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TRANSDERMAL DRUG DELIVERY SYSTEM: A NOVEL TECHNIQUE TO ENHANCE THERAPEUTIC EFFICACY AND SAFETY OF DRUGS

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ABSTRACT

The conventional oral dosage forms has significant drawbacks of low bioavailability due to hepatic first pass metabolism and tendency to produce rapid blood level spikes (Both high and low), leading to a need for frequent dosing, which can be both cost ineffective and inconvenient. To improve such characters transdermal drug delivery system (TDDS) was emerged which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body thereby reducing both the size and number of doses. The TDDS has numerous advantages over the more traditional drug delivery system. These include high bioavailability, absence of first pass hepatic metabolism, maintenance of steady plasma level of the drug, increase therapeutic efficiency. This review article provides an overview of TDDS, its advantages over conventional dosage forms, Limitations**,** various components of Transdermal patches, types of Transdermal patches, methods of preparation and Ideal requirements for TDDS**,** regulatory issues over transdermal drug delivery and its physicochemical methods of evaluation.

Key words*:* Transdermal drug delivery systems**,** Transdermal patches, skin penetration**,** Topical drug delivery

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INTRODUCTION:

Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a therapeutically effective dose of drug across a patient's skin [1, 2.] Conventional systems of medication which require multi dose therapy have numerous problems and complications such as poor bioavailability due to hepatic first pass metabolism. This is removed by TDDS. 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 skin [3.] Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs [4.] Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. Emerged [5]. Over the last two decades, many more transdermal products have been approved for sales in market (Table: 1),

Table 1: Marketed Transdermal Drug Delivery Product

Product name	**Drug**	**Manufacturer**	**Indication**
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism (males)
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrualsyndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Habitraol	Nicotine	Novartis	Smoking cessation
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
CombiPatch	Estradiol/Norethindrone	Noven ,Inc./Aventis	Hormone replacement therapy
Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Duragesic	Fentanyl	Alza/Janssen Pharmaceutic	a Moderate/severe pain
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension

Advantages of Transdermal Drug Delivery Systems [6]

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are:

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

Limitations of Transdermal Drug Delivery Systems [7, 8, 9]

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin
- Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitization
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favourable, o/w partition coefficient
- The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
- Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin is impermeability.

- Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
- Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

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 heart 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 good stability and compatibility with the drug and other components of the system and they should provide effective released of a drug throughout the device with safe status[16]. The polymers used for TDDS can be classified as:

Natural Polymers: e.g. cellulose derivatives, zein, gelatine, shellac, waxes, gums, natural rubber and chitosan etc.

Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc.

Synthetic Polymers*:* e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

The polymers like polyethylene glycol17, eudragits18, ethyl cellulose, polyvinylpyrrolidone19 and hydroxypropyl methylcellulose20 are used as matrix type TDDS. The polymers like EVA 21, silicon rubber and polyurethane 22 are used as rate controlling TDDS.

Selection of Drugs

The selection of drug for transdermal drug delivery depends upon various factors

Physicochemical Properties [10, 11]

- The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml)
- The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible.
- Substances having a molecular weight of less than 1000 units are suitable.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.
- Hydrogen bonding groups should be less than 2.

Biological Properties [12]

- Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day)
- The drug should have short biological half life
- The drug should be non irritant and non allergic to human skin
- The drug should be stable when in contact with the skin
- The drug should not stimulate an immune reaction to the skin
- Tolerance to drug must not develop under near zero order release profile of transdermal delivery
- The drug should not get irreversibly bound in the subcutaneous tissue
- The drug should not get extensively metabolized in the skin

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 [13]. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability [14.] 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]

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 tacky and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue [16, 17] 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 Excipients 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[18] *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, Ethylene-ethacrylate copolymers. Uncompounded HMPSA are Polyesters, Polyamides and Polyurethanes.

Backing Laminate

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 [19, 20]. 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

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 [17, 21].

Other Excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir [22, 23]. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch [23, 24.]

APPROACHES TO DEVELOPMENT TRANSDERMAL THERAPEUTIC SYSTEMS [23, 24]

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies can be classified into four approaches as follows

Membrane permeation – controlled systems

Adhesive dispersion – type systems.

Matrix diffusion – controlled systems.

Micro reservoir type or micro sealed dissolution controlled systems.

Membrane Permeation – Controlled Systems

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied (Figure-1). The rate of drug release from this type of Transdermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate controlling membrane [25, 26.]

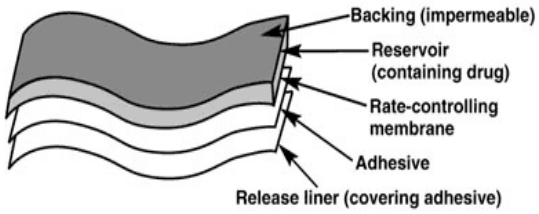

Figure1. Polymer membrane permeation-controlled TDDS

TransdermScop (Scopolamine) for 3 days protection of motion sickness and **TransdermNitro** (Nitroglycerine) for once a day medication of angina pectoris.

Adhesive Dispersion – Type Systems

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in case of hot-melt adhesives) onto an impervious backing layer (Figure-2). The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlling drug delivery system [25, 26]

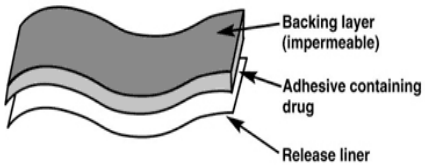

Figure 2. Adhesive diffusion controlled TDDS

Deponit (Nitroglycerine) for once a day medication of angina pectoris.

Matrix Diffusion Controlled System

The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated

from a drug-impermeable backing layer (Figure-3). Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim [25, 26]

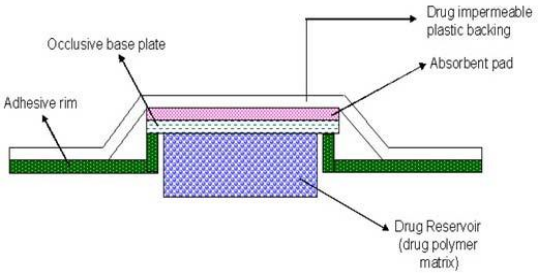

Figure3. Matrix diffusion controlled TDDS

Nitro Dur (Nitroglycerine) used for once a day medication of angina pectoris.

Microreservoir Controlled TDDS

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs (Figure 4). The thermodynamically unstable dispersion is stabilized quickly by immediately cross linking the polymer in situ. A Transdermal system therapeutic system thus formed as a medicated disc

Positioned at the center and surrounded by an adhesive rim[25, 26].

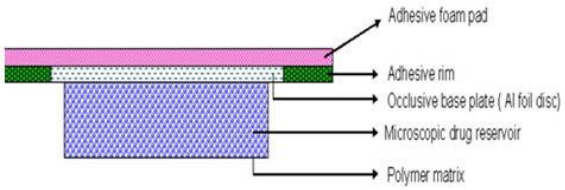

Figure4. Microreservoir controlled TDDS

Nitro-dur® System (Nitroglycerin) for once a day treatment of angina pectoris.

IDEAL REQUIREMENTS FOR TDDS [27]

- Shelf life up to 2 years
- Small size patch (i.e., less than 40 cm2)
- Convenient dose frequency (i.e., once a day to once a week)
- Cosmetically acceptable (i.e., clear, white colour)
- Simple packaging (i.e., minimum number of pouches and steps required to apply the system)
- Easy removal of the release liner (i.e., for children and elderly patients)

- Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma)
- No residue i.e., ―cold flow‖ around the edge of the patch in storage or after application to skin or beneath the patch after removal)
- No unacceptable dermal reactions (i.e., contact dermatitis, skin sensitization, photo toxicity, photosensitization, erythema, itching, stinging, burning, etc.)
- Consistent biopharmaceutical performance (i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same individuals over time.

EVALUATION PARAMETERS [28, 29]

The evaluation methods for transdermal dosage form can be classified into following types:

Physicochemical evaluation

In vitro evaluation

In vivo evaluation

Stability studies

PHYSICOCHEMICAL EVALUATION:

Interaction Studies [30]

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

Thickness of the Patch [31]

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight Uniformity The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance.

The average weight and standard deviation values are to be calculated from the individual weights.

Folding Endurance

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

Percentage Moisture Content

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

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100

Percentage Moisture Uptake

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

Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100

Water Vapour Permeability (WVP) Evaluation: [32]

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following **formula: WVP=W/A**

Where, **WVP** is expressed in gm/m^2 per 24hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs and

A is the surface area of the exposure samples expressed in m^2.

Drug Content

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

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 [15].

Uniformity of Dosage Unit Test[33]

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

Polariscope Examination:

This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch [34].

Shear Adhesion Test:

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung 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 take for removal, greater is the shear strength [34].

ADHESIVE STUDIES:

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 [34]

Peel Adhesion Test:

In this test, a length of tape is adhered to a surface and then the tape is removed by lifting away from the surface in a specified manner (Figure 5). Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. The results are reported as the force required for a given width of tape. 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 180º angle, and the force required for tape removed is measured.

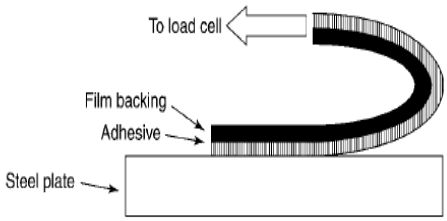

Figure5. Peel Adhesion test

Thumb Tack Test:

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

Flatness Test: [35]

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

% constriction = $I_1 - I_2 / I_1 X\ 100$

Where, I_1 = Initial length of each strip. I_2 = final length of each strip.

