr>
</tbody>
</table>
### Table 4: List of Transdermal Products

<table>
<thead>
<tr>
<th>Product name (active drug)</th>
<th>Matrix or Membrane Patch</th>
<th>Duration of Application</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alora (Estradiol)</td>
<td>Matrix</td>
<td>3 to 4 days</td>
<td>Post Menstrual Syndrome</td>
</tr>
<tr>
<td>Androderm (Testosterone)</td>
<td>Membrane</td>
<td>24 hours</td>
<td>Hypogonadism (males)</td>
</tr>
<tr>
<td>Catapres TTS (Clonidine)</td>
<td>Membrane</td>
<td>7 days</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Climara (Estadiol)</td>
<td>Matrix</td>
<td>7 days</td>
<td>Post Menstrual Syndrome</td>
</tr>
<tr>
<td>CombiPatch (Estradiol/Norethindrone acetate)</td>
<td>Matrix</td>
<td>3 to 4 days</td>
<td>Hormone Replacement Therapy</td>
</tr>
<tr>
<td>Duragesic (Fentanyl)</td>
<td>Membrane</td>
<td>72 hours</td>
<td>Moderate/Severe Pain</td>
</tr>
<tr>
<td>Estraderm (Estradiol)</td>
<td>Membrane</td>
<td>3 to 4 days</td>
<td>Post Menstrual Syndrome</td>
</tr>
<tr>
<td>Minitran (Nitroglycerin)</td>
<td>Matrix</td>
<td>12 to 16 hours</td>
<td>Angina Pectoris</td>
</tr>
<tr>
<td>Nicoderm (Nicotine)</td>
<td>Membrane</td>
<td>24 hours</td>
<td>Smoking Cessation</td>
</tr>
<tr>
<td>Nicotrol (Nicotine)</td>
<td>Matrix</td>
<td>16 hours</td>
<td>Smoking Cessation</td>
</tr>
<tr>
<td>Nitradisc (Nitroglycerin)</td>
<td>Matrix</td>
<td>24 hours</td>
<td>Angina Pectoris</td>
</tr>
<tr>
<td>Nitrodisc (Nitroglycerin)</td>
<td>Matrix</td>
<td>12 to 16 hours</td>
<td>Angina Pectoris</td>
</tr>
<tr>
<td>Ortho-Evra (Norelgestromin/estradiol)</td>
<td>Matrix</td>
<td>7 days</td>
<td>Birth Control</td>
</tr>
</tbody>
</table>