



REVIEW ARTICLE

THEORETICAL ASPECTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

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Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver the drug through the skin in order to achieve systemic absorption of drug at a predetermined rate over a prolonged period of time. Its main advantages includes controlled drug release with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. There are factors such as physiochemical as well as biological which affect the bioavailability of transdermal medicament. Due to technological advancement, many new techniques which have attained attention are iontophoresis, phonophoresis, electroporation micro needles etc. Different types of transdermal patches can be prepared by varying methods. Transdermal patches can be evaluated by interaction studies, folding endurance, thickness of the patch, weight uniformity, drug content and *in vitro* studies. This review covers general aspects like advantages, methods of preparation of transdermal patches, evaluation, basic components of transdermal drug delivery system.

Key words: Transdermal delivery, Skin, Controlled release, Transdermal patch, Franz diffusion cell.

INTRODUCTION

The most common and popular route of drug delivery is the oral route. However, this route of administration suffers from some significant drawbacks including first pass metabolism and drug degradation in gastrointestinal tract due to enzymes, pH etc.

To overcome these difficulties, a novel drug delivery system was developed (Chien, 1992; Banker, 1990; Guy, 1996). In transdermal drug delivery system (TDDS), transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver drug through the skin and to the systemic circulation at a predetermined rate over a prolonged period of time.

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively (Jain, 2001; Allen Jr. et al 2001). Transdermal patch consists of a special

membrane to control the rate at which the drug contained in the reservoir within the patch can pass through the skin and then into the bloodstream.

A drug is applied in a relatively high dose 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 in 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. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch.

Transdermal patches were developed in the 1970s and the first was Transderm-SCOP which was approved by the FDA in 1979 for the treatment of motion sickness and nausea. It was

a three-day patch that delivered scopolamine drug. In 1981, patches for nitroglycerin were approved, and therefore a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol etc. have been developed and used (Patel *et al* 2012).

Also many drugs have been attempted to be formulated as various types of transdermal patches (Bhatt *et al* 2006; Mohabe *et al* 2011; Khan *et al* 2012) or nanoemulsion for TDDS (Talegaonkar *et al* 2011).

Drug molecules in contact with the skin surface can penetrate by three potential pathways, these are through the sweat ducts, via the hair follicles and sebaceous glands (collectively called the shunt or appendageal route) or directly across the stratum corneum (Darwhekar, 2011). This review article aims at compiling some basic theoretical aspects of transdermal drug delivery which are essential before undertaking any conventional or advanced transdermal related research project.

Merits and demerits

Merits of TDDS

- Improved bioavailability and longer duration of action resulting in a reduction in dosing frequency
- Steady permeation of drug across the skin, allowing consistent serum drug level; often a goal of therapy
- Reduced side effects and in addition, if toxicity develops from a drug administered transdermally, the effects could be moderated by removing the patch
- Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects
- Topical patches are a painless, noninvasive way to deliver substances directly into body
- This is an effective route to deliver drugs that are broken down by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver
- Transdermal patches are alternative to oral route for people who cannot, or prefer not to take medications or supplements orally. It is of great advantage in patients who are nauseated or unconscious
- Topical patches are cost-effective, convenient; especially notable parameter in some patches is that it requires only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.

Demerits and limitations of TDDS

- Many drugs especially those with hydrophilic structures permeating the skin too slowly, may not achieve therapeutic level
- The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age (Latheeshjhal *et al* 2011)
- TDDS cannot deliver ionic drugs
- TDDS cannot achieve high drug levels in blood/plasma
- TDDS cannot be developed for drugs of large molecular size
- TDDS cannot deliver drugs in a pulsatile fashion
- TDDS cannot be developed if drug or formulation causes irritation to skin.

Significant properties of transdermal patches are summarized in **Table 1**. Factors to be considered for transdermal dose calculation are enlisted in **Table 2**.

Anatomy and physiology of skin

Human skin comprises of three distinct (Keleb *et al* 2010) but mutually dependent tissues:

- The stratified, vascular, cellular called as "epidermis"
- Underlying dermis of connective tissues
- Hypodermis (**Figure 1**).

Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids.

Stratum corneum

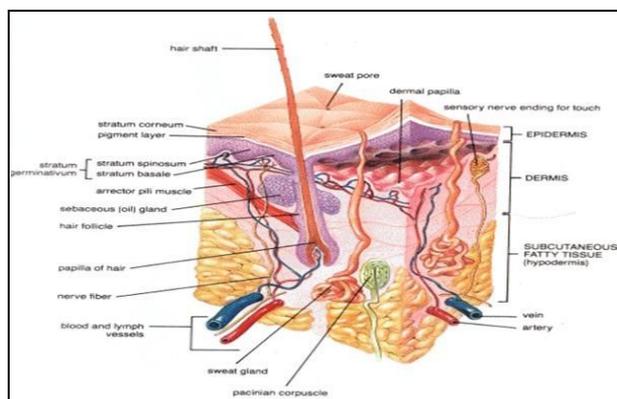
This is the outermost layer of skin also called as horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein "bricks" embedded in lipid "mortar." The lipids are arranged in multiple bilayers. There is sufficient amphiphilic

Table 1. Significant properties of TDDS

Properties	Comments
Shelf life	Up to 2 years
Patch size	< 40 cm ²
Dose frequency	Once a daily to once a week
Aesthetic appeal	Clear, tan or white color
Packaging	Easy removal of release liner and minimum number of steps required to apply
Skin reaction	Non irritating and non-sensitizing
Release	Consistent pharmacokinetic and pharmacodynamic profiles
Dose	Should be low
Half life (h)	10 or less
Molecular weight	< 400
Skin reaction	Non irritating and non sensitizer
Oral bioavailability	Low
Therapeutic index	Low

Table 2. Factors to be considered for transdermal dose calculation

Physiochemical	Pharmacokinetic	Biological
Solubility	Half life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular Weight	Total body clearance	Allergic reactions
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting Point	Bioavailable factor	Skin permeability

**Fig. 1.** Structure of human skin

material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form.

Viable epidermis

This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the

stratum basale. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

Dermis

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired (Tortara, 1999; Schofield and Rees, 2002; Vyas and Khar, 2012).

Factors affecting transdermal bioavailability

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

Physicochemical factors*Skin hydration*

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

Temperature and pH

The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values.

The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

Diffusion coefficient

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

Drug concentration

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

Partition coefficient

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready

to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

Molecular size and shape

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

Biological factors*Skin condition*

Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

Skin age

The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS.

Blood flow

Changes in peripheral circulation can affect transdermal absorption.

Regional skin sites

Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

Skin metabolism

Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

Species differences

The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration (Shingade *et al* 2012; Sharma *et al* 2011).

Basic components of TDDS

Schematic presentation of basic components (The drug, Polymers, Permeation enhancers, Adhesive, Backing layer) of transdermal patches is depicted in **Figure 2**.

Drug

The drug is in direct contact with release liner. *e.g.* Nicotine, Methotrexate and Oestrogen. Some of the desirable properties of a drug for transdermal delivery:

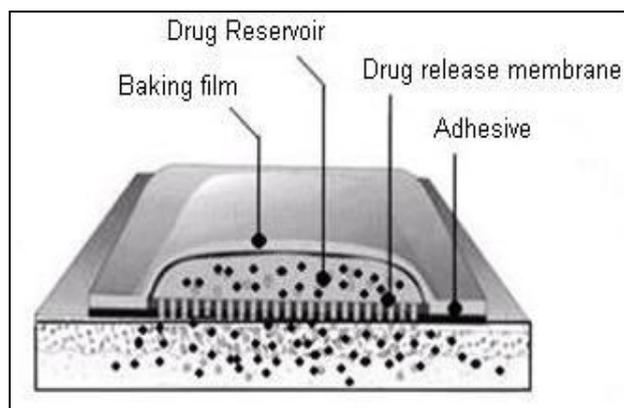


Fig. 2. Different parts of transdermal patch

- The drug molecule should possess an adequate solubility in oil and water
- The drug should have a molecular weight less than approximately 1000 daltons
- The drug should have low melting point
- The drug molecule would require a balanced partition coefficient to penetrate the stratum corneum.

Polymers

These polymers control the release of the drug from the drug reservoir.

- *Natural polymers*
e.g. Shellac, gelatin, waxes, gums, starch etc.
- *Synthetic polymers*
e.g. Polyvinyl alcohol, polyethylene, polyamide, polypropylene, polyurea, polymethylmethacrylate etc.

Permeation enhancers

Substances exist which temporarily diminish the impermeability of the skin are known as accelerants or sorption promoters or penetration enhancers. These include water, pyrrolidones, fatty acids and alcohols, azone and its derivatives, alcohols and glycols, essential oils, terpenes and derivatives, sulfoxides like dimethylsulfoximide (DMSO) and their derivatives, urea and surfactants.