Percentage Elongation Break Test[35]:

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

Elongation percentage = L_1-L_2/L_2 ×100

Where, $\mathbf{L_1}$is the final length of each strip and $\mathbf{L_2}$ is the initial length of each strip.

Rolling Ball Tack Test: [36]

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive(Figure 6). The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

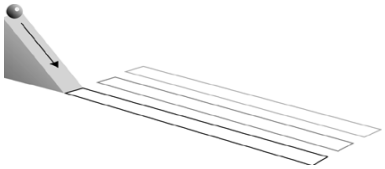

Figure6. Rolling ball tack test

Quick stick (peel-tack) Test[37]: In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min (Figure 7). The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

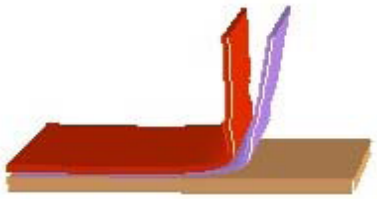

Figure7. Quick stick (peel-tack) tests

Probe Tack Test:

The Experimental technique known as probe tack is designed to test the adhesive properties of film for very short contact times. In this test, a flat- ended cylindrical probe is bought in contact with the adhesive film which is deposited on a rigid substrate. The probe is then maintained in contained under a controlled pressure for a certain contact time. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams (Figure 8).

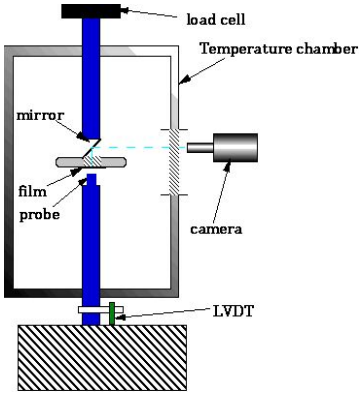

Figure8. Probe Tack test

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. The test performed with an apparatus (Figure-9) which was fabricated according to PSTC-7 (pressure sensitive tape council) specification [14.]

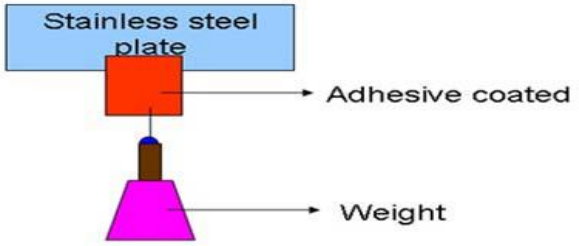

Figure9. Shear strength properties or creep resistance

IN VITRO EVALUATION:

***In vitro* drug release studies[30]:**

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

***In vitro* skin permeation studies:**

An in vitro permeation study can be carried out by using diffusion cell (Figure10). Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or H LC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated mg cm^2 vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load mg cm^2.

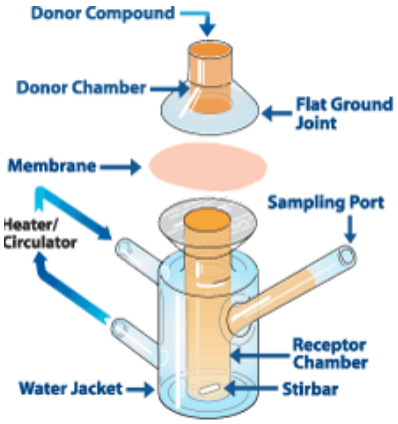

Figure10. Cell Franz diffusion apparatus

IN VIVO EVALUATION STUDIES

***In vivo* Evaluation**

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

Biophysical models

Animal models:

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both *in vitro* and *in vivo* experiments. Rhesus monkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man [15].

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 [15.]

Biophysical Models

Models based on steady-state mass balance equation, solution of Fick's second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been described in the literature. It can be concluded that many techniques for in-vivo evaluation of transdermal systems have been put forward there is scope for further refinement. Some of the unresolved issues include the barrier function of the skin with age, skin metabolism, in-vivo functioning of penetration enhancers etc.

Skin Irritation study[33]:

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm^2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

Stability studies[30]:

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

REGULATORY STRATEGY FOR INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND NEW DRUG APPLICATION SUBMISSIONS FOR TDDS

Standard irritation and sensitization studies should be performed with the patch itself in animals/humans. Negotiate the timing and implementation of the toxicology requirements. The dermatology division at FDA should review dermal aspects of the IND and new drug Application (NDA).Primary review should occur at the division that handles the indication under study. Dose ranging studies are required in Phase 2. Single Phase 3 study could be negotiated.

FUTURE OF TRANSDERMAL THERAPY

Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches. At that time, biotech medicinal was still being developed. During the past decade, the number of drugs formulated in

the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The reason is the only a limited number of drugs fit the molecular weight, and potency requirements for transdermal absorption.

APPLICATIONS OF TRANSDERMAL PATCHES [38, 39, 40]

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

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