Mini Review: Recent Trends in Transdermal Drug Delivery Systems

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ABSTRACT:
Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver for systemic effects at predetermined and control rate. Since last decade TDDS gained a lot of interest due to its advantages over the conventional dosage forms and oral controlled release delivery, notably avoidance of hepatic first pass effect. Optimizations of drug release through the skin into the systemic circulation and simultaneously minimize the metabolism of drug in the skin is the major goal of transdermal products. The market value of TDDS products are increasing with rapid rate ,more than 35 products have now been approved for sale in US and approximately 16 active ingredients approved globally for use as a TDDS. Transdermal drug delivery is a recent technology which promises a great future. It has a potential to limit the use of needles for administering wide variety of drugs but cost factor is an important thing to consider since developing nations like India is hidden part of TDDS therapy due to its higher cost. The present review outline the latest developments overall evaluation methods and technologies of TDDS.

Keywords: Transdermal drug delivery system, Stratum corneum, Permeation enhancers, Electroporation, Iontophoresis.

INTRODUCTION[1-4]:

The ideal drug delivery method to regulate and sustain drug release through the skin is transdermal. Control-release drug systems, which contain the same medication and are generally quick-release systems, restrict drug release and increase drug efficiency. Many medications are administered orally these days, but the first pass metabolism makes the dose higher and the effects of the drug weaker. Transdermal medication delivery systems were therefore created to decrease the number of dosages while increasing the effectiveness and bioavailability of the medicament. These systems deliver the medication systemically at a consistent rate and sustain it for a long time, thereby removing many issues with oral products like decreased bioavailability, enhanced first-pass hepatic metabolism, relatively short residence time, dose dumping, and inflexibility in dosing. An excellent transdermal medication candidate must satisfy a variety of physical and chemical criteria, including being highly lipophilic by nature, having a melting point over 150^0 C, having a molecular weight above 500 Dalton, having log p values between 1 and 5, and not having any local toxicity or skin irritation.

The term "transdermal delivery," which refers to the administration of medications through the skin for a systemic impact, was first used in 1981 when Ciba-Geigy introduced TransdermV (now sold as Transdermal Scope) as a motion sickness treatment. The FDA authorised Transderm SCOP, the first transdermal device, in 1979 for the treatment of travel-related motion sickness and nausea.

A transdermal patch, also known as a skin patch, is an adhesive patch that is applied to the skin and contains medication that is intended to be applied on to the surface of the skin and entered into the bloodstream.

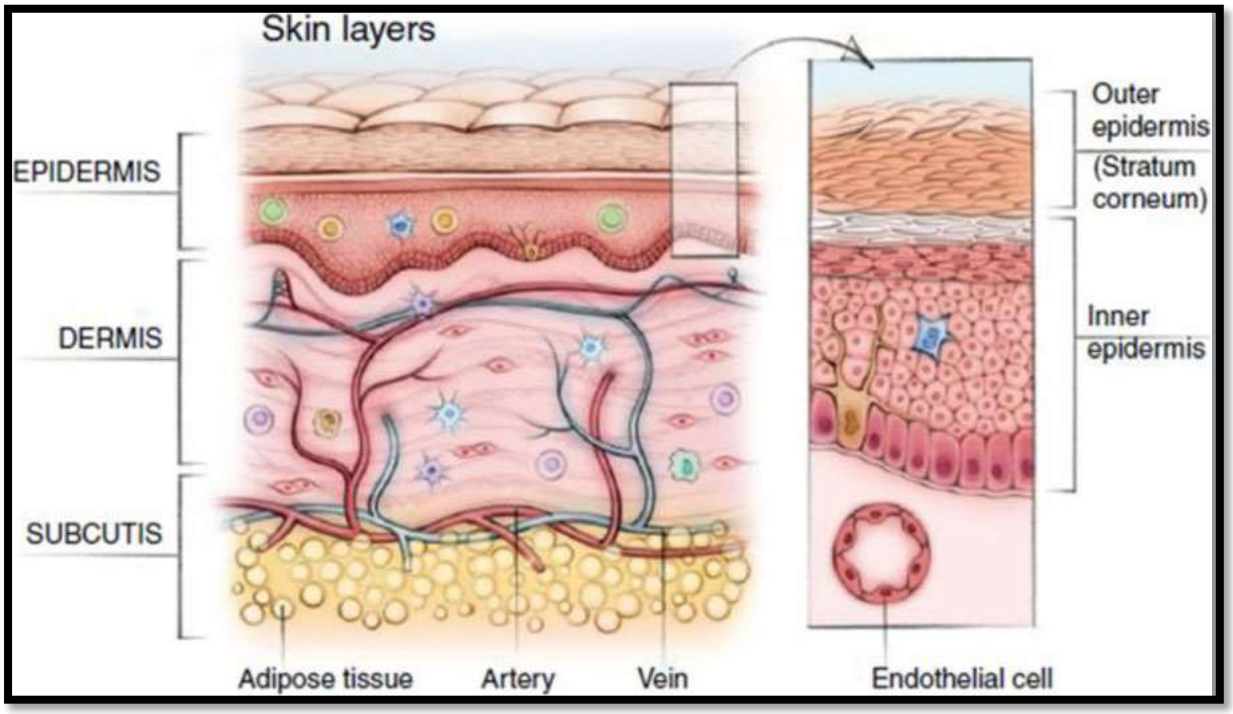

Fig 1: The Structure of Skin

ADVANTAGES[5-6]:

- They are able to prevent problems with gastrointestinal drug absorption caused by stomach pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
- When the oral route is inappropriate, as in the case of vomiting and diarrhoea, it might serve as a substitute for oral medicine administration.
- They avoid the inconvenience of parenteral therapy because they are non-invasive.
- They provide prolonged therapy with a single application, boosting compliance compared to other dosage forms.
- By removing the application from the skin's surface, drug therapy can be stopped quickly.
- If TDDS toxicity occurs, the patch is easy to take off. It lessens systemic medication interactions.

