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Review Article

Review on Transdermal Drug Delivery System

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ABSTRACT

Transdermal medication delivery has emerged as a creative means of achieving systemic drug absorption at a predefined rate over an extended period. Its primary benefits are reduced dose frequency, avoiding first-pass metabolism by entering directly into the systemic circulation, suitability for elderly patients who cannot take pharmaceuticals orally and ability to be self-administered with fewer adverse effects. This review covers general aspects like drug absorption pathways through the skin, the kinetics of drug absorption, different factor affecting the transdermal permeability, various type of transdermal patches, their components and evaluation parameter. Additionally, some marketed transdermal patches and therapeutic applications of transdermal drug delivery system have been discussed. Moreover, the article includes various generation of advancements in the transdermal drug delivery system and its future aspects. The success of all the TDDS depends on the skill of the drug to permeate skin in sufficient quantities to achieve its desired therapeutic effect. This review article provides a detailed study of transdermal that is benefit, disadvantages, mechanism, factors affecting skin permeation and types. Characterization of transdermal patch is use to check its quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content & uniformity.

Keywords: Transdermal patch, Permeability, Polymer Matrix, Rate Controlling Membrane, Permeation Enhancers.

INTRODUCTION

At present, the most common form for the delivery of drugs is oral route. While this has the notable advantage of easy administration, it also has significant drawbacks -namely poor bio availability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery system is also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e. peptides, proteins) to their site of action, without incurring significant immunodeficient or biological inactivation. Transdermal drug delivery is defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.

Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness[1].

Advantages [2,3]:

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

- The drugs by pass the hepatic and presystemic metabolism i.e., Avoidance of first pass metabolism thereby increasing bio availability.
- Risks and inconveniences of IV therapy are avoided.
- Self –administration is possible.
- Minimizing undesirable side effect.
- Avoiding the fluctuation in drug level.
- Maintain plasma concentration of potent drug.

- Termination of therapy is easy at any point of time.
- Ability to deliver the drug more selectively to a specific site.
- Provide suitability for self administration.
- Enhance therapeutic efficacy [2,3].

Disadvantages [2,3]:

- 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's 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[2,3].

PHYSIOLOGY OF SKIN [4]:

Skin of an average adult body covers a surface of approximately $2m^2$ and receives about one-third of the blood circulating through the body. Skin contains an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body.

Skin Pathways for Transdermal Drug Delivery Systems:

When drugs are applied on the skin surface, penetration into and through the skin can occur via various routes. Drugs penetrate either via the stratum corneum (transepidermal) or via the appendages (transappendageal). During penetration through the stratum corneum, two possible routes can be distinguished, Penetration alternating through the corneocytes and the lipid lamellae (transcellular route) and Penetration along the tortuous pathway along the lipid lamellae (intercellular route).

Generally, it is accepted that the predominant route of penetration through the stratum corneum is the intercellular route. This is mainly caused by the densely cross-linked cornified envelope coating the keratinocytes. However transcellular transport for small hydrophilic molecules such as water cannot completely be excluded. The appendage route or shunt route includes either the duct of the exocrine sweat glands or the follicular duct. The content of the exocrine sweat glands is mainly hydrophilic, while the content of the follicular duct is lipophilic. This is mainly due to the sebum excreted into the opening of the follicular duct. It is generally accepted that due to its large surface area, passive skin permeation mainly occurs through intact stratum corneum[4].

Basic Components of TDDS [5,6]:

A. Polymer matrix [Table 1]:

- Polymer is a crucial and indispensable part of the transdermal drug delivery system. Rate-controlled medication delivery has been accomplished using a variety of polymeric material types.
- The physicochemical characteristics of the drug and polymer used in the device's construction determine the drug release mechanism.
- For a polymer to be employed in a transdermal system, it must meet the following requirements.

1. The polymer's chemical functionality, glass transition temperature, and molecular weight must permit the diffusion and release of the particular medication.
2. The polymer should make it possible to include a significant quantity of drug.
3. Neither physically nor chemically should the polymer and the medication interact.
4. The polymer should be pricey and simple to build into the required product.
5. In the presence of the medicine and any other excipients used in the formulation, at high humidity levels, or at body temperature, the polymer must be stable and must not disintegrate.

Table 1: Polymer Matrix

Natural polymer	Synthetic elastomer	Synthetic polymer
Gelatin	Neoprene	Polyethylene
Gum Arabic	Silicon Rubber	Polystyrene
Starch	Butyl Rubber	PVC
Shellac	Chloroprene	PVP
Zein	Polysiloxane	Polyester

B. Drug substance:

Choosing the right drug substance is crucial to the creation of a successful transdermal product. Important pharmacological characteristics that influence how well it diffuses through the apparatus and through the skin include:

- **Physical and chemical attributes**

➢ The drug's molecular weight should be below 600 Dalton.

➢ The log P should fall between 1 and 7

➢ The melting point must be below 200° C.

➢ The minimum number of hydrogen bonding groups is two.

➢ It must have an advantageous oil:water partition coefficient.

➢ Transdermal administration is not appropriate for medications that are strongly acidic or alkaline in solution.

➢ Solubility should be more than 1 mg/ml in both mineral oil and water.

C. Penetration Enhancers:

✓ They are regarded as an essential component of the majority of transdermal formulations and increase skin penetration.

✓ They can alter the skin's resistance to penetration by reacting with the skin's surface or the applied substance.

The following qualities should be present in an ideal penetration enhancer:

1) Pharmacological inertness, affordability, and Cosmetically Acceptable.

2) Nontoxic.

3) Nonirritating.

4) Nonallergenic.

5) Quick onset; predictable and appropriate duration of action for the medicine used, Chemical penetration enhancers' reversible impact on the stratum corneum's barrier properties.

6) Compatible with the delivery system both chemically and physically.

7) Easily fitted into the delivery system.

- **Two Types of Principles Have Been Employed to Increase Drug Permeation Through Skin;**

1. Physical Enhancers.
2. Chemical Enhancers.

1. Physical Enhancers.

When chemical enhancement's limitations were reached, physical enhancement technologies became popular.

Methodologies:

I. Electrically Based Techniques:

- ◆ Electroporation.
- ◆ Ultrasound.
- ◆ Iontophoresis.

II. Structure Based Technique:

- ◆ Microneedles.

III. Velocity Based Technique:

- ◆ Jet-propulsion.

I. Electrically Based Techniques:

a) **Iontophorosis**:

- It works by creating a repulsion between the charged electrode and the solute.
- Current applied 0.5Ma/cm ²

Ex: Lidocaine, Vincristine.

b) Electroporation:

- Application procedure using high transdermal voltages generated by electrical pulses.
- Controllable by modifying the electrical pulse.

C) Ultrasound:

- It produces physical air pressure above topical skin.
- Medication delivery with low frequency range.

II. Structure Based Technique:

a) Microneedles:

- ■ Microneedle is micro size needles which are used in set of arrays
- ■ To boost skin permeability, they produce a silicon-based physical tunnel through the top epidermis.
- ■ These Needles Easily Pierced in Epidermal Layer of The Skin.

III. Velocity Based Technique:

a) Jet-Propulsion:

✓ It Splits the Drug into Skin.

✓ High velocity jet(100m/s) of compressed gas (Helium) (2022).

2. Chemical Enhancers:

Chemical boosters mechanism for increasing chemical penetration. There are three major methods through which penetration enhancers can function.

- The stratum corneum lipid's highly organised structure is disturbed.
- Compatibility with intercellular proteins.
- A more effective medication partition and enhancer and solvent into stratum corneum.

Classification of Chemical Enhancers:

a. Sulphoxides- DMSO, DMF.

b. Azones- 1-dodecylazacycloheptan-2-one.

c. Pyrrolidones- N-methyl-2-pyro.

d. Essential oils, terpenes, terpenoids, L-Menthol.

e. Oxazolidinones- 4-decyloxazolidin-2-one.

f. Fatty acids- lauric acid, myristic acid and capric acid.

g. Glycol- diethylene glycol and tetraethylene glycol.