Surfactants

These 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:

Sodium lauryl sulphate, Decyldecylmethylsulphoxide etc.

Nonionic surfactants:

Pluronic F 127, Pluronic F68 etc. Enhancer actions can be classified by lipid-protein partitioning concept. This hypothesis suggests that enhancers act by one or more ways selected from three main possibilities.

Lipid action:

Some enhancers interact with the organized intracellular lipid structure of the stratum corneum so as to disrupt it and make it more permeable to drug molecules. Some solvents act by extracting the lipid components and thus make the horny layer more permeable.

Protein modification:

Ionic surface active molecules in particular tend to interact well with the keratin in the corneocytes, to open up the dense keratin structure and make it more permeable. The intracellular route is not usually prominent in drug permeation, although drastic reductions to this route could open up an alternative path for drug penetration.

Partitioning promotion:

Many solvents can enter the stratum corneum, change its solvent properties and thus increase the partitioning of a second molecule into the horny layer. This molecule may be a drug, a coenhancer or a cosolvent. *e.g.* Ethanol has been used to increase the penetration of the drug molecules nitroglycerin and estradiol.

Adhesive

It serves to adhere the patch to the skin for systemic delivery of drug. The adhesive must possess sufficient adhesion property so that the TDDS should remain in place for a long time. Pressure sensitive adhesives are commonly used for transdermal patch to hold the skin. Commonly used adhesives are silicone adhesives, polyisobutylenes adhesives and polyacrylate based adhesives (Sharma *et al* 2011; Latheeshjall *et al* 2011).

Backing layer

It protects the patch from the outer environment. The backing layer should be impermeable to drug and penetration enhancers. It does a function of holding the entire system and protects drug reservoir from atmosphere. The commonly used backing materials are polyesters, aluminized polyethylene terephthalate and siliconized polyethylene terephthalate.

Useful considerations while applying transdermal patch

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

Types of transdermal patch

Single-layer Drug-in-Adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different, however, that it adds another layer of drug-in-adhesive, usually separated by a membrane. This patch also has a temporary liner-layer and a permanent backing.

Reservoir

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 porous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix (**Figure 3**). In this type of system, the rate of release is zero order.

Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it (**Figure 4**).

It is divided into two:

Drug in adhesive system

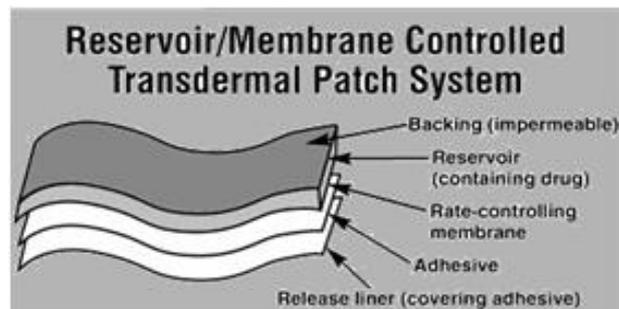


Fig. 3. Reservoir controlled transdermal patch system

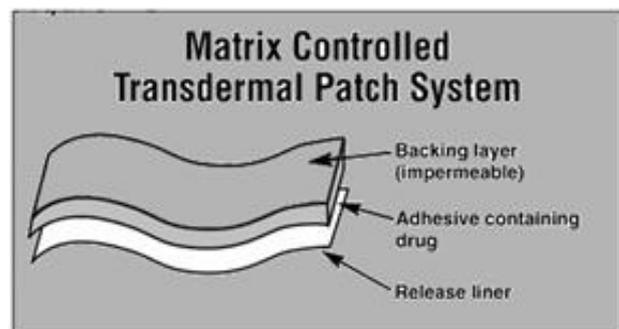


Fig. 4. Matrix controlled transdermal patch system

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

Matrix-dispersion system

In this type the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disc is fixed on to 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 with the circumference to form a strip of adhesive rim.

1. Vapour patch

In this type of patch, the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new in the market and release essential oils upto 6 h and are used mainly in cases of decongestion. Vapour patches containing nicotine that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

2. Micro reservoir system

In this type, the drug delivery system is a combination of reservoir and matrix-dispersion

system. 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 unreachably, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents (Patel *et al* 2012; Latheeshjlal *et al* 2011).

Technologies for developing transdermal drug delivery systems (Sharma *et al* 2011)

The technologies further can be classified in four basic approaches:

- Polymer membrane partition-controlled TDDS
- Polymer matrix diffusion-controlled TDDS
- Drug reservoir gradient-controlled TDDS
- Microreservoir dissolution-controlled TDDS.

