Advances In Transdermal Drug Delivery Systems Formulation Approaches, Development Strategies and Evaluation Methods

Ishan P. Aboti [1], Rupal A. Kalbhut[2], Arpita Jena[3,] Suraj D. Thakare[4]
[1]*Department of Pharmaceutical Science, Tulaskar college of Pharmacy Hinganghat, Wardha Maharashtra, India*
[2]*Department of Pharmaceutical Science, Kamla Nehru College of Pharmacy, Butibori, Nagpur, 441108 Maharashtra, India*
[3,4] *Department of Pharmaceutical Science, Siddhivinayak College of Pharmacy, Warora, 442914 Chandrapur, Maharashtra, India*

***Abstract*—A transdermal drug delivery method involves applying a relatively large dosage of the medication to the inside of a patch that is worn on the skin for a long time. The medication reaches the bloodstream through the skin through a diffusion mechanism. The medicine will continue to diffuse into the blood for a considerable amount of time due to the high concentration on the patch and the low concentration in the blood, keeping the drug's concentration in the blood flow constant. To address the challenges associated with oral medicine administration, the transdermal drug delivery method was developed. Due to hepatic first pass metabolism, the traditional oral dose forms have serious drawbacks, including low bioavailability. For instance, gelatin, zein, cellulose derivatives, etc. In a transdermal patch, backing films are essential because they shield the active layer. Thickness, weight uniformity, drug content, in vitro research, moisture content, and swelling index—basic components of TDDS—can all be used to assess transdermal patches.**

***Index Terms*—TDDS, Peel adhesion, Shear strength, Reservoir Type, Membrane**

I. INTRODUCTION

Instead of taking medication orally, it is thought to be preferable to deliver it to the general circulation through the skin. In addition to being weary of taking tablets, patients frequently forget to take their medications. Additionally, avoiding the gastrointestinal system would prevent partial first pass inactivation by the liver and eliminate the frequent GI discomfort. Additionally, consistent medication absorption over hours or days is typically better than blood level spikes and troughs brought on by oral dosing forms. The transdermal products that are now on the market provide these benefits. Transdermal drug delivery refers to self-contained, discrete dose forms that, when applied to undamaged skin, transfer the medication to the systemic circulation at a regulated rate through the skin.

In 1981, the FDA authorized the first transdermal patch. Currently available TDDS include oestradiol (alone or in combination with levonorgestrol or norethisterone) for hormone replacement, testosterone for hypogonadism, fentanyl for chronic pain, clonidine and nitroglycerine for cardiovascular disease, scopolamine (Hyoscine) for motion sickness, and nicotine to help quit smoking. Parkinson's illness, attention deficit and hyperactivity disorder, and female sexual dysfunction are among the products in late stages of research that will further expand the use of TDD into new therapeutic areas. In order to improve the driving power of diffusion (thermodynamic activity) and/or increase skin permeability, such dosage formulations have been devised and/or changed more recently. These methods include liposomes, prodrugs, permeability enhancers, and other vesicles.

1.Epidermis:

The skin is the largest organ in the body and, on average, accounts for about 6 lbs of our body weight. Skin has as its primary function to keep the body hydrated or to keep water inside the body and also prevents foreign substances from entering the body from the environment. The major divisions of the skin, from top to bottom are the epidermis, dermis and the hypodermis. The hypodermis portion is where fat is stored, as shown by the ovals in the figure representing adipocytes. Therefore, in order to have drug delivery via the skin, the drug must pass through the epidermis into the dermis where it can be absorbed by capillaries into the circulatory system. Of the five layers of the epidermis, the most important barrier layer is the outer layer, or stratum corneum. The stratum corneum is made up of dead, keratinized cells called keratinocytes, or sometimes corneocytes. There are three possible ways that drug molecules can pass through stratum corneum. The drug can be absorbed by various pathways through the skin depending on the physicochemical properties of the drug. Both lipophilic and hydrophilic drugs are absorbed from different routes.

