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TRANSDERMAL DRUG DELIVERY SYSTEM (PATCH)

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ABSTRACT

Transdermal drug delivery system (TDDS) are topically administered medicaments. Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredient, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers, and it avoid first pass effect. Transdermal patches delivers the drugs for systemic effects at a predetermined and controlled rate. Through a diffusion process, the drug enters the bloodstream directly though the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into 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. Characterization of transdermal patch is use to check it's quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity & cutaneous toxicological studies. 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 TDDS products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDDS products have now been approved for sale in the US, and approximately active ingredients are approved for use in transdermal drug delivery products globally.

KEYWORDS: Transdermal patches, marketed TDDS, hydro propylene methyl cellulose, controlled release.

INTRODUCTION

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. 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.[5] The idea of delivering drugs through skin is old, as the use is reported in 16th century in which the husk of castor oil plant in water was placed on an aching head. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation. Until recently, the use of transdermal patches for pharmaceuticals has been limited Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories: therapeutic and cosmetic), aroma patches, weight loss patches and patches that.[3] Now a day's transdermal drug delivery systems are a consistent source of interest because of the benefits that they afford in overcoming many drawbacks associated with other modes of antifungal drug delivery (i.e. oral, intravenous). Because of the Skin particularly the stratum corneum, provides a barrier for the penetration of the majority of the substances. Gels are semisolid formulations, which have an external solvent phase, may be hydrophilic or hydrophobic in nature, Recent studies have reported other types of gels for dermal drug application, such as niosomal gels, liposomal gel, erythrosomal gel, microsphere gel.[4] TDDS basically consists of adhesive drug-containing devices of defined surface area that delivers a predetermined amount of drug to the intact skin at a preprogrammed rate, which is able to penetrate through different layers of skin to reach the systemic circulation. Currently, the transdermal route, along with oral treatment, ranks as the most successful innovative research area in drug delivery. Backing layer, drug containing layer, rate controlling membrane, adhesive and release liner are the components of TDDS though all layers may not be available in all types of TDDS as there are several types of transdermal patches.[11] There are single layer drug in adhesive, multilayer drug in adhesive, vapour patch, reservoir system and matrix system. Similarly natural polymers, synthetic polymers, synthetic elastomers and biopolymers have been used in TDDS.[17] With the advent new era of pharmaceutical dosage forms (TDDS) established itself as an integral part novel drug delivery systems. Transdermal drug delivery is the non in-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body-through its layers, to the circulatory system. BASIC Components used for transdermal drug delivery system: Polymer matrix, Drug, Permeation enhancer, Adhesive and backing membrane Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness**.** It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone.

There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days.[12]

Adavantage Of Tdds

1. Avoids chemically hastle GI environment drug degradation in acidic & basic environment is prevented
2. No GI distress & the factors like Gastric emptying, Intestinal motility, Transit time, do not effect this route as in oral route
3. Avoidance of significant presystemic metabolism (degradation in GIT or by the liver) therefore need lower dose.
4. Allows effective use of drugs with short biological half- life
5. Reduced inter & intra patient variability
6. Enhance therapeutic efficacy, reduced fluctuations (rapid blood level spikes low & high) due to optimization of blood concentration – time profile
7. Reduction of dosing frequency and enhancement of patient compliance[9]

Disadvantages of TDDS

1. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
2. Higher cost.
3. Should not use ionic drug.
4. May cause allergic reactions.
5. A molecular weight less than 500 Da is essential.
6. Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for permeate to transverse SC and underlying aqueous layers.
7. Transdermal therapy is feasible for certain potent drugs only.
8. Transdermal therapy is not feasible for ionic drugs.
9. It cannot deliver drug in pulsatile fashion.
10. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skins impermeability.[8]

Ideal Characteristics of TDDS

1. The skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin.
2. For the therapeutic action of the drug, there is a need of optimum partition coefficient.

3. The drug should have a low melting point (less than 2000C) should use.
4. Patch size should be less than 40 cm2
5. Shelf life upto 2 yrs.
6. The half-life t½ of the drug should be short;
7. The drug should be non-irritating and non-allergic;
8. The drug should be potent with a daily dose of the order of a few mg/day;
9. The drug should have a molecular weight less than approximately 1000 Daltons;
10. The drug should have affinity for both-lipophilic and hydrophilic phases. Extreme partitioning characteristic are not conducive to successful drug delivery via the skin;
11. However for a number of drugs, there may also be significant transdermal absorption at pH values at which the unionized form of the drug is predominant.[10]

Conditions in which Transdermal patches are used

Transdermal patch is used when

1. When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
2. Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.
3. It can be used in combination with other enhancement strategies to produce synergistic effects.[11]

Basic Components of TDDS

1. Polymer matrix / Drug reservoir
2. Drug
3. Permeation enhancers
4. Pressure sensitive adhesive (PSA)
5. Backing laminates
6. Release liner
7. Other excipients like plasticizers and solvents[13]

1. Polymer Matrix: The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are:

a. Natural Polymers: e.g., cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b. Synthetic Elastomers: e.g., polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.
c. Synthetic Polymers: e.g., polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polymethylmethacrylate, Epoxy[7]

The criteria for the polymers are

i. The polymer should be chemically non-reactive or it should be an inert drug carrier;
ii. The polymer must not decompose on storage or during the life span; achieve contact between the transdermal patch and the skin. Adhesion is understood to be the net effect of three phenomenon's namely;
iii. Peel: The resistance against the breakage of the adhesive bond;
iv. Track: The ability of a polymer to adhere to a substrate with little contact Pressure and;
v. Creep: The viscous relaxation of the adhesive bond upon shear.[12]

2. Drug. Drug solution in direct contact with release liner.

I. Physiochemical properties

(a) The drug should have a molecular weight
(b) Less than 1000 Daltons.
(c) The drug should have affinity for both
(d) lipophilic and hydrophilic phases.
(e) The drug should have a low melting point.[29]

II. Biological properties

a. The drug should be potent with a daily
b. Dose of the order of a few mg/day.
c. The half life (t½) of the drug should be short.
d. The drug must not produce allergic response.
e. Tolerance to the drug must not develop
f. under the near zero-order release profile of transdermal patches.[16]

3. Permeation enhancers: These compounds are useful 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 example are Dimethyl sulfoxide, Propylene glycol, 2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Pluronic Cardamom oil, Caraway oil, Lemon oil, Menthol, dlimonene, Linoleic acid.[15]

4. Pressure sensitive adhesives The pressure-sensitive adhesive (PSA) affixes the Transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Adhesives must be skin-compatible, causing minimal irritation or sensitization, and removable without inflicting physical trauma or leaving residue. In addition, they must be able to dissolve drug and Excipient in quantities sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability. PSAs used in commercially available Transdermal systems include polyacrylate, polyisobutylene, and polysiloxane.[28]

Polyacrylates, are most widely used. In general, all acrylic adhesives are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of polyacrylate matrices.

Polyisobutylenes (PIBs), in contrast, are characterized by a low solvent capacity for drugs. PIBs are often used in membrane-controlled systems where the initial burst of drug released from the adhesive layer should be limited. PIB-based adhesives are mixtures of high and low molecular weight polymers, which provide cohesion and tackiness, respectively. By adjusting the composition of the PIB formulation, cold flow and adhesiveness can be customized for each system.

Silicone, adhesives are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicones, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups. To address this problem, special silicones have been developed that are rendered resistant to amine-catalyzed condensation through end-capping of silanol functional groups.

Hot Melt Pressure Sensitive Adhesives (HMPSA), HMPSA melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flowless state. They are thermoplastic in nature. Compounded HMPSA are Ethylene vinyl acetate copolymers, Paraffin waxes, Low density polypropylene, Styrene-butadiene copolymers, Ethylen-ethacrylate copolymers. Uncompounded HMPSA are Polyesters, Polyamides and Polyurethanes.[13]

The ideal characters of adhesive materials are

a. High biocompatibility (low irritancy, toxicity, allergic reaction etc.);
b. Good adhesive to oily, wet, wrinkled and hairy skin;
c. Good environment resistance against water and humidity;
d. Easy to remove from the skin;
e. High permeability of moisture to avoid excessive occlusion and for the drug itself and;
f. Non-reactive towards drug.[26]

There are three types of adhesive used mainly

a. Silicone type adhesive;
b. Poly-isobutylene adhesive and;
c. Poly-acrylate based adhesive.[24]

❖ **Backing laminates:** Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear pigmented, or metallized 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. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability. 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 will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate Examples of some backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethylene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate.[15]

5. **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 metalised laminates.[23]

6. **Other excipients:** Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.[14]

Factors affecting transdermal permeation

Physicochemical properties of the penetrant molecules.

A. Partition coefficient

a. lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.

b. It may be altered by chemical modification without affecting the pharmacological activity of the drug.[22]

B. pH conditions

a. Applications of solutions whose pH values are very high or very low can be destructive to the drug.

b. With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.[21]

C. Penetrant concentration

a. Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.

b. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.[20]

TYPES OF TDDS

There are five main types of transdermal patches

1. **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 to the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.In this system drug and excipients is inclusive with skin adhesive which serve as formulation foundation as a single breaking layer. The rate of release of drug through diffusion phenomenon.

Fig.1. Single layer drug in adhesive patch and its different.[27]

2. **Multi-layer Drug-in-Adhesive:** The multi-layer drug-in-adhesive patch is similar to the single-layer system; the multi-layer system is different, however, in that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. This patch also has a temporary liner-layer and a permanent backing. The drug release from this depends on membrane permeability and diffusion of drug molecules.In this system drug and excipients incorporated with adhesive but both layer of adhesive separated by single layer membrane. The released of drug occurred through diffusion phenomenon

Figure no 2: Multi layer drug in adhesive patch and its *differen* component.[27]

3. **Reservoir** Unlike the single-layer and multi-layer drug-in-adhesive systems, the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. The drug reservoir is totally encapsulated in a shallow compartment molded from a drug-

impermeable metallic plastic laminate, with a rate-controlling membrane made of a polymer like vinyle acetate on one surface. This patch is also backed by the backing layer. In this type of system the rate of release is zero order. In the reservoir system, inclusion of liquid compartment containing drug solution/suspension between baking layer and semipermeable membrane followed by adhesive layer and release liner.[27]

Fig no. 3: Reservoir transdermal system.

4. **Matrix Type** 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. Also known as a monolithic device. This system is designed by inclusion of semisolid matrix having drug in solution or suspension form which is in direct contact with the release liner.

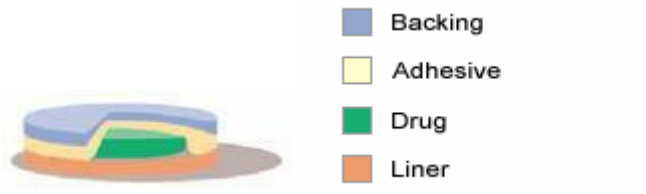

Fig.4. Single layer drug in adhesive patch with its different *component.*[27]

5. **Vapour Patch** In a vapour patch, the adhesive layer not only serves to adhere the various layers together but also to release vapour. Vapour patches release essential oils for up to 6 hours and are mainly used for decongestion. Other vapour patches on the market improve quality of sleep or aid in smoking cessation.[9]

VARIOUS METHODS FOR PREPARATION OF TDDS

A. **Solvent casting technique:** Transdermal patches containing drug will be prepared by solvent casting technique. The patches will be prepared by incorporation glycerin (15% w/w of dry polymer) as a plasticizer and polyethylene glycol 400 (PEG 400, 10% w/w of dry polymer) as a permeation enhancer. The polymeric casting solution will be prepared by dissolving HPMC (hydroxypropyl methylcellulose) in a chloroform: methanol (1:1)

mixture by using a magnetic stirrer. Glycerin 15% (w/w of dry polymer) and PEG 400 is added into the above mixture. The drug 50mg will be added slowly to the solution and dissolved by continuous stirring for 30min. This polymeric solution will be poured in the laboratory fabricated moulds. The moulds will be kept on a horizontal surface and covered by a inverted funnel to control the rate of evaporation. The polymeric solution is allowed to dry for 24hrs. After 24hrs the dried films/patches will be then detached and cut to generate transdermal patches of $1cm^2$ diameter. The formulated patches will be stored in dessicator until further evaluation. A thin layer of hydroallergenic adhesive polymer is applied on the external surface of transdermal patches to provide contact between transdermal patches and skin.[30]

B. **Asymmetric TPX membrane method** 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.[18]

C. **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 hr and cast on a glass plate to a predetermined 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 min of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hr.

D. **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 sameorganic 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. The total contents are to be stirred for 12 hr 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 hr. The dried films are to be stored for another 24 hr at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. These type of films are to be evaluated within one week of their preparation.[32]

E. **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.[33]

F. **By using "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 hr 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.[1]

G. **By using "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 thespecified 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.[2]

H. **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 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.[19]

I. **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 0.5ml 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 desiccators 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.[10,34]

J. **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 aconcentration 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.[9]

EVALUATION OF PATCHES

Physical Appearance:- All the prepared patches will be visually inspected for colour, clarity, uniformity, flexibility and smoothness.

Folding endurance:- of the film will be determined manually by repeatedly folding a small strip at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Flatness Flatness:- of patch will be observed by cutting three longitudinal strips: one from centre, one from the left side and one from the right side. The length of each strip will be measured and the variation in length because of non-uniformity in flatness will be measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.[20]

Constriction(%) = (l1-l2)/l1

Where; l1 = initial length of each strip l2 = final length

Weight Variation:- The patches will be subjected to mass variation by individually weighing six dried patches of 1cm2 and then mean ± S.E.M (mg/cm2) was calculated.

Tensile strength:- Tensile strength can be determined by using physical balance. The polymeric patch will be pulled by gradually adding weights to the pan to increase the pulling force till the patch broke. The percentage elongation (i.e. the distance travelled by the pointer before the patch broke) will be calculated as Kg/cm2.[22]

Percentage Moisture:- Content The patches of $1cm^2$ will be cut and weighed individually and placed in a desiccator containing activated silica at room temperature for 24hrs. Each

patch will be weighed repeatedly after a specified interval until they showed a constant weight. The percent moisture content is calculated using following formula:

%Moisture content= Initial weight - Final weight× 100

Drug content:- The patches of 1cm2 will be cut and transferred to 100ml flasks which contain buffer medium. The formulation will be then sonicated for 8 hours, after 8 hours the content of each flask will be filtered through whatman filter paper. Filtrate will be diluted properly and absorbance will be determined using UV Visible spectrophotometer at 272 nm. The percentage of drug content of various formulations (T1, T2, T3) are calculated by the following formula.

Drug content = test absorbance × standard dilution×average weight Standard absorbance ×test dilution.

% Drug content = $practical\ yeid \times 100 \div label\ caim$

In vitro drug diffusion studies Diffusion rate of the prepared patches will be studied by using Franz diffusion cell at 50 rpm & 370 ± 0.50 C temperature. Phosphate buffer of pH 7.4 (20 ml) will be used as a dissolution medium. Samples of 5ml each will be withdrawn at 15min, 30min, 1, 2, 4, 6, 8, 10 and 12 hours. The samples will be suitably diluted with the dissolution fluid and assayed for drug at 272 nm by using the corresponding dissolution medium as a blank. Each sample withdrawn vessel will be replaced with a drug free dissolution medium to maintain the desired concentration.

Drug Content Uniformity:- Amount of drug entrapped in a patch will be determined by completely dissolving a patch of size 2x2 cm2 in 100ml phosphate buffer solution (pH 7.4). Complete dissolution will be achieved by placing the solution containing patch on shaker for about 24 hrs. Solution will be then filtered and drug content will be estimated spectrophotometrically after suitable dilution.

In-Vitro Skin Permeation Studies:-n-vitro skin permeation studies will be carried out using rat's skin. Rat will be sacrificed and skin will be removed from abdominal portion. Appropriate size of sikn will be shaved using depilatory cream and this skin will be then used as a barrier between donor and receptor compartment of Franz diffusion cell. Transdermal patch will be placed upon it (facing towards stratum corneum of the skin). Receptor compartment will be filled with Phosphate buffer (pH 7.4) and magnetic bead will be placed inside the receptor compartment. Franz diffusion cell will be placed upon magnetic stirrer and

temperature will be maintained at about 37±0.5ºC. Samples will be withdrawn at different time interval and equal amount of phosphate buffer will be then added to the receptor compartment in order to maintain volume of the receptor compartment constant. Samples thus withdrawn will be analysed by means of U.V Spectrophotometer in order to estimate amount of drug present in the sample.

Skin Irritation Studies:- Skin irritation studies will be carried out in order to detect irritation and sensitization under conditions of maximal stress which may occur over a prolong contact with the skin surface. For this study rat will be used as an animal model. Patch wil be applied to the shaved skin of the rat on one side of the back and secured using adhesive tape. On other back side of the rat, control patch (without drug) will be placed in a similar manner. Animal will be then kept under observation for a period of 48hrs to detect any sign of erythma, redness, sensitization or any other allergic reaction.

Stability studies_ Stability of a TDDS is a very important factor to be considered while formulating such system because it affects therapeutic efficacy of the system as well as patient compliance. Here, formulated patches will be wrapped in aluminium foil and kept at room temperature for a period of 30 days. After completion of 30 days, patches will be analysed for their drug release profile across rat's skin.

Table no 1: Some marketed products of transdermal paches.

SN.	PRODUCT NAME	DRUG	MANUFACTURER	INDICATION
1.	Alora	Estradiol	Thera Tech/proctor & Gamble	Postmenstrual syndrome
2.	Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism (males)
3.	CatapresTTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
4.	Climaderm	Estradiol	Ethical Holdings/Wyeth Ayerest	Postmenstrual syndrome
5.	Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
6.	Combi Patch	Estradiol/Norethindrone	Noven, Inc./Aventis	Hormone replacement therapy
7.	Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
8.	Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Pharmaceutical moderate/severe pain
9.	Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
10.	Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd	Postmenstrual syndrome
11.	FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
12.	Habitraol	Nicotine	Novartis	Smoking cessation

13.	Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
14.	Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
15.	Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd	Smoking cessation
16.	Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
17.	Nitrodur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
18.	Nuvelle	Estrogen/Progesterone	TS Ethical Holdings/Schering	Hormone replacement therapy
19.	Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control

CONCLUSION

Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. This article provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems as a ready reference for the research scientists who are involved in TDDS. The foregoing research 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 is a realistic practical application as the next generation of drug delivery system**.**

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CONFLICT OF INTEREST

There is no conflict of interest amoung the authors.

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