Various methods for preparation of TDDS

Asymmetric TPX membrane method

A prototype patch can be fabricated using a heat sealable polyester film (type 1009, 3 m) with a concave of 1 cm diameter will be used as the backing membrane. Drug sample is dispensed into concave membrane, covered by TPX {poly-(4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive (Hadgraft and Guy, 1989).

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-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are stirred for 12 h and poured into circular teflon mould. The moulds are 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 h. The dried films are stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects (Wiechers, 1992).

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 min to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation (Yamamoto *et al* 1990).

“IPM membranes” method

In this method, drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane (Al-Khamis *et al* 1986).

“EVAC membranes” method

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene 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; 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 is placed over the gel and the edges are sealed by heat to obtain a leak proof device (Anon, 1980).

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 one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesives are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks (Mayorga *et al* 1996).

Preparation of TDDS by using proliposomes

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of

mannitol powder in a 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 min. 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 aliquot (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 freezing temperature until characterization (Deo *et al* 1997; Yan-yu *et al* 2006).

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 rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The 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 (Crawford and Esmerian, 1997).

Evaluation of transdermal patches

(Robinson and Yang, 1999; Darwhekar *et al* 2011; Vishvakarama *et al* 2012; Naik *et al* 1995)

Thickness of the patch

The thickness of the drug loaded patch can be measured in different points by using a digital micrometer to determine thickness of the prepared patch (Shivaraj *et al* 2010).

Weight uniformity

The prepared patches are dried at 60°C for 4 h 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 weight (Bharkatiya *et al* 2010).

Folding endurance

A strip of specific area is cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Percentage moisture content

The prepared films are weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h after which the films are reweighed and percentage moisture content is determined using below mentioned formula:

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

Percentage moisture uptake

The weighed films are kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, reweigh the films and determine the percentage moisture uptake from the below mentioned formula:

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Drug content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then, the solution is filtered through a filter medium and analyze the drug content with the suitable method such as UV or HPLC technique.

Polariscope examination

This test is performed to examine the drug crystals from transdermal patch by polariscope. A specific surface area of the piece is kept on the object slide and observed for the drug crystals to distinguish whether the drug is present as crystalline form or amorphous form in a patch.

Shear adhesion test

This test is performed to evaluate cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross-linking, type and amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specific weight is hung up

from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time taken to pull the tape from plate, greater is the shear strength.

Peel adhesion test

In this test, the force required to remove an adhesive coating from a substrate is referred to as peel adhesion. 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 required to pull the tape is measured.

Thumb tack test

This test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

Flatness test

Three longitudinal strips are cut from different portions of the films. The length of the each strip is measured and the variation in length because of non-uniformity in flatness is measured by determining percentage constriction, with 0% constriction equivalent to 100% flatness.

Percentage elongation break test

The percentage elongation break is determined by noting the length just before the break point, the percentage elongation is determined from the below mentioned formula:

$$\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100$$

where L1 is the final length of each strip and L2 is the initial length of each strip (Yuk *et al* 1991).

Quick stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90° 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 gms per inch width (Vyas and Khar, 2002).

Skin irritation study

Skin irritation and sensitizing testing is performed on healthy rabbits (average weight 1.2 to 1.5 kg). Clean the dorsal surface of the

rabbit and remove the hair. Again, clean the shaved surface by rectified spirit and the test formulations are applied over the skin. The patch is removed after 24 h and the skin is observed and can be classified into 5 grades on the basis of the severity of skin injury.

Stability studies

Stability studies are conducted according to the ICH guidelines at 40°C and 75% RH for 6 months. The samples are analyzed for the drug content.

In vitro release studies (Patel *et al* 2012)

Franz diffusion cell

The *in vitro* diffusion study is carried out with the rat abdominal skin using Franz diffusion cell. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment is open at the top and is exposed to atmosphere. The temperature is maintained at 37±0.5°C and receptor compartment is provided with sampling port. The diffusion medium used is phosphate buffer pH 7.4. The diffusion study is done to get an idea of permeation of drug through barrier from the transdermal system. *In vitro* studies are also done for TDDS development. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, K-C type of diffusion cell was used. Diffusion cell generally comprises two compartments, one containing the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. albino rat abdominal skin. The cell consists of sampling port and temperature maintaining jacket. The outlet and inlet is connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The stainless steel pin is used to stir the receptor solution using magnetic stirrer. The mice/rat abdominal skin is placed on receptor compartment and both compartments are held tight by clamps. Phosphate buffer pH 7.4 is used as receptor solution. The volume of diffusion cell can be 15 ml and content is stirred with bent stainless steel pin. The temperature is maintained at 37±2°C with the help of magnetic stirrer. The diffusion is carried out for 24 h and 1 ml sample is withdrawn at predetermined time intervals for 24 h. The same volume of phosphate buffer pH 7.4 is added to receptor compartment to maintain sink conditions and

the samples are analyzed to find out amount of drug released from the sample solutions.

The Paddle over disc (USP apparatus 5/PhEur 2.9.4.1)

This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains dissolution medium at $32\pm 0.5^\circ\text{C}$.

The cylinder modified USP basket (USP apparatus 6/PhEur 2.9.4.3)

This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at $32\pm 0.5^\circ\text{C}$.

The reciprocating disc (USP apparatus 7)

In this method, patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method (PhEur 2.9.4.2) may be used.

In vitro permeation studies

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually 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 K-C diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually $32\pm 5^\circ\text{C}$ 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. Design of system, patch size, surface area of skin, thickness of skin and temperature

etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux *i.e.* drug permeated per cm^2 per sec.

Horizontal-type skin permeation system

This has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5 ml) for each compartment and a small membrane area (0.64 cm^2). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600 rpm. The system is controlled by thermostated water through a water jacket surrounding the two compartments.

Flow-through diffusion cell

Flow through diffusion cells have the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to allow appropriate loading of the compound and a low volume (0.3 ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

Popular uses/market study

- The first commercially available vapour patch of nicotine to reduce smoking was approved in Europe in 2007.
- 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.
- Nitroglycerin patches are used for the treatment of angina in lieu of sublingual pills.
- The anti-hypertensive drug Clonidine is available in transdermal patch form under the brand name Catapres-TTS.
- Emsam, a transdermal form of the MAO-I selegiline, became the first transdermal delivery agent for an antidepressant approved for use in the US in March 2006 (Patel *et al* 2012).

Various technologies for enhancement of drug absorption through transdermal patch

Iontophoresis

Iontophoresis is a system in which a charged drug molecule is propelled through the skin by applying low electrical current (Pathak *et al* 2006). A typical iontophoresis device consists of two electrodes, anode (+) in a reservoir containing the positively-charged drug in a solution and cathode (-) in a negatively-charged salt solution. When voltage is applied to the electrodes, it creates a mild electrical current that repulses positively charged drug molecules through the skin into the blood stream. The advantage of the system is the controlled delivery of drug and can be turned on and off when required. The limitation of the system is irritation and pain, which limits the dose of the drug. It is currently applied for the rapid delivery of lidocaine for local anaesthesia.

Electroporation

Electroporation is the creation of aqueous pores in the lipid bilayers by the application of short electrical pulses. Electroporation may combine with iontophoresis to enhance the permeation of peptides such as vasopressin, calcitonin and neurotensin.

Sonophoresis

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.

Microporation

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. Microporation is a process by which micro-pores or channels are created in the skin which then can facilitate the transport for drug molecules across the stratum

corneum. There are several methods to create these microchannels, the most prominent includes mechanical microneedles, thermal or radiofrequency ablation and laser ablation.

Microneedles

An array of microscopic needles made from metal, polymers, silicon or glass can be used to create pathways of microdimension in the skin. The drug can be delivered by variety of mechanisms including:

- directly coating on solid microneedles
- delivering drug through hollow microneedles
- incorporating the drug inside the needle during fabrication.

Thermal or radiofrequency ablation

Exposure of skin to short, high temperature pulses cause structure disruption of stratum corneum without significantly heating or damaging the deeper tissues. This creates micro-pores in the skin very similar to created by micro needles.

Laser ablation

Skin ablation can also be achieved by the application of laser rays of specific defined wavelength which are directly absorbed by the skin. Pulse laser energy causes the water in the outer skin layer to superheat and evaporate. The resulting micro-explosion results in tissue ablation (Aslam, 2010; Dubey, 2012).

CONCLUSION

The use of transdermal drug delivery devices has experienced a remarkable increase in recent years. This interest in transdermal products can be attributed to many advantages offered by this unique route of administration. Although, the transdermal patches have become a proven technology that offers variety of significant clinical benefits over other dosage forms, the systems still offer many challenges in evaluation and testing area of transdermal patches.

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