DISADVANTAGES[5-6]:

- Some patients experience contact dermatitis at the application site from one or more system components, which makes cessation necessary.
- Due to the natural restrictions on drug entry imposed by the skin's impermeability, only strong medications are appropriate candidates for transdermal patches.

- Some medications, such as the transdermal scopolamine patch, are painful when applied behind the ear.
- Long-term adherence is challenging.
- Ionic medicines are incompatible with TDDS.
- There may be dose dumping.
- The use of drugs with affinity for both the lipophilic and hydrophilic phases.
- High levels of drugs in the blood cannot be obtained.

LIMITATIONS[7-8]:

- It is unable to give medications that require high blood levels.
- Skin sensitivity and irritation may be brought on by a medicine or drug formulation.
- On the same individual, from person to person, and with age, the barrier function of the skin varies from one place to another.
- When the medicine is heavily metabolized in the skin and the molecular size is large enough to prevent the molecules to diffuse through the skin.
- It could trigger an allergic reaction.

THE SKIN AS A BARRIER[9-11]:

Despite the fact that the purpose of this text is to provide insight into new technologies and approaches in topical and transdermal medication delivery, a quick review on the skin as a barrier is required to help readers grasp the fundamental ideas that underlie the development of the new technologies. The epidermis, or the outermost surface of the skin, is made up of five layers: the stratum corneum (SC), stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale, with the stratum corneum serving as the outermost layer.

The skin's surface area is approximately $2m^2$. The SC is a thick matrix of terminally developed keratinocytes scattered across lipids and it is thought to be the percutaneous absorption process' rate-limiting stage. Both hydrophilic and large-sized molecules can't pass through a healthy, intact SC.Transdermal medication administration is only possible with substances having a molecular weight of up to 500 Dalton due to the SC's resistance to molecular diffusion . Additionally, the state and health of the skin may have a complete impact on how well the drug candidate penetrates the skin barrier.

The dermal layer, which is made up of connective tissues (collagen and elastin), fibroblasts, and other extracellular components like hair follicles and glands, follows the viable epidermis, which is covered by multiple skin layers made of viable keratinocytes. For the treatment of skin-related illnesses, advanced nanotechnologically generated nanocarriers can penetrate the epidermis and reach target locations. By making the drug more soluble and partitioning into the skin, these nanocarriers get beyond the stratum corneum barrier and make it easier to deliver the required dosage of the drug to the target region.

TRANSDERMAL DELIVERY SYSTEM DESIGN[12-15]:

TDDS classified in to three types

1. Reservoir system
2. Matrix system
3. Micro reservoir system

1. Reservoir system:

There is a distinct drug layer included in the reservoir transdermal system. The drug layer could be an adhesive layer-separated liquid compartment containing a drug solution or

suspension. Drugs can also be found in suspension, gel, or solution forms and incorporation of rate controlling membrane. (Fig2)

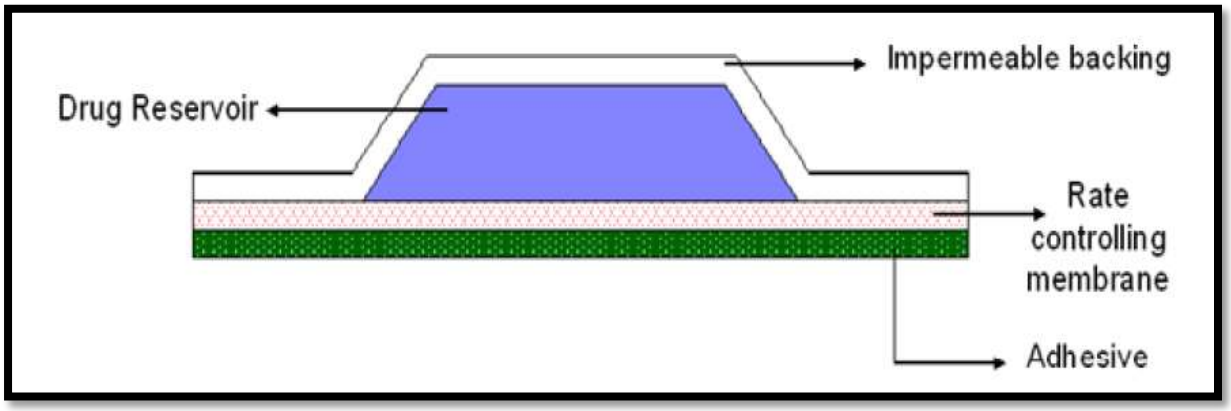

Fig 2: Reservoir system

2. Matrix system:

The controlled medication delivery technology known as matrix tablets releases the medicine continuously. In a matrix system, the drug ingredient is uniformly mixed with the material that regulates the rate by the crystalline, amorphous, or, in some rