International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 618-630 www.ijprajournal.com ISSN: 2456-4494

A Over View of Total Transdermal Drug Delivery System

Arpan Sen[1*], Abul Hassan Mollick[2], Nilotpal Tumung[3]
[1,]*Deartment of Pharmaceutics, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India*

Submitted: 15-03-2022 Accepted: 28-03-2022

ABSTRACT
Transdermal drug delivery systems (TDDS), often known as "patches," are dosage forms that release a therapeutically effective quantity of medicine via the skin of a patient. The full morphological, biophysical, and physicochemical features of the skin must be studied in order to transfer medicinal substances via the human skin for systemic effects. Transdermal administration has an advantage over injectables and oral methods because it improves patient compliance and avoids first-pass metabolism. Transdermal delivery not only allows for regulated, consistent drug administration, but it also allows for continuous input of medications with short biological half-lives and prevents pulsed entrance into systemic circulation, which can result in unwanted side effects. The TDDS review articles provide valuable information about Transdermal drug delivery systems and their evaluation process details as a ready reference for research scientists involved in TDDS, various components of Transdermal patches, and approaches for Transdermal patch preparation, evaluation of Transdermal system, general clinical considerations in the use of TDDS, and TDDS limitations.
Key words : Transdermal, Drug delivery systems, Patches, Skin.

I. INTRODUCTION

The pace at which the liquid medicine contained in the reservoir within the patch may flow through the skin and into the bloodstream is controlled by a specific membrane in a Transdermal patch (Skin patch). [1] A controlled drug delivery system is a dosage form that delivers one or more medications continuously in a predefined pattern for a certain length of time, either systemically or to a specific target organ. The major goals of controlled medication administration are to assure patient safety and efficacy while also increasing patient compliance. Better control of plasma drug levels and less frequent doses are used to achieve this. Transdermal treatment systems are characterised as self-contained discrete dosage forms that administer the drug(s) via the skin when applied to undamaged skin, to the systemic circulation at a predetermined rate. [2]

Transdermal-Scoop, the first Transdermal drug delivery (TDD) device, was invented in 1980 and included the medication Scopolamine for motion sickness treatment. A membrane-moderated system is used in the Transdermal device. A micro porous polypropylene sheet serves as the membrane in this device. The drug reservoir is a combination of mineral oil and poly-isobutylene in which the medicine is dissolved. Over the course of three days, this study will be released. [3]

DEFINITION: A Transdermal patch, also known as a skin patch, is a medicated adhesive patch that is applied to the skin and is used to deliver a particular amount of medication into the circulation. [4]

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Figure-1 Transdermal patch patch.[1]

ADVANTAGE AND DISADVANTAGE

Advantages:

I. They can prevent problems with gastrointestinal drug absorption caused by stomach pH, enzymatic activity, and drug interactions with food, drink, and other orally administered medications.

II. When the route of delivery is problematic, such as with vomiting and diarrhoea, they might be used to replace oral medicine administration.

III. Transdermal Nitro-glycerine, for example, is used to prevent the first pass effect. When taken orally, it is rapidly metabolised by the liner.

IV. They're non-invasive; therefore they don't have the drawbacks of parenteral treatment.

V. They offered prolonged treatment with a single application, which improved compliance over other dosage forms that required more frequent dosing, such as trans-dermal coniine day.

VI. The reservoir of drug in the therapeutic delivery system and its regulated release extends the action of medicines with a start half-life.[5]

VII. Drug therapy can be stopped quickly simply removing the drug of the application from the skin's surface.

VIII. Keeping unfavourable side effects to a minimum.

IX. Allows for the use of medicines with short biological half-lives and a limited therapeutic window.

X. Physiological and pharmacological responses are improving.

XI. It is simple to terminate therapy at any moment.[1]

Disadvantages

I. I Contact dermatitis from one or more of the system components cause contact dermatitis at the application site, prompting termination.

II. Because of the natural limits of drug entrance imposed by the skin's impermeability, only strong medicines are appropriate candidates for Transdermal patch.

III. Some medications, such as scopolamine Transdermal patch, are painful when applied behind the ear.

IV. It is tough to adhere for a long time.[1]

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APPLICATIONS

- Nicotine Transdermal patches that deliver nicotine at a controlled dose to aid in the cessation of tobacco use.
- Nitro-glycerine Patches are also sometimes used to treat Angina.
- Attention Deficit Hyperactivity Disorder (ADHD) Transdermal administration agent.