Types of Permeation Enhancers:

a) Sulfoxides Dimethylsulfoxide (DMSO):

- It is an efficient penetration enhancer that enhances permeation by lowering skin resistance to drug molecules or promoting drug partitioning from the dose form.
- It has been proposed that DMSO either denatures the intercellular structural proteins of the SC or enhances lipid fluidity by disrupting the ordered structure of the lipid chains.
- DMSO may also change the physical structure of the skin via elution of lipid, lipoprotein, and nucleo protein components from the SC.

b) Alcohols:

- Alcohols can alter transdermal penetration through a variety of methods. The alkanols alkyl chain length is a key characteristic in the promotion of permeability enhancement.

c) Polyols:

- Propylene glycol action is hypothesised to come from keratin solvation inside the SC; the occupancy of proteinaceous hydrogen bonding sites lowering drug tissue binding and hence enhancing penetration.

d) Alkanes:

- Long chain alkanes (C7-C16) have been demonstrated to improve skin permeability via non-destructively altering the SC barriers.

Additional Excipients:

Adhesives:

All transdermal devices must be adhered to the skin with a pressure sensitive adhesive that can be applied to the face or the rear of the device.

Both adhesive layers must meet the following requirements:

i. When in touch with the skin, it should not produce irritation, sensitization, or an imbalance in the natural skin flora.

ii. Should actively adhere to the skin.

The three primary types of polymers evaluated for potential medical applications TDDS [Fig 1] Includes:

- ✓ Pressure sensitive adhesives of the polyisobutylene type.
- ✓ Pressure sensitive acrylic adhesives.
- ✓ Pressure sensitive silicone adhesives[5,6].

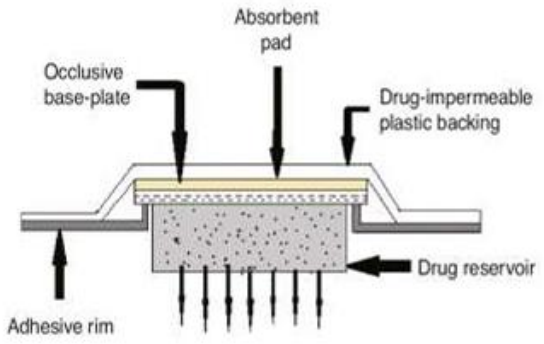

Figure 1: Transdermal Drug Delivery System Device

Table 2: Ideal Properties of drugs for TDDS

Parameters	Properties
Drug	Should be low (low than 20 mg/day)
Half-life	10 or less (h)
Molecular weight	<400 Da
Partition Coefficient	Log P (Octanol-Water) between 1.0 and 4.0
Skin permeability Coefficient	>0.5 x 10-3 cm/h
Lipophilicity	10 < Ko/w < 1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<2000C

DESIGN OF TRANSDERMAL DELIVERY SYSTEM[7,8]:

The basic components of any transdermal delivery system include the drug dissolved or dispersed in an inert polymer matrix that provides support and platform for drug release. There are two basic designs of the patch system that dictate drug release characteristics and patch behavior:

1) Matrix or Monolithic:

The inert polymer matrix binds with the drug and controls its release from the device.

2) Reservoir or Membrane:

The polymer matrix does not control drug release. Instead, a rate controlling membrane present between the drug matrix and the adhesive layer provides the rate limiting barrier for drug release from the device.

TECHNOLOGIES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS:

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

Polymer membrane permeation-controlled TDD Systems:

In this system the drug reservoir is sandwiched between a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane. The drug molecules are permitted to release only through the rate- controlling polymeric membrane. The rate-controlling membrane can be either a microporous or nonporous polymeric membrane, e.g., ethylene-vinyl acetate copolymer, with drug permeability. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure-sensitive adhesive polymer, e.g., silicone adhesive, may be applied to provide intimate contact of the TDD system with the skin surface.

Ex: Transderm-Nitro system, Transderm-Scop system, the Catapres TTS system, the Estraderm system, and the Duragesic system.

