TRANSDERMAL DRUG DELIVERY SYSTEMS: AN OVERVIEW

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Summary

With the advent of modern era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex process involving extensive efforts. This review article describes the methods of preparation of different types of transdermal patches *viz*., matrix patches, reservoir type, membrane matrix hybrid patches, drug-in-adhesive patches and micro reservoir patches. In addition, the various methods of evaluation of transdermal dosage form have also been reviewed.

Keywords: Transdermal drug delivery, polymeric formulations, controlled release dosage form

Introduction

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. Today about 74% 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. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms 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. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. 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. This article provides an overview of types of Transdermal patches, methods of preparation and its physicochemical methods of evaluation.

There are two important layers in skin: the dermis and the epidermis. The

outermost layer, the epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum. This is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, it can enter the blood stream. A process known as passive diffusion, which occurs too slowly for practical use, is the only means to transfer normal drugs across this layer. The method to circumvent this is to engineer the drugs be both water-soluble and lipid soluble. The best mixture is about fifty percent of the drug being each. This is because "Lipid-soluble substances readily pass through the intercellular lipid bi-layers of the cell membranes whereas water-soluble drugs are able to pass through the skin because of hydrated intracellular proteins". Using drugs engineered in this manner, much more rapid and useful drug delivery is possible.The stratum corneum develops a thin, tough, relatively impermeable membrane which usually provides the rate limiting step in transdermal drug delivery system. Sweat ducts and hair follicles are also paths of entry, but they are considered rather insignificant.

Transdermal Permeation

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration[1]. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows[2-3]:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ.

Basic Components of TDDS

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix / Drug reservoir:

Polymers are the backbone of 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 biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status[4].

Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle

Pharmacia concentrates on silicon rubber[5]. Similarly
Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethylcellulose for isosorbide dinitrate matrix[6-8]. The polymers utilized for TDDS can be classified as[1-2]:

- **Natural Polymers**: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc*[9].
- **Synthetic Elastomers**: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc*.
- **Synthetic Polymers**: e.g. polyvinyl alcohol, polyvinyl- chloride, poly-ethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl-pyrrolidone, polymethyl-methacrylate *etc*.

The polymers like cross linked polyethylene glycol[10], eudragits[11], ethyl cellulose, polyvinylpyrrolidone[12] and hydroxypropylmethylcellulose[13] are used as matrix formers for TDDS. Other polymers like EVA[14], silicon rubber and polyurethane[15] are used as rate controlling membrane.

Drug:

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non-compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery[16-17]. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day)[18]. Table 1 enlists the currently available drugs for transdermal delivery. In addition 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:

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate[19]. Penetration enhancers interact with structural components of stratum corneum *i.e.*, proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability[20]. Over the last 20 years, a tremendous amount of work has been directed towards the search for specific chemicals, combination of chemicals, which can act as penetration enhancers. Some of the permeation enhancers are Fatty Acids and Esters, Ethanol, Dimethyl sulfoxide, Pyrrolidones etc.

Pressure sensitive adhesives:

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, exert a strong holding force. Additionally, it should be removable

from the smooth surface without leaving a residue[21-22]. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs[23]. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physicochemically and biologically compatible and should not alter drug release[24].

Backing Laminate:

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient 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 occlusivity 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[25-26]. 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 metallized laminates[23, 27].

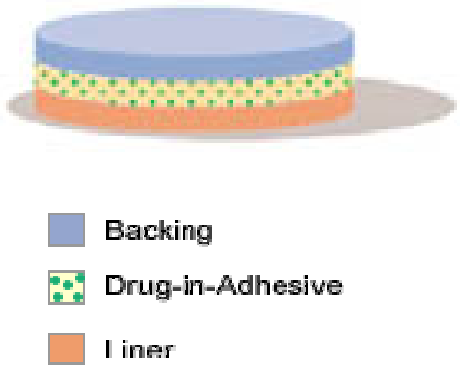
Other excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir[13,28]. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch[29-30].

TYPES OF TRANSDERMAL PATCHES: [31-35]

a) Single layer drug in adhesive:

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.



b) Multi -layer drug in adhesive:

This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.



c) Vapour patch:

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system:

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the ratecontrolling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system:

i. Drug-in-adhesive 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 (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system:

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk 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.

f) Microreservoir 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 unreachable, 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.

VARIOUS METHODS FOR PREPARATION TDDS:

a. Asymmetric TPX membrane method[36] :

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used 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.

(**Asymmetric TPX membrane preparation):** These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, themembrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

b. Circular teflon mould method:[37]

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 to be stirred for 12 hrs and then poured into a circular teflon mould. 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.

c. Mercury substrate method:[38]

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.

d. By using "IPM membranes" method:[39]

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. 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.

e. By using "EVAC membranes" method: [40]

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. 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 will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f. Aluminium backed adhesive film method: [41]

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 adhesive are soluble in chloroform. 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.

g. Preparation of TDDS by using Proliposomes: [42,43]

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 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 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.

h. By using free film method: [44]

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.

Evaluation of Transdermal Patches Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

- Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

Upon the success of physicochemical and in vitro studies, in vivo evaluations may be conducted.

Physicochemical Evaluation:

Thickness: The thickness of transdermal film is determined by traveling microscope11, dial gauge, screw gaug45 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[46].

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[47].

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

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula[48].

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below[48].

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

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100 \quad (1)$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value[12].

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation[49].

$$\text{Tensile strength} = F/a.b\ (1+L/l) \quad (2)$$

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point.

In another study, Tensile strength of the film was determined with the help of texture analyzer50. The force and elongation were measured when the films broke.

Water vapor transmission studies (WVT):

For the determination of WVT, Rao et al.,[29] weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive allowed setting for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch[29].

In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccator was measured by using hygrometer. The weighed vials were then placed in desiccator and procedure was repeated[49,51].

$$WVT = W/ST \quad (3)$$

W is the increase in weight in 24 h; S is area of film exposed (cm2); T is exposure time

Microscopic studies: Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope[52].

Adhesive studies: The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors[53]:

Peel Adhesion properties: It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate. Minghetti performed the test with a tensile testing machine Acquati model AG/MC 1 (Aquati, Arese, Italy) [53,54].

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[55-58].

Thumb tack test: The force required to remove thumb from adhesive is a measure of tack.

Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min.

Probe tack test: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

Shear strength properties or creep resistance : Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by

measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification[54].

***In vitro* release studies:**

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their *in vivo* performance[59]. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system e.g., Higuchi[60], First order[61], Zero order[62] and Peppas and Korsenmeyer model[63]. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug.

There are various methods available for determination of drug release rate of TDDS.

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 medium at 32 ±5°C[64]

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 ±5°C[65].

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[66].

Diffusion Cells e.g. Franz Diffusion Cell and its modification

Keshary- Chien Cell: In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid i.e., buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically30,67.

The pH of the dissolution medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). PhEur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models in order to ascertain the release mechanism[66].

***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[68].

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 keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic 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. 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 cm2 per second[45].

Preparation of skin for permeation studies: Hairless animal skin and human cadaver skin were use for permeation studies. Human cadaver skin may be a logical choice as the skin model because the final product will be used in humans. But it is not easily available. So, hairless animal skin is generally favored as it is easily obtained from animals of specific age group or sex.

Intact Full thickness skin: Hair on dorsal skin of animal are removed with animal hair clipper, subcutaneous tissue is surgically removed and dermis side is wiped with isopropyl alcohol to remove residual adhering fat. The skin is washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20C till further use. The skin is defrosted at room temperature when required.

Separation of epidermis from full thickness skin: The prepared full thickness skin is treated with 2M sodium bromide solution in water for 6 h. The epidermis is separated by using a cotton swab moistened with distilled water. Then epidermis sheet is cleaned by washing with distilled water and dried under vacuum. Dried sheets are stored in desiccators until further use[69-70].

In vivo Studies

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
-Human volunteers

Animal models

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale[71]. 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[3,72]. Rhesus monkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man[73].

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. Though human studies require considerable resources but they are the best to assess the performance of the drug[74].