FACTORS AFFECTING TRANSDERMAL PERMEATION:

Factors	Explanations
Partition coefficient	For optimum Transdermal permeability, a lipid/water partition coefficient of 1 or more is necessary.Chemical modifications can be made to it without altering the drug's pharmacological action.
P^H conditions	The use of solutions with extremely high or low pH values might be harmful to the skin. Changes in pH that modify the ratio of charged and uncharged species and their Transdermal permeability can impact the flow of ionisable medicines at moderate pH levels.
Penetrant concentration	In the case of membrane-related transport, a rise in dissolved drug concentration induces a proportionate increase in flux. Excess solid drug acts as a reservoir and helps maintain a steady drug composition for a long time when the concentration is higher than the solubility.
Release characteristics	The release rate is determined by the drug's solubility in the vehicle. The following elements influence medication release mechanism: In the delivery methods, whether the drug molecules are dissolved or suspended. The drug's interfacial partition coefficient between the delivery mechanism and the skin tissue.
Composition of the drug delivery systems	The composition of drug delivery systems, such as boundary layers, thickness, polymers, and vehicles, affects not only the rate of drug release, but also the permeability of the stratum corneum through hydration, interaction with skin lipids, or other sorption-promoting effects, such as benzocaine permeation being reduced by low molecular weight PEG.
Enhancement of Transdermal permeation	The majority of medications will not enter skin at high enough rates to be therapeutically effective. Most medications' Transdermal permeability may be increased by includes a permeation promoter in the drug delivery system, allowing for therapeutically relevant Transdermal permeation. [6].

ANATOMY AND PHYSIOLOGY OF SKIN

Human skin is made up of three separate yet interdependent tissues: The "epidermis" is a stratified, vascular, and cellular layer. Hypodermis is the connective tissues underlying dermis. [1]

Epidermis:

The thickness of the multi-layered epidermis varies based on cell size and the number of epidermis cell layers, ranging from 0.8 mm on the palms and soles to 0.06 mm on the eyelids.

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Corneum stratum. This is the skin's outermost layer, sometimes known as the horny layer. When dry, it is around 10 mm thick, but when completely hydrated, it expands to many times that thickness. Coenocytes are dead, keratinized cells that are arranged in 10 to 25 layers. It's malleable but reasonably impervious. The stratum corneum is the most important barrier to drug entry. The horny layer's architecture may be modelled as a wall-like structure. The keratinized cells in this model serve as protein producers. "Bricks" are lipid "mortar" embedded in "bricks." Multiple bilayers of lipids are present.

Dermis:

The dermis is a 3 to 5 mm thick layer made up of a connective tissue matrix that contains blood arteries, lymph vessels, and nerves. The cutaneous blood supply plays an important role in body temperature control. It also delivers nutrition and oxygen to the skin while eliminating 0.2 mm of the skin's surface area, as well as sink conditions for most molecules that penetrate the skin barrier. As a result of the blood supply, the dermal concentration of a permeate is kept relatively low, and the ensuing concentration gradient across the epidermis is crucial for Transdermal permeation.

Hypodermis:

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It's a fat storage compartment. This layer aids temperature regulation, nutritional support, and mechanical protection. It contains sensory pressure organs and carries major blood vessels and nerves to the skin. Transdermal drug delivery necessitates drug penetration through all three layers and into systemic circulation, whereas topical drug administration necessitates just stratum corneum penetration and subsequently drug retention in skin layers. [1]

FUNCTION OF SKIN

The skin is one of the body's major organs, with a complex structure that reflects its many biological roles. Recent studies on biological roles have been published. The function most relevant to its involvement in Transdermal distribution in recent studies is that of being a barrier to the outer environment. The skin is thought to be an effective barrier to most hydrophilic and ionic substances, preventing penetration and consequently systemic absorption. As will be detailed below, it may be somewhat permeable to substances with a moderate lipophilicity. The skin's role in thermoregulation, which is demonstrated by the existence of hair and fur for insulation, sweat glands for evaporative heat loss, and a wide range of blood perfusion for adjusting heat transmission to the environment, is a second function of the skin that has an influence on our issue. All of these processes may have an impact on the pace and amount of topical chemical absorption throughout the skin. Mechanical support, neurosensory reception, endocrinology (e.g., Vitamin D activation and metabolism), immunology, and glandular secretion are some of the other roles of skin. The skin's histological structure is illustrated in this heterogeneous organ, which is made up of three layers and a variety of appendages. [7]

DRUG DELIVERY ROUTES ACROSS HUMAN SKIN

When a molecule enters healthy skin, it comes into touch with cellular detritus, normal microbial flora, sebum, and other things. The chemical can then infiltrate by one of three routes: Hair follicles a) Sweat ducts b) Sweat ducts c) Sebaceous glands (sebaceous glands) (collectively called the shunt or appendage route) alternatively, you might go straight across the SC.

TYPES OF TRANSDERMAL PATCHES

Single-layer Drug-in-Adhesive :

The medication is included in the sticky layer of this system. The adhesive layer of this sort of patch not only helps to glue the numerous layers together, as well as the entire system to the skin, but it also functions to release the medicine. A temporary liner and a backing surround the adhesive layer.[8]

The multi-layer drug-in adhesive:

The multi-layer drug-in adhesive patch is similar to the single-layer device in that the medication is released via both sticky layers. One layer is for quick medication release, while the other is for controlled drug release from the reservoir. The multi-layer method, on the other hand, is distinguished by the addition of a second layer of drug in adhesive, normally separated by a membrane (but not in all cases). A temporary liner layer and a permanent backing are also included in this patch.[8]

Reservoir:

The reservoir Transdermal system, unlike the single-layer and multi-layer drug-in-adhesive systems, has a distinct drug layer. The drug layer is a liquid compartment divided by the adhesive layer that contains a drug solution or suspension. The backing layer also supports this patch.[8]

Matrix:

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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.

Vapour Patch:

The adhesive layer in this form of patch not only helps to bind the numerous layers together, but it also functions to release vapour. The vapour patches are a relatively new product on the market, and they emit essential oils for up to 6 hours. The vapour patches emit essential oils and are mostly used to treat decongestion. Other types of vapour patches on the market include controller patches that increase sleep quality. [8].

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

Passive diffusion is the basis for Transdermal permeation. The stratum corneum - the skin permeability barrier – must be penetrated before a topically administered medication may operate locally or systemically. Drug molecules may infiltrate the skin through hair follicles or sweat ducts during the initial transitory diffusion stage, and subsequently be absorbed through the follicular epithelium via the intact stratum corneum, which becomes the major channel for Transdermal permeation. A multistep procedure involves the release of a therapeutic drug from a formulation applied to the skin surface and its transfer to the systemic circulation.

Permeation enhancers:

These are the substances that increase skin permeability by acting as a barrier to the flow of a desired penetrant and are found in almost all Transdermal formulations. To obtain and sustain therapeutic medication concentrations in the blood, skin resistance to drug diffusion must be lowered in order for drug molecules to traverse skin and therapeutic levels in the blood to be maintained.

Adhesive layer:

All Transdermal devices must be adhered to the skin with a pressure sensitive adhesive that may be applied to the face or the rear of the device. During contact with the skin, it should not produce irritation, sensitization, or an imbalance in the natural skin flora. It should cling to the skin tenaciously. TDDS studied three key kinds of polymers for possible medicinal uses.

Polymer matrix:

Transdermal medication delivery methods rely on polymer, which is an essential component. To accomplish rate controlled medication administration, many polymeric materials have been employed. The method of drug release is determined by the drugs physicochemical qualities as well as the polymer employed in the device's construction. For a polymer to be employed in a Transdermal system, it must meet the following requirements.

Drug reservoir components:

It must be compatible with the drug and must allow for drug transport at the desired rate. If an ointment is used, the drug reservoir must possess the desired viscosity attributes to ensure reliable manufacturing process. It must possess the desired adhesive and cohesive properties to hold the system together. Materials used are: mineral oils, polyisobutylene, and colloidal silica, HPC.[9]

Backing laminate:

The backing laminate's main purpose is to give support. They should be able to keep the medicine from escaping through the top of the dosage form. Drugs and permeation enhancers must not pass through them. They should have a low rate of moisture vapour transfer. They need to be as elastic, flexible, and tensile as possible. Chemical compatibility with the drug, enhancer, adhesive, and other excipients is required. They must be reasonably priced and enable for printing and adhesive lamination.

Release liner:

The release liner must be removed before the Transdermal system can be used, and it prevents the medicine from migrating into the adhesive layer during storage. It also aids in the prevention of contamination. It consists of a nonexclusive or occlusive base layer and a release coating layer comprised of silicon or Teflon. Polyesters, foil, Mylar, and metalized laminates are examples of other materials. [10]

Formulation Of Transdermal Patches

1) Membrane permeation – controlled system: Multilaminate processes, such as Transdermal Nitro, can be used in these systems. Three substrates are kept together by two layers of drug-containing glue in these items. The medicine is first transformed into the physical/chemical form needed for inclusion into the final product. To obtain a homogeneous solution, the drug adhesive components and excipients are combined with a solvent. These adhesive compositions are applied as a thin coating to moving objects and then dried to eliminate the solvent. The dried adhesive film and other layers are then laminated together to produce a five-layer product that includes a release linear contact adhesive control membrane, a drug reservoir, and a backing substrate. The finished

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dosage form is then printed and die cut from the lamination. Individual foil pouches are then used to package the finished product. The items are automatically put into a continually moving web of pouch stock that is sealed around the dosage form after inspection.

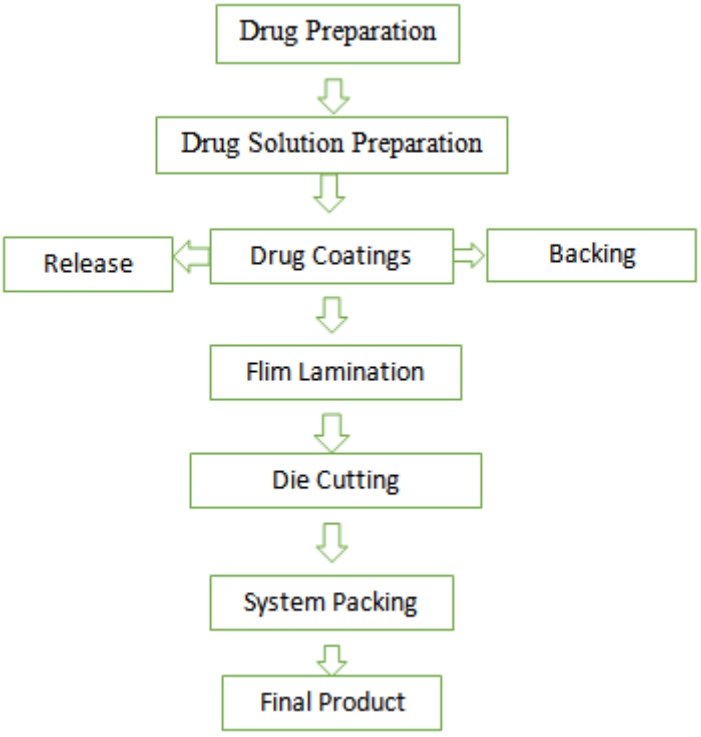

Figure- 6 Multilaminate Transdermal dosage form manufacturing process flow diagram. [11]

2) Adhesive dispersion type system:

The manufacturing process these systems can be divided into following parts.

(I) Preparation of individual matrix solution: To make a standard or stock solution, the raw ingredient [polymer, tackifier, and softening agent] is dissolved in an organic solvent. The matrix solution is then made by combining the stock solution with the chemicals listed in the formulation. The active substance is mixed in with additional non-soluble chemicals.

(II) Coating the individual matrix layers: Coating the solution creates the distinct layers (above). Using a coating machine to remove the solvent from smooth paper or film webs. This machine is made up of two parts.

(A) The coating unit (B) Drying unit.

(a) Coating unit: Coating solvent-based compositions onto the suitable web. Depending on the matrix solution's viscosity, solid content, flow ability, and surface tension.

(b) Drying Unit: Closed to the outside and immediately attached to the drying machine to prevent evaporation of the solvent and active ingredient. By passing the coated web through a drying channel with a transport system such as a cranked shaft or a conveyor belt, the solvent from the adhesive spots is evaporated.

(i) Building the multilayer laminate: The multilayer matrix system is constructed via lamination. Two matrix layers are laminated here, each sticking to one side of the web. After that, a carrier material from the two-layer laminate is removed, and a third layer is pressed with the laminated side to the two-layer laminate's laminated side. This process is continued until the lamination is finished.

(ii) Separating unit of the multilayer laminate: Individual units are punched out of the thin rolls from which the bulk product is slit lengthwise. As a result, the release rate of the active component is affected by the precision of the processes. The liner is then placed to the system, along with any necessary release aids.

(iii) Packaging: Primary packing consists of sealed, four-cornered cardboard boxes, with secondary packaging in cardboard boxes occurring before to shipping.

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(3) Matrix diffusion controlled system: The medication is suspended in an insoluble hydrophobic matrix that is stiff and non-swell able. Insoluble polymers like PVC and fatty compounds like stearic and beeswax are employed for stiff matrix. The drug is usually kneaded using a solution of Polyvinyl chloride in an organic solvent for plastic materials, and the granular waxy matrix is made by distributing the drug in molten fat and congealing it. Swell able matrix systems are useful for maintaining the release of extremely water-soluble drugs after the granules have been compacted into tablets. These matrices are usually made of hydrophilic gums, which can be natural (guar gum, tragacanth), semi-synthetic (HPMC, CMC), or synthetic (HPMC, CMC) (poly acryl amides) The medicine and the gum are granulated together and crushed into tablets using a solvent such as alcohol. The simultaneous absorption of water and desorption of medication from such initially dehydrated hydro gels is accomplished by a swelling regulated diffusion process. The gum expands and the drug diffuses out of it, leaving a swollen area free of drug. [11]

(4) Micro sealed dissolution–Controlled system or Encapsulation: One of various micro encapsulation procedures coats or encapsulates the drug particles with slowly dissolving materials such as cellulose, PEGs, poly-methacrylate, and waxes. The resultant pellets can be placed in a firm gelatine capsule as is. The solubility and thickness of the coating, which can range from 1 to 200 microns, determine the coat's dissolving role. [12]

PRACTICAL ISSUES

Sites of application of TDS patches: The ease with which the SC can be infiltrated varies greatly from site to site. The skin of the hands, face, and genitalia are more easily permeable, whereas the skin of the truncal region is the least permeable. However, this fluctuation has no bearing on routine site usage or the application of Transdermal devices to the skin. The majority of commercially available Transdermal devices or topical treatments come with instructions to apply the patch, gel, or cream to a skin location over the organ where the therapeutic effect is needed**.** The apparent consequence is that there is a preferred pathway from that skin location to the target site (for example, cardio active medications applied to the chest wall, anti-motion sickness agents applied to the retro auricular area, and anti-inflammatory drugs administered to the skin over the painful joint). Despite thorough investigation, no such channels or specific mechanisms have been discovered. The only alternative path from the application site to the objective is the one generated in the patient's mind as a result of a promotional message from the manufacturer. [13]

Age: Except in early newborns, percutaneous penetration does not change greatly with age, and the patient's age has little impact on the Transdermal route's practicality. It may be difficult to establish adequate and long-lasting patch adhesion in this population, and it may also be difficult to develop a device with suitable pharmacokinetics. Transdermal devices are good for the elderly, who are less trustworthy when it comes to taking oral medications and may have gastrointestinal issues that make oral treatment less effective. Because the skin of the elderly is less readily irritated, they are more tolerant of the irritation caused by Transdermal devices.

Adhesion: The majority of Transdermal devices are adhesive patches that either retain the drug-bearing matrix in occlusive contact with the skin or contain the medication inside the adhesive. The adhesive's effectiveness is a key factor in determining whether a Transdermal system will succeed or fail.

Occlusion: If drugs are kept in occlusive contact with the skin, they enter more quickly. The fundamental reason for this is that it induces an increase in SC hydration due to the blockage of normal trans epidermal water loss at the skin surface – similar to how emollients promote SC hydration**.** [14]

Characterization And Assessment Tools For Transdermal Patch Preparation

To describe and define Transdermal patches, a variety of evaluation and evolution tests should be undertaken, including dissolution, in vitro drug release, in vitro skin permeability, sticky characteristics, and excipient control. These tests are listed below and are in accordance with the European Medicines Agency's Quality of Transdermal Patches Guidelines, which were developed by the Committee for Medicinal Products for Human Use. Other forms of physical, chemical, and biological testing, evaluations, and assessments, such as material interaction, patch thickness, and weight uniformity, should also be carried out, Folding endurance, moisture content, moisture absorption or weight gain, water vapour permeability, medication content, flatness, stability, swell ability, and skin irritation tests are among tests that are performed.[10]

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Drug-polymer interaction studies:

Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray powder diffractometry (XRPD), nuclear magnetic resonance (NMR) spectroscopy, and infrared (IR) radiation are some of the thermal and physic-analytical techniques that can be used to determine drug-polymer interactions in a lipid matrix (82–84). Because each chemical has a distinct peak in the DSC, IR, and NMR spectra, it is feasible to identify components in a eutectic drug-polymer combination. A florescence agent is linked to the polymer, the complex is incubated with cells, and the polymer-cell complex is observed under a co focal microscope to detect interactions between cell surface and polymer. The effect of the polymer on lipid membrane fluidization/stabilization may be investigated using NMR.[14]

Patch thickness:

A digital micrometre screw gauge is used to take readings at three to five points on the patch to determine its thickness. To ensure that patch thickness is suitable, the mean thickness and standard deviation of such numerous measurements are calculated**.**

Weight uniformity:

Weighing ten randomly selected patches and computing the average weight and standard deviation determines weight homogeneity. Individual patch weights should not differ much from the average.

Folding endurance:

Folding endurance is the number of times a patch can be folded without breaking when it is sliced equally and repeatedly folded at the same location until it breaks.

Moisture content:

To calculate the moisture content of a Transdermal patch, the patch is accurately weighed, placed in a desiccators with fused calcium chloride for 24 h and then reweighed (87). Percentage of moisture in the patch is calculated using the following equation

Moisture content (%) = (Initial mass -Final mass)*100 / Initial mass

Moisture uptake or mass gain:

Mass gain in a Transdermal patch usually signifies moisture uptake. To measure moisture uptake, the patch is weighed, placed in a desiccators with a saturated KCl solution, and incubated up to 24 h with RH maintained at about 84 %. The patch is then reweighed and moisture uptake is calculated using equation (2).

Moisture uptake (%) = (Final mass -Initial mass) * 100 / Initial mass

Evaluation of water vapour permeability: A natural air circulation oven is used to determine water vapour permeability (WVP) in a patch, where:

WVP = W/A

Where water vapour permeability is expressed in gm^{-2} per 24 h, W = amount of water vapour (g per 24 h) permeated in the patch, and A is the surface area (m^2) exposed on the patch sample.

Drug content:

A certain region of a Transdermal patch is dissolved in a specific volume of a chosen solvent to determine the medication concentration. The solution is shaken continuously for up to 24 hours, and then ultrasonicated for a set amount of time before being filtered. A suitable analytical approach is used to determine the drug content in the filtrate.[15]

Flatness test:

A Transdermal patch is cut into three longitudinal strips: one from the right side, one from the left side, and one from the centre. The length of each strip is measured (90). The following equation is used for flatness determination:

Constriction (%) = $(I_1 – I_2) \times 10$

Where I_1 = strip initial length, I_2 = strip final length.

Stability studies:

Prepared Transdermal patches are stored for six months at 40 ± 0.5 °C and RH of 75 ± 5 %. After the six-month storage, the samples are taken out of storage at intervals of 0, 30, 60, 90, and 180 days and analysed to determine the drug content.

Determination of adhesive properties:

Peel force testing, adhesive strength tests, and tack tests are some of the tests that may be used to describe adhesive qualities. To assess the adhesive qualities of a medication in a Transdermal formulation, in vitro and in vivo testing can be utilised.

Tack test using a probe:

The value of tack is the force necessary to draw a probe away from the sticky polymer at a constant pace. To assess the amount of force necessary to break the binding of the surface of a pressure sensitive adhesive in a Transdermal patch, the probing tack test can be performed instead of the thumb test. Force vs. time plots the force necessary to break the bond over a particular time period.[16]

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Quick stick test/Peel tack test:

This test involves pulling an adhesive tape over the Transdermal patch at an angle of 90° and a speed of 12 inches/min. The tack value is the peeling force needed for breaking the bond between substrate and adhesive.

Peel adhesion test:

The force required to remove a sticky polymer covering from a particular substrate is known as peel adhesion. A piece of tape is placed to a plate of stainless-steel backing membrane and then withdrawn at 180° from the test material to assess peel adhesion. After then, the force necessary to pull the tape is calculated. The test is carried out to ensure that the adhesive does not harm the skin and that no residue is left behind.[17]

Tensile strength: A tensiometer is used to determine tensile strength. A patch is attached to the tensiometer assembly, the weight necessary to break it is calculated, and the patch's elongation is recorded as a consequence (with the pointer on the instrument). The patch's tensile strength is calculated as the average of three patch measurements**.** The tensile strength of the patch is

Tensile strength = break force / a*b (1 + ΔL/L)

where, a = patch width, b = patch thickness, L = patch length, ΔL = patch elongation at breakage point, and break force = weight (kg) required for patch breakage.

Swell ability: To determine the swell ability of a Transdermal patch, the sample is applied to a preweighed cover slip in a Petri dish containing 50 mL phosphate buffer, pH 7.4. Sample absorption takes place during time t (usually about 30 min) (95). After time t has elapsed, the cover slip is removed from the Petri dish, washed and weighed. The change in mass is equal to the mass of water absorbed by the patch. Percentage swelling (S) is determined by the following equation.

$S (\%) = (W_t - W_0) * 100 / W_0$

Where S = % swelling, W_0 = original mass of the patch at time zero, Wt = patch mass at time t after swelling.

In vitro drug release:

An in vitro drug release evaluation experiment can give reliable indication of the rate and extent of drug release from a Transdermal patch. A number of methods can be used to evaluate drug release from the Transdermal formulation with an appropriate, non-rate-limiting membrane. However, alternative methods, with improved discriminative power compared to the compendia methods, may be employed. A number of methods can be used to evaluate drug release from a Transdermal formulation and they include:

i) The paddle over disc (USP apparatus 5/Ph Eur 2.9.4.1) which is similar to the USP paddle dissolution apparatus, except that temperature is adjusted to skin temperature (32 ± 5 ℃) and a disc or cell containing the formulation is immersed at the bottom of the vessel.

ii) The cylinder modified United States Pharmacopeia (United States Pharmacopeia Convention, Inc.) (USP) basket which is similar to the USP basket type dissolution apparatus method, except for a hollow cylinder immersed in medium and temperature maintained at 32 ± 5 °C.

iii) The reciprocating disc method in which the formulation is placed into holders and oscillated in small volumes of buffer medium.

iv) Paddle over extraction cell method (Ph Eur 2.9.4.2) may also be used. Besides, diffusion cells include the Franz-diffusion cell and its modification the Keshary-Chien cell widely used to evaluate drug release from the Transdermal formulation.

Ex vivo skin permeation studies:

Ex vivo skin permeation tests may not be a good predictor of in vivo release, but they can be a good indicator of product quality since they represent the thermodynamic activity of the active ingredient in the product. Ex vivo skin permeation investigations should be constant across the Transdermal preparation's shelf life. A vertical diffusion cell, also known as the Franz diffusion cell, is used in ex vivo permeation experiments. Ex vivo permeation testing was done using two compartments for diffusion, one with a diffusion area of 1.54 cm2 and the other with a capacity of up to 10 ml. A biological membrane made from an animal, such as pig ear skin or rat skin, can be employed to separate the two compartments for the permeation investigation The acceptor medium is commonly a phosphate buffer solution with a pH of 7.5. The receptor solution in the diffusion cell's receptor compartment is kept at 32 0.5 °C and constantly stirred with magnetic rods. The patch is positioned between the upper and lower compartments, with the drug-releasing surface facing the receptor. The buffer media in the inner compartment is constantly stirred at a consistent pace. Typically, 500L samples are obtained at predetermined intervals. When a sample is taken, it is replaced by a buffer of a similar volume. The collected materials are diluted and analysed using an analytical HPLC technique. At regular intervals, drug penetration is monitored, and volume vs time graphs are created are constructed.[8]

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Skin irritation study:

The skin irritation potential of various Transdermal patches may be assessed either visually for erythematic and edoema using the pH test or microscopically for any histopathological changes using a light microscope. To test Transdermal patches for skin irritation, albino rats with an average weight of up to 230 g can be utilised. Patches were put to an area of the rat's back measuring 8.1 cm2 after it was cleansed with rectified spirit and shaved 24 hours before the experiment (100). After 24 hours, the patch is removed and the area is disinfected using a disinfectant swab. Visual inspection is carried out on the application areas for any possible changes in skin erythema and edoema. Draize scale can be used to score the changes involving erythema and edema between 0 and 4 (101). This is rated based on the degree of severity of skin reactions (101). pH is calculated according to the following equation:

pH= {Sum of erythema grade on many days + Sum of edema grade on a number of days}/Number of animals (102). [9]

TDDS MARKETED PRODUCTS

The market for Transdermal products has been steadily increasing, and this trend is expected to continue. TDD products are continuing to provide actual therapeutic value to patients all across the world. In the United States, more than 35 TDD products have been approved for sale, and roughly 16 active components have been approved for usage in TDD products across the world.