2. Dermis:

The connective tissue matrix that makes up the 3–5 mm thick layer of dermis comprises blood arteries, lymph vessels, and nerves. The cutaneous blood supply plays a crucial role in controlling body temperature. Additionally, it eliminates waste and pollutants from the skin while supplying nutrients and oxygen. The majority of molecules that penetrate the skin barrier find a sink in capillaries, which extend to within 0.2 mm of the skin's surface. Thus, a permeate's dermal concentration is kept extremely low by the blood supply, and the ensuing concentration differential across the epidermis provides the necessary concentration gradient for transdermal permeation.

3.Hypodermis:

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It acts as a place to store fat. This layer offers mechanical protection, nutritional support, and aids in temperature regulation. It may have sensory pressure organs and transport the main blood vessels and nerves to the skin. In contrast to topical drug delivery, which only requires penetration through the stratum corneum before the medication is retained in the layers of skin, transdermal drug administration requires the drug to pass through all three of these layers and enter the systemic circulation.[2]

Anatomy and physiology of skin [2-5]:

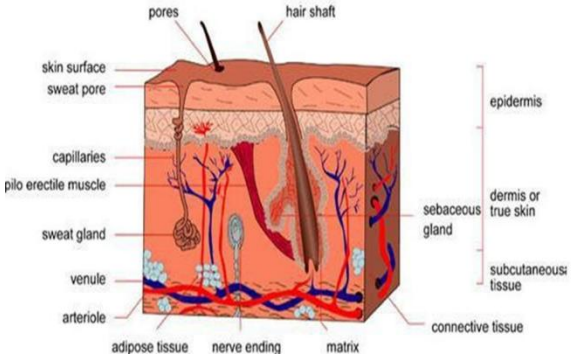

Figure 1: Structure of skin

1. Transfollicular route: -Transfollicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs. These ducts offer a continuous channel across the stratum conium for drug transport but various factors like secretion from glands, content and amount of secretion etc., affect the transport of drugs through this route. However trans appendageal route occupies only 0.1% of total skin surface and therefore contributes a little.
2. Transcellular route: - Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway. Corneocytes are surrounded by lipids connecting these cells. So a drug requires a number of partitioning and diffusion steps. It is the most widely used route by various types of drugs. The highly hydrated keratin provide aqueous pathway to the hydrophilic drugs. A number of partitioning and diffusion steps are needed to pass the drug through the cell matrix.

3. Intercellular route: - As the name indicates intercellular the drug diffuses through the lipid bilayer between the cells. In this route, the molecule stays in the lipid bilayer and winds around the keratinocytes on its way to the dermis.

Although both paths are possible, the most common route of drug penetration is the intercellular route because most drug molecules are more soluble in the lipid environment of the bilayer than in the protein environment of the keratinocytes.

II. METHODS FOR ENHANCING TRANSDERMAL DRUG DELIVERY

Skin penetration can be enhanced by following methods: -

1.Drug/prodrug: The prodrug approach has been used to improve the dermal and transdermal delivery of drugs with unfavorable partition coefficients. The prodrug design entails the addition of a promoiety to increase the partition coefficient as well as the parent drug's solubility and transport in the stratum conium. For instance, the very polar 6-mercaptopurine's inherent low permeability was raised

2.Eutectic system: A combination of elements or chemical compounds with a single chemical composition that solidifies at a lower temperature than any other composition is called a eutectic system. Regular solution theory states that a material's solubility in a particular solvent, including skin lipids, increases with decreasing melting point [7].

3. Liposomes and vehicles: Liposomes are colloidal particles that may encapsulate medications and are created as concentric bimolecular layers. There are several instances of cosmetic goods with vesicles encasing the active components. These include enzymes, unscrewing and tanning agents, humectants like urea and glycerol, etc. The most popular composition is phosphatidylcholine derived from soybean or egg yolk, while several other possible components have been assessed. [7]

4.Solid lipid Nanoparticles: Solid lipid nanoparticles (SLN) have recently been investigated as carriers for enhanced skin delivery of sunscreens, glucocorticoids, triptolide, and vitamins A and E. It is believed that the occlusive film that forms on the skin's surface increases skin hydration, which is the main cause of their improved skin penetration [8].

5. Iontophoresis: This technique uses a low-level electric current administered either directly to the skin or indirectly through a dosage form to penetrate a topically applied medicinal substance. Electrode type, current intensity, and system pH are factors that influence the design of an aionophoretic skin delivery system. One or more of the following processes may be responsible for the increased drug penetration brought about by this methodology: Electro-perturbation for both charged and uncharged solutes, electro-repulsion for charged solutes, and electro-osmosis for uncharged solutes [9].

6.Electroporation: This technique applies high-voltage pulses to the skin in an attempt to create temporary pores. The most common methods are high voltages (100 V) and brief treatment times (milliseconds). Small molecules, proteins, peptides, and oligonucleotides, as well as biopharmaceuticals with molecular weights more than 7kDA, have all had their skin permeability effectively increased by the method [9].

7. Ultrasound (sonophoresis and phonophoresis): This method uses ultrasonic energy to improve solute transdermal transport either concurrently or by pre-treatment. It increases skin permeability by using low frequency ultrasound (55 kHz) for an average of 15 seconds [9].

8.Photomechanicalwavesandlaserradiation: Lasers are widely used to rejuvenate the face and cure dermatological disorders including acne. This technique ablates the stratum corneum without seriously harming the underlying epidermis by directly and carefully exposing the skin to a laser [11].

9.Radio frequency: The skin is exposed to high frequency alternating current, which causes heat-induced microchannels to develop in the membrane. The quantity and depth of microchannels created by the device regulate the pace of medication distribution. Less than a second is needed fortreatment[12].

10. Magnetophoresis: This technique increases the diffusion of a diamagnetic solute through the skin by applying a magnetic field that serves as an external driving force. Additionally, structural changes brought

on by skin exposure to a magnetic field may enhance permeability [12].

11.Microneedle-based devices: This approach provided the basis for the first drug delivery patents for percutaneous drug administration. To deliver the medication, these 50–110-millimeter microneedles will pierce the SC and epidermis.

12. Skin Abrasion: The top layers of the skin are directly removed or disrupted with this procedure. These devices are based on methods used by doctors to treat skin imperfections such as acne, scars, hyperpigmentation, and superficial skin resurfacing.

13.Needle-less Injection: Using an appropriate energy source, liquid or solid particles are fired through the skin's outer layers at supersonic speeds to accomplish transdermal administration. The drug particles entrained inside the jet flow are said to travel at a speed high enough for skin penetration when compressed gas (helium) is forced through the nozzle. Pain, fear, and safety concerns are avoided with this approach [13].

14. Application of pressure: A potentially non-invasive and straightforward technique for determining the skin permeability of compounds like caffeine is the application of mild pressure, such as 25 kPa.

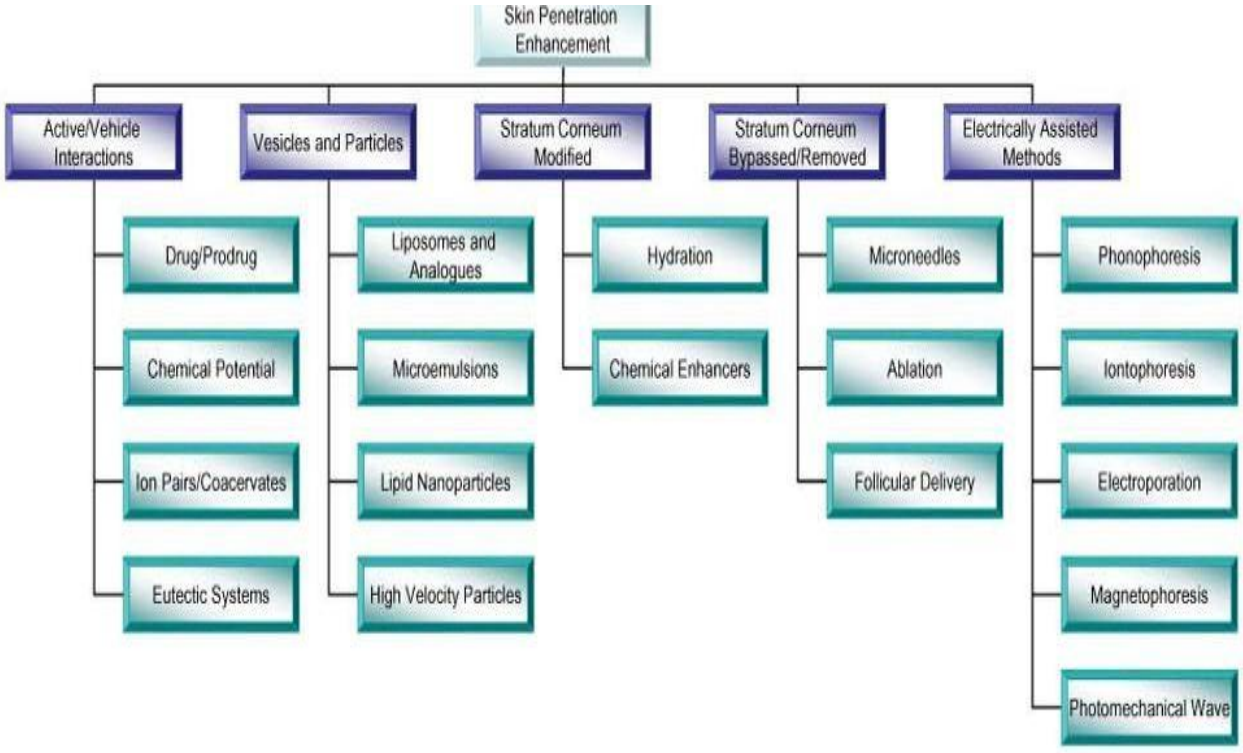

Fig:- 2 Various methods used to enhance the Skin penetration

III. APPROACHES USED IN DEVELOPMENT OF TDDS [14, 15, 16]

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 type of system, drug reservoir is encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous as shown in fig.4. The drug molecules are permitted to release only through the

rate – controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogenously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in anun bleachable, viscous liquid medium (e.g. Silicon fluids) to form a paste like suspension. Examples of this system are Transderm-nitro, Transderm-scop, Catapres and Estraderm etc.

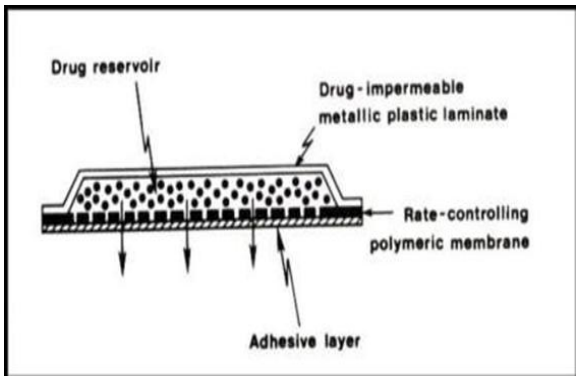

Fig 4: Membrane permeation-controlled system.

Adhesive Dispersion – Type Systems: This is a simplified form of the membrane-permeation controlled system. As shown in fig.5, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non-medicated, rate- controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion – controlled delivery system.

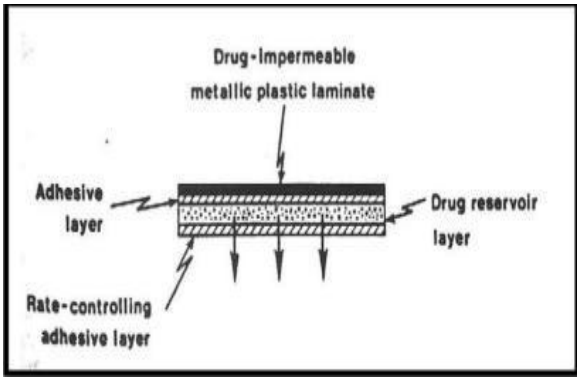

Fig 5: Adhesive dispersion type system

Matrix Diffusion-Controlled Systems: In this method, the drug particles are uniformly distributed inside a hydrophilic or lipophillic polymer matrix to create the drug reservoir. After that, the medicated polymer is molded into a medicated disc with a predetermined thickness and surface area. After that, a drug reservoir with a polymer disc is adhered to an occlusive base plate in a compartment made of a plastic backing membrane that is impermeable to drugs (fig. 6). For instance, Nitro-Door administers nitroglycerin to treat angina pectoris.

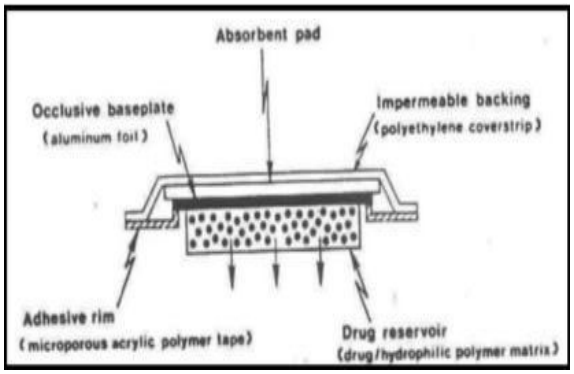

Fig.6: Matrix diffusion-controlled system

4. Micro reservoir type or Micro sealed Dissolution: - Drug delivery systems of the reservoir and matrix diffusion types can be combined to create the micro reservoir type. The medicated disc is then placed in the center of this transfer mal therapeutic system, and an adhesive rim is placed around it (fig. 7). such as nitroglycerine. The addition of a semisolid matrix with a medication solution or suspension in direct contact with the release liner is what distinguishes the Matrix system design.

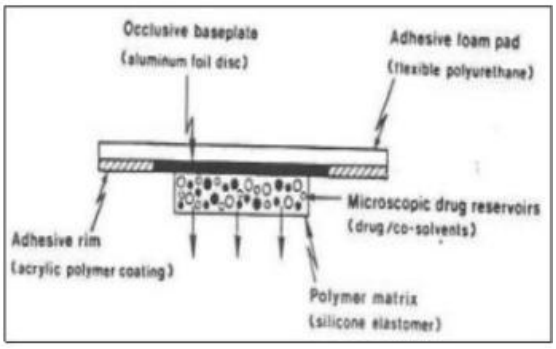

Fig.7: Micro reservoir type-controlled system

IV. FORMULATION METHODS FOR TRANSDERMAL DRUG DELIVERY [17, 18, 19, 20]

Membrane permeation – controlled system:
These systems, like Transdermal Nitro, can be multilaminate processes. These items are made up of two layers of drug-containing adhesive holding three substrates together. The medication is first transformed into the chemical and physical form needed to be added to the product. To create a homogenous solution, the excipients and drug adhesive components are then combined with a solvent. These adhesive compounds are applied as a thin layer to moving materials, which are then dried to eliminate the solvent. The dried adhesive film is then laminated with additional layers to create a five-layer product that includes a drug reservoir, backing substrate, and release linear contact adhesive control membrane. After printing, the laminate was die-cut to create the final dosage form.

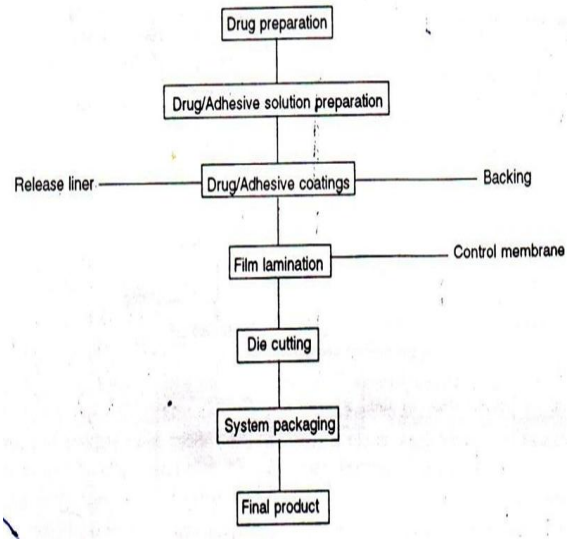

Fig.8:-Multilaminate transdermal dosage from manufacturing process flow diagram

(B) Adhesive dispersion type system: The following components make up the production process for these systems.
(I) Individual matrix solution preparation:-To create a standard or stock solution, the raw ingredient (polymer, tackifier, softening agent) is dissolved in an organic solvent. The stock solution was then combined with the chemicals listed in the formulation to create the matrix solution. Other non-soluble additives are introduced together with the active substance.

(II) Coating the individual matrix layers: -The solution (above) is coated to create the individual layers. Using a coating machine, remove the solvent from the smooth paper or film web. There are two units in this machine.
(a)The coating unit (b) and the drying unit
(a) Coating unit: The proper web is coated with the solvent-based formulations. based on the matrix solution's viscosity, solid concentration, flow capacity, and surface tension.

(b) Drying Unit: To prevent solvent and this active agent evaporation, it is directly connected to the drying unit and closed to the outside world. By passing the coated web through a drying channel using a conveyor belt or cranked shaft transport system, the solvent is removed from the glue.

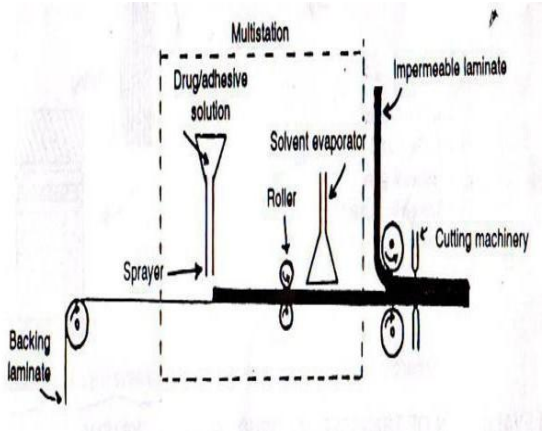

Fig.9: The process and equipment involved in the manufacture of an adhesive dispersion system

(I) Creating the multilayer laminate: The multilayer matrix system is constructed via lamination. Here, two matrix layers are laminated, each sticking to one side of the web. After removing the two-layer laminate's carrier material, a third layer is applied, pressing its laminated side against the two-layer laminate's laminated side. Until the final lamination is finished, this process is repeated.

(II) The multilayer laminate's separating unit: Each unit is punched out of the resulting narrow rolls after the bulk product is cut lengthwise. Here, operational

precision is crucial, which has an impact on the active ingredient's release rate. Next, using the required release aids, the liner is placed to the system.

(III) Packaging: - Primary packaging is done using sealed, four cornered while secondary packaging in cardboard boxes precedes shipment.

(C) Matrix diffusion-controlled system: The medication is distributed across a hard, non-swellable, hydrophobic, insoluble matrix. Insoluble polymers like PVC and fatty compounds like stearic and beeswax are utilized to make stiff matrices. When using plastic materials, the drug is often kneaded with a Polyvinyl chloride solution in an organic solvent. The drug is then dispersed in molten fat and congealed to create a granulated waxy matrix. After that, the granules are compacted into tablets. Swellable matrix systems are widely used to prolong the release of drugs that are very soluble in water. These matrices are often made of hydrophilic gums, which can be synthetic (poly cryamides), semi-synthetic (HPMC, CMC), or natural (guar gum, tragacanth).

(D) Microsealed dissolution–Controlled system or Encapsulation: The drug particles are coated or encapsulated using a variety of microencapsulation procedures using materials that dissolve slowly, such as cellulose, PEGs, polymethacrylates, or waxes. It is possible to fill hard gelatin capsules with the resultant pellets. The solubility and thickness of the coating, which can vary from 1 to 200 microns, determine the dissolving role of the coat.

V. EVALUATION OF TDDS

1.Physicochemical Assessment of Transdermal Patches
2.In- vivo
3.In-vitro

1. Thickness: Using a traveling microscope, dial gauge, screw gauge, or micrometer at several film sites, the thickness of a transdermal film is measured.

2.Weight Uniformity: Ten randomly chosen patches are weighed separately, and the average weight is determined. The average weight and the individual weight shouldn't differ too much.

3.Drug Content Determination: 100 mg of precisely weighed film is dissolved in 100 mL of a suitable solvent in which the drug is soluble. The mixture is then constantly agitated in a shaker incubator for 24 hours. After that, the entire mixture is sonicated. The medication in solution is measured spectrophotometrically using the proper dilution following sonication and filtering.

4.Content Uniformity Test: Ten patches are chosen, and each patch's content is ascertained. Transdermal patches pass the content uniformity test if nine out of ten patches have content between 85% and 115% of the prescribed value and one patch has content at least 75% to 125% of the given value. However, an extra 20 patches are tested for drug content if three of them have content between 75% and 125%. The transdermal patches pass the test if the range of these 20 patches is between 85% and 115%.

5. Moisture Content: Each produced film is weighed and stored for 24 hours at room temperature in a desiccator containing calcium chloride. The films are weighed again after a specified interval until they show a constant weight.
% Moisture content = Initial weight – Final weight

6.Moisture Uptake: Weighed films are stored for 24 hours at room temperature in a desiccator. After that, they are removed and placed in a desiccator with a saturated potassium chloride solution at 84% relative humidity until they reach a consistent weight. The formula for calculating moisture uptake is shown below. Moisture uptake is equal to final weight minus initial weight times 100.

7. Flatness: The surface of a transdermal patch should be smooth and should not shrink with time. A flatness study can be used to illustrate this. One strip is cut from the patch's center and two from each edge to determine its level of flatness. Each strip's length is measured, and the percentage of constriction is used to calculate the length variation. 100% flatness is equal to zero percent restriction.

8. Folding Endurance: Assessing folding endurance is figuring out how many times a film can be folded under harsh circumstances. Folding endurance is measured by folding the film repeatedly at the same

location until it breaks. The folding endurance value is the number of times the films could be folded in the same spot without breaking.

9. Tensile Strength: Corked linear iron plates are used to sandwich individual polymeric films in order to measure tensile strength. An iron screen holds one end of the films in place, while a freely moveable thread is attached to the other end via a pulley. Gradually add the weights to the pan that is fastened with the thread's hanging end. The elongation of the film is measured using a pointer on the thread. It is noticed that the weight is just enough to shatter the film. The following formula can be used to determine the tensile strength.

Tensile strength is equal to F/a.b (1+L/l).
F is the force required to break;
a is width of film;
b is thickness of film;
L is length of film;
l is elongation of film at break point.

10.Tack properties: The polymer's capacity to stick to a substrate under little contact pressure. Tack is influenced by the polymer's molecular weight, composition, and application of tackifying resins.

11. Thumb tack test: Tack is measured by the amount of force needed to remove the thumb from the glue.

12.Rolling ball test: This test measures how far a stainless-steel ball moves along an adhesive that faces up. The ball will move farther if the adhesive is less sticky.

13. Quick stick (Peel tack) test: The tape is pulled away from the substrate at a 90-degree angle at a pace of 12 inches per minute to determine the peel force needed to break the binding between an adhesive and substrate.

14. Probe tack test: Tack is the amount of force needed to draw a probe away from an adhesive at a predetermined rate.

2.In vitro evaluation
a) The Paddle over Disc: (USP apparatus 5/ Ph Eur 2.9.4.1) this method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C.

b) The Cylinder modified USP Basket: (USP apparatus 6 / Ph Eur 2.9.4.3) this method issimilar to the USP basket type dissolution apparatus, except that the system is attached to
The surface of a hollow cylinder immersed in medium at 32 ±5°C.

c) The reciprocating disc: (USP apparatus 7) in this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method (Ph Eur 2.9.4.2) may be used.

d) Horizontal-type skin permeation system: This has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5ml) for each compartment and a small membrane area (0.64cm2). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600rpm. The system is controlled by thermostated water through a water jacket surrounding the two compartments.

e) Franz diffusion cell: The cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm2. The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment.
Flow-through diffusion cell: flow through diffusion cells have the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to aloe appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

3.In vivo studies: -
In vivo evaluations are the true depiction of the drug

performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using animal models human volunteers.

a) 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.

b) 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.

VI. TYPES OF TRANSDERMAL PATCHES

6.1Drug-In-AdhesiveSingle Layer
The medicine is included directly into the skin-contacting adhesive in the Single-layer medicine-in-Adhesive technology. The adhesive in this transdermal system design contains the medicine and all of the excipients beneath a single backing sheet, acting as both the formulation basis and a means of adhering the system to the skin.