Skin irritation studies: White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin[12,46]. Mutalik and Udupa carried out skin irritation test using mice. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of group I was served as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals were sacrificed and skin samples were processed for histological examination. The results of this study showed that the prepared systems (both blank and drug loaded) and USP adhesive tape produced negligible erythema and edema. While standard irritant, formalin produced severe edema and erythema. The histopathologic examination of the skin also indicated that adhesive tape and prepared patches produced mild inflammation and edema[65].

Stability studies: The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines[75].

Regulatory requirements: A transdermal patch is classified by U.S. Food and Drug Administration (FDA) as a combination product, consisting of a medical device combined with drug or biologic product that the device is designed to deliver. Prior to sale, any transdermal patch product must receive approval from FDA, demonstrating safety and efficacy for its intended use[70]

Transdermal Market

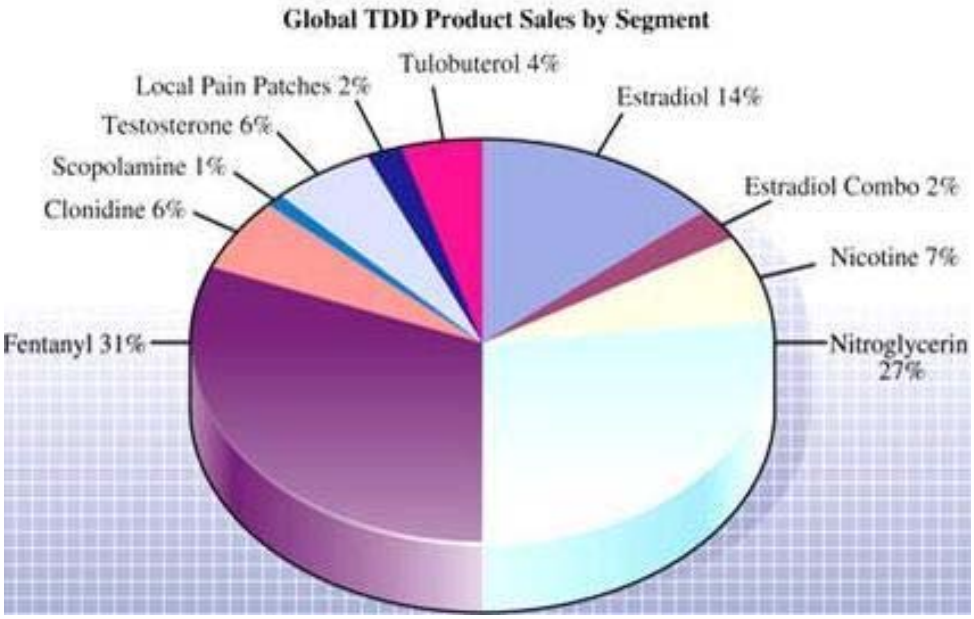
The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally[76]. The table 1 gives detail information of the different drugs which are administered by this route and the common names by which they are marketed;it also gives the conditions for which the individual system is used[77].

Table 1

Product name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/ Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/ Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/ Norethindrone	Noven , Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/ Solvay Healthcare Ltd.	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris

Nuvelle TS	Estrogen/Progeste	Ethical Holdings/Schering	Hormone replacement therapy
Ortho-Evra	Norelgestromin/ estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Transderm Scop	Scopolamine	Alza/Norvatis	Motion sickness
Transderm Nitro	Nitroglycerin	Alza/Norvatis	Angina pectoris
Vivelle	Estradiol	Noven Pharmaceuticals/ Norvatis	Postmenstrual syndrome

The pie diagram given below shows that Fentanyl and nitroglycerine are the drugs most popularly marketed using transdermal patches76



ADVANCE DEVELOPMENT IN TDDS:

Drug in adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-

fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch[76] .

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called"active" transdermal technologies include iontophoresis (which uses low voltage
electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.[76]

Conclusion

This article provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

Since 1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the TDDS, many new researches are going on in the present day to incorporate newer drugs via the system. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. Transdermal patches can be divided into various types like matrix, reservoir, membrane matrix hybrid, micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS. After preparation of transdermal patches, they are evaluated for physicochemical studies, in vitro permeation studies, skin irritation studies, animal studies, human studies and stability studies. But all prepared and evaluated transdermal patches must receive approval from FDA before sale. Future developments of TDDSs will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use.

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