Polymer matrix Diffusion-Controlled TDD Systems:

In this approach the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and the medicated polymer formed is then molded into medicated disks with a defined surface area and controlled thickness. This drug reservoir-containing polymer disc is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. In this system the adhesive polymer is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disc. Ex: Nitro-Dur system and the NTS system.

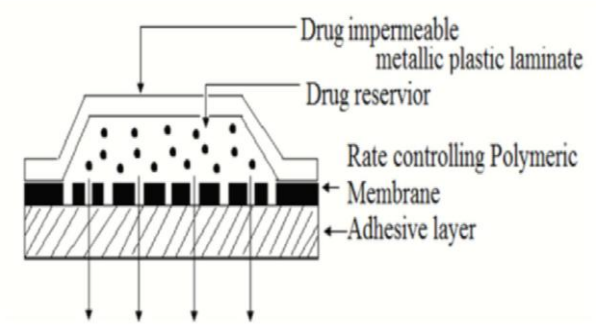

Figure 2: Transderm-Nitro system

Drug Reservoir Gradient-Controlled TDD Systems:

To overcome the non zero-order drug release profiles, polymer matrix drug dispersion-type TDD system can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layer. Ex: Deponit system.

Microreservoir Dissolution-Controlled TDD Systems:

This type of the delivery system can be considered a hybrid of the reservoir and matrix dispersion type delivery systems. In this approach the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-miscible drug solubilizer, e.g., polyethylene glycol, and then homogeneously dispersing the drug suspension, with controlled aqueous solubility, in a lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chain in situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness.

Ex: Nitrodiscsystem[7,8].

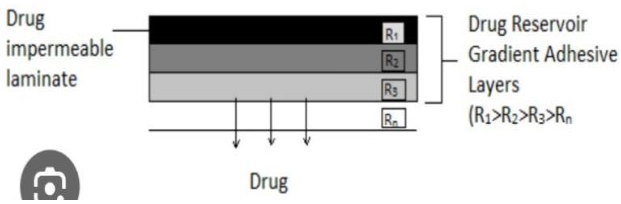

Figure 3: Drug Reservoir Gradient-Controlled TDDS

PREPARATION OF TRANSDERMAL PATCHES [9,10,11]:

Transdermal drug delivery patches can be prepared by various methods:

Mercury Substrate Method:

In this method required amount of drug is dissolved in predetermined amount of polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is keep aside until air bubbles removed completely and then poured in to 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 dried films are to be stored in a desiccator.

Circular Teflon Mould Method:

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Plasticizer added into drug polymer solution. The total contents are to be stirred and then poured into a circular teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in a desiccator.

Glass Substrate Method

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and dry ANUMBRA petridish. The rate of solvent evaporation is controlled by inverting a glass funnel over

the petridish. After over night, the dried films are taken out and stored in a desiccator.

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 custom made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks [9,10,11].

EVALUATION TEST OF TRANSDERMAL PATCH [12-15]:

Drug Excipients Interaction Studies:

The drug and excipients should be compatible to produce a stable product, and it is mandatory to detect any possible physical and chemical interaction. Interaction studies are commonly carried out using thermal analysis, FT-IR studies, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, and absorption maxima etc.

Drug Content:

A specified area of the 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 content with the suitable method (UV or HPLC technique). Each value represents average of three samples.

Weight Uniformity:

The prepared patches are to be dried at 60°C for 4 hrs 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.

Thickness of the Patch:

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.

Flatness Test:

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

Percentage Moisture Uptake:

The weighed films are to be kept in desiccators 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.

Moisture Loss:

The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40C. After 24 hrs the films are to be reweighed and determine the percentage of moisture loss from the below formula.

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100.

Water Vapor Transmission Rate (WVTR) Studies:

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in oven at 100^0 C for some time. About 1g anhydrous calcium chloride was placed in the cells and respective polymer film was fixed over brim. The cell was accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after storage. The amount of water vapor transmitted was found using following formula.

Water Vapor Transmission Rate = Final Weight –Initial Weight/ Time X Area

It is expressed as the number of grams of moisture gained/hr/cm.sq

Swellability:

The patches of 3.14 cm^2 was weighed and put in a petri dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

The degree of swelling (S) was calculated using the formula,

$$S (\%) = Wt – Wo /Wo \times 100$$

Where S is percent swelling

W t is the weight of patch at time t and Wo is the weight of patch at time zero.

Folding Endurance:

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

Tensile Strength:

Tensile strength of the film determined with universal strength testing machine. The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one is fixed and upper one is movable. The test film of size (4 × 1 cm2) is fixed between these cell grips and force is gradually applied till the film broke. The tensile strength of the film is taken directly from the dial reading in kg. Tensile strength is expressed as follows.

Tensile strength =Tensile load at break / Cross section area

Probe Tack test:

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive and when a bond is formed between probe and adhesive. 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.

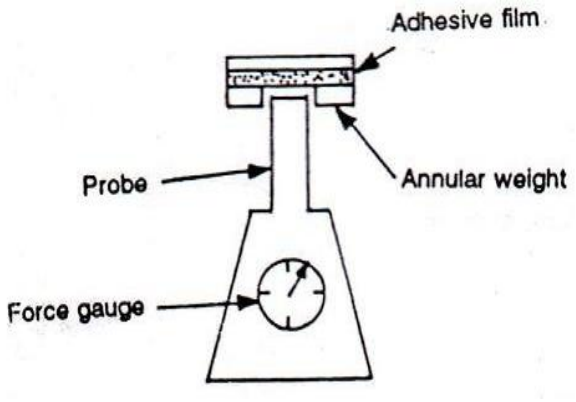

Figure 4: Probe tack test for adhesive evaluation

In-vitro drug release studies:

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 high-performance liquid chromatography (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. Full thickness abdominal skin of male wistar rats weighing 200 to 250 g. Hair from the abdominal region is to be removed carefully by using an 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 diffusion medium or phosphate buffer pH 7.4 before starting the experiment.

Diffusion cell filled with diffusion medium and placed on a magnetic stirrer with a small magnetic bead for uniform distribution of the diffusion. 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 high performance liquid chromatography (HPLC).

Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug-2 permeated (mg/cm) vs. time in hours and permeability -2 coefficients were deduced by dividing the flux by the initial drug load (mg/cm).

***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:

1) Animal models:

The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc.

2) 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[12-15]

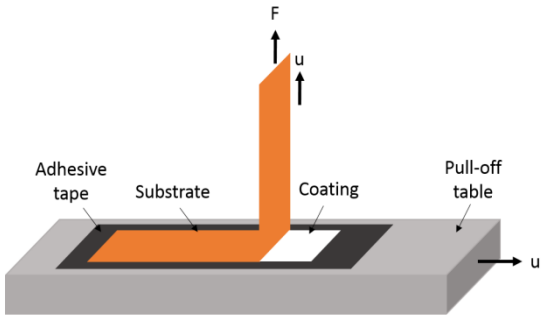

Figure 5: Peel adhesion test for adhesive evaluation.

TRANSDERMAL PATCHES IN PRESENT SCINERIO [16]:

MARKETED PRODUCTS:

The market for transdermal products has been in a significant upward trend that is likely to continue for the future. More than 35 TDD products have been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The table 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.

Table 3: TDDS Marketed Products

Product Name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech/Proctol and Gamble	Post menstrual syndrome
Androderma	Testosterone	TheraTech/GlaxosmithKline	Hypogonadism in males
Captapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Post menstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Post menstrual syndrome
Combipatch	Estradiol/Nore thindrone	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	Estradial	Parke-Davis	Postmenstrual syndrome

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.

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 Ionotophoresis 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[16].

Applications of TDDS[18]:

- Nicotine transdermal patch marketed as Nico dermis to help in smoking cessation. It is the highest selling patch in United State.
- Two opioid medications Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans) used to provide round-the-clock relief for severe pain available in patch form
- Estradiol patches available as Estraderm for treat menopausal symptoms as well as postmenopausal osteoporosis. It is also available in combination with levonorgestrel as Climara Pro for menopausal symptoms.
- Nitroglycerin transdermal patches for the treatment of angina pectoris, prescribed in place of sublingual pills.
- Transdermal patch of clonidine available for treatment of hypertension.
- Transdermal patch of the selegiline (MAO inhibitor) became the first transdermal delivery agent for major depressive disorder.
- Transdermal delivery agent Methylphenidate for the Attention Deficit Hyperactivity Disorder (ADHD) [18].

CONCLUSION

This review article concluded that an older drug by formulating them in new dosage form as generator enthusiasm among the research scientist. If a drug has a physical chemistry and pharmacology TDDS is an effective route of administration. TDDS are gaining popularity and

attracting the attention of researches, there will be the formulation of many new drugs in a transdermal form, while designing the TDDS it should be kept in mind that the formulation may not alter the physiology of the skin. The transdermal patches ha several basic components like drug reservoir, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. 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. Future development of TDDSs will likely focus on the increased controlled of therapeutic regimen and continuing expansion of dug available for use.

REFERENCES

1. Jain, Controlled and Novel Drug Delivery, CBS Publishers, and Distributors, 2002; 107.
2. Chowdary K.P.R and Naidu R.A.S, Transdermal Drug Delivery, A Review of Current Status, Indian Drugs, 1995;32(9):414-422.
3. Hadgraft J, Guy R. H. Transdermal Drug Delivery, New York: Marcel Dekker, 2nd ed 35: 14-16.
4. Hadgraft J.W, and Somers G.F, Review Article Percutaneous absorption, International Journal of Pharmaceutics, 2005;305: 2-12.
5. Heather AE. Transdermal drug delivery: Penetration Enhancement Techniques, Current drug delivery, 2005;(2):23-33. https://doi.org/10.2174/1567201052772915
6. Singh MC, Naik AS, Sawant SD, Transdermal drug delivery system with major emphasis on transdermal patches: a review, J Pharm Res, 2010; 3(10):2537-2543.
7. Lyn Margetts, and Richard Sawyer, Transdermal Drug Delivery: Principles And opioid Therapy, Continuing Education in Anaesthesia, Critical Care & Pain, 2007;7(5):171-176.
8. Nikhil Sharma, Geta Agarwal, Rana A.C, A Review Transdermal Drug Delivery System a tool for Novel Drug Delivery System, IJDDR, 2011;3(3):70-75.
9. Azhar Ahmed, Nirmal Karki, Rita Charde, Manoj Charde, Bhushan Gandhare, Transdermal Drug Delivery Systems, An overview, International Journal of Biomedical and Advance Research, 2011;02(01):38-56.
10. Parthasarathy G, Bhaskar Reddy K and Prasanth V.V, Formulation and Characterization of Transdermal Patches of Naproxen with various polymers, International Journal of Comprehensive Pharmacy, 2011;6(7): 1-3.
11. Kavitha K and More Mangesh Rajendra, Design and Evaluation of Transdermal Films of Lornoxicam, IJPBS, 2011; 2(2):54-62.
12. Koteshwar K.B, Udupa N and Vasantha Kumar, Design and Evaluation of Captopril Transdermal Preparations, Indian Drugs, 2020;15(29):680-685.
13. Priyanka Arora, Biswajit Mukherjee, Design Development Physicochemical and in-vitro Evaluation of Transdermal Patches Containing Diclofenac Diethylammonium Salt, Journal of Pharmaceutical Sciences, 2002;91(9):2076-2089.
14. Sankar V, Velrajan G, Palaniappan R and Rajasekar S, Design and Evaluation of Nifedipine Transdermal Patches, Indian journal of Pharmaceutical, Sciences, 2003; 65(5): 510-515.
15. Manvi F.V, Dandagi P.M, Gadad A.P, Mastiholimat V.S and Jagdeesh T, Formulation of Transdermal Drug Delivery System of Ketotifen Fumarate, Indian journal of Pharmaceutical Sciences, 2003; 65(3): 239-243.
16. www.answer.com/topic/transdermal /patch date of access.
17. Wikipedia. org/wiki/transdermal@patches.
18. Sa chan R and Bajpai M, October-November, 2013; 2(6): 773-790.

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