Example:

Product Name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	EthicalHoldings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/Norethindrone	Noven , Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris.[11]

ADVANCE DEVELOPMENT IN TDDS

Drug in adhesive technology has become the dominant approach for passive Transdermal administration, and adhesives and excipients are two areas of formulation study. Adhesive research focuses on modifying the adhesive to enhance skin adherence over time, improve medication stability and solubility, decrease lag time, and boost delivery rate. Because there is no one-size-fits-all adhesive that can accept all medication and formulation chemistries, the Transdermal formulator can maximise the Transdermal patch's efficacy by personalising the adhesive chemistry.[18] The development of Transdermal technologies that employ mechanical energy to improve drug flow over the skin by either modifying the skin barrier (mainly the stratum corneum) or increasing the energy of the drug molecules has been a rich field of study over the last 10 to 15 years. Ionotophoresis, which employs low voltage electrical current to push charged medicines through the skin, is one of these so-called "active" Transdermal methods.[19]

- Electro oration 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 .[20]

FUTURE ASPECTS

Rationale for Transdermal Drug Delivery (TDD):

The rationale for administering a medicine Transdermal must be based on an unmet medical need that this route may address, hence providing value to a pharmacological therapy. Stable plasma

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 618-630 www.ijprajournal.com ISSN: 2456-4494

level time profiles over prolonged time periods, for example, may minimise not just dosage frequency, but also pharmaceutical adverse effects and daily doses that must be delivered via other means.[21]

Because Transdermal medication administration is a simple, painless, and convenient method of administration, patient compliance is often high, particularly among the elderly and young, as well as those who have difficulty swallowing or suffer from nausea or emesis.[22]

Furthermore, Transdermal patches may help a pharmaceutical business compete in a big market sector. In the cardiovascular field, nitro-glycerine patches were successfully introduced in the nitrate market more than 30 years ago, and the recent introduction of rivastigmine patches in the indication Alzheimer's and dopamine agonist patches in the indications Parkinson's disease (PD) and Restless Legs Syndrome (RLS).[23]

There is a drug-driven justification in circumstances where the active component fits the parameters for Transdermal candidates (see below) and difficulties with oral administration may be resolved by this route. Finally, Transdermal systems can help with lifecycle management of authorised pharmaceuticals by bolstering the patent/IP position and building relationships with important consumers, including as patients, physicians, health authorities, and carers, as well as providing brand augmentation.[24]

General Aspects to be considered for TDD:

Before the drug is absorbed by the vascular network and/or lymphatic system in the dermis, it has to overcome several hurdles:

- The stratum corneum (SC), the main diffusion barrier of the skin.
- Antigen presenting cells of viable epidermis reporting to the immune system like Langerhans cells and also cells filtering UV radiation or forming a barrier against chemicals.

• Immune and inflammatory cells of the dermis, such as mast cells, that reacts to mechanical or chemically caused irritation. The position of nerve terminals in the dermis must be examined if the outermost skin layer to be disturbed by micro needles or laser beams.[25]

The drug molecule can take a variety of pathways to cross the SC in passive diffusion controlled systems. Most lyophilise medicines are thought to be transported via the para- or intercellular convoluted route between corneocytes. The medicine must diffuse across bilayer of ceramides, which are connected with free fatty acids (and their esters) and cholesterol, in order to take this route. [26] The par cellular lipid matrix's structural features, which are both tough and impermeable, are ideal for skin's barrier demands. Human skin has on average about 100 to 200 sweat pores/cm^2. Hair follicle density is in the same order of magnitude depending on age and region of the skin. Depending on physicochemical properties of the drug and formulation drug, uptake by this pathway may also not be negligible despite the small skin area fraction of about 0.1%.[27]

The transcellular pathway requires repeated drug partition and diffusion across structured bilayer, and seems to be usually less important [28].

II. CONCLUSION

For many inject able and orally administered medications with adequate physicochemical and pharmacological qualities, TDDS is a novel approach in the domain of dosage form. TDD guarantees that a pharmacologically active substance arrives to a relevant in vivo site with minimum side effects. Because of the TDDS's numerous benefits, several new studies are being conducted to add newer medications into the system. Various gadgets that aid in improving medication absorption and penetration are also being investigated. To provide good adhesion and controlled release of medication to systemic circulation via skin over a period of many hours days, TDDS rely significantly on polymers, penetration enhancers, backing laminates, plasticizers, and liners. There are several types of Transdermal patches, each with its own set of features. such as reservoir, matrix, and micro reservoir systems. After the Transdermal patches have been prepared, standardised approaches are used to test the various parameters. The Transdermal route is becoming the most widely accepted route of drug administration due to recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane. This drug delivery overcomes the challenges associated with current popular drug delivery; thus, it shows a promising future. Various medications in the form of Transdermal patches are commercially available depending on the duration of the therapy.

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