6.2 Drug in Adhesive with Multiple Layers
The addition of a semisolid matrix with a medication solution or suspension in direct contact with the release liner is what distinguishes the Matrix system design. The skin adhesion component is integrated into an overlay and surrounds the semisolid matrix in a circular pattern.

6.3 Adhesive-in-Drug Reservoir
A liquid compartment with a medication solution or suspension that is kept apart from the release liner by a semi-permeable membrane and adhesive is what distinguishes the Reservoir transdermal system design. The product's adhesive ingredient that causes skin adherence can be applied in a concentric pattern around the membrane or as a continuous layer between the membrane and the release liner.

6.4 Adhesive-in-Drug Matrix
The addition of a semisolid matrix with a medication solution or suspension in direct contact with the release liner is what distinguishes the Matrix system design. The skin adhesion component is integrated into an overlay and surrounds the semisolid matrix in a circular pattern.

6.5 Fundamental Elements of a Transdermal Patch
- Drug reservoir and polymer matrix
- Enhancers of permeation
- PSA, or pressure-sensitive adhesive
- Backing laminates

6.6 Release liner and other excipients like plasticizers and solvents

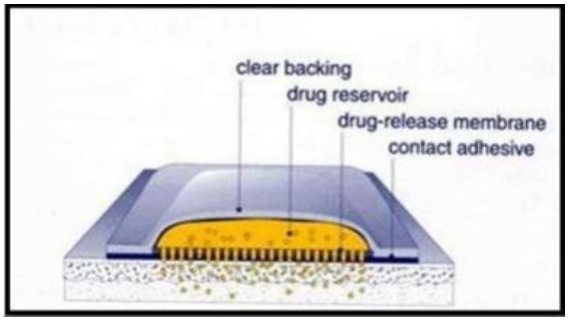

Figure 10: Components of trandermal patches.

VII. RECENT ADVANCES IN TRANSDERMAL DELIVERY SYSTEM [24, 25, 26, 27]

Latest research done in field of transdermal patches is stated below:
1)Patch technology for protein delivery:- Transdermal delivery of large protein is a novel and exciting

delivery method trans pharma uses its unique printed patch technology for transdermal delivery of protein thereby complementing its via Derm delivery technology. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-MicroChannels, forming a highly concentrated protein solution in situ.The delivery of the dissolved molecules is then carried out, via the RF-Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient.

2)Testosterone transdermal patch system in young women with spontaneous premature ovarian failure:- In premenopausal women, the daily testoterone production is approximately 300 μg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone.

3)Transdermal patch of oxybutynin used in overactive bladder:- The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe underthe brand name of Kentera. OXYTROL is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three to four day interval.

4)Nanotechnology gaining hold:-This technology combines the advantage of a needle and the transdermal patch. The devices are dime-sized pieces of polymer with hundreds of hollow microneedles between 100 and 1,000 micrometers long.These small needles penetrate the top layers of skin and allow the drug to pass through with ease.

5)Pain relief: - Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch. One is Lidoderm, a lidocaine percent patch, which is used for post herpetic neuralgia. Other exciting advancements in pain control include the E-Trans fentanyl HCl patch. . This credit card-size patch is an active delivery device that has a self-contained battery that delivers pulses of fentanyl HCl, a strong narcotic. This mimics the use of intravenous self-controlled analgesic systems that are very expensive.

6)Poke with patch approach: - Involves piercing into the skin followed by application of the drug patch at the site of treatment.

7)Coat and poke approach: - Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

8)Biodegradable micro needles: - Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

9)Hollow micro needles: - Involves injecting the drug through the needle with a hollow bore.

VIII. ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

- 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

- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- Predictable and extended duration of activity.
- Minimizing undesirable side effect.
- Provides utilization of drug with short biological half life, narrow therapeutic window.
- Avoiding the fluctuation in drug level.
- Maintain plasma concentration of potent drug.

IX. LIMITATIONS OF TDDS

- Limited skin permeability.
- Restricted to potent drug
- Cannot use for large molecule (>500 Dalton)
- Significant lag time
- Difficulty for adhesion.
- The drug undergoes degradation in the skin.
- Variation in absorption efficiency at different sites of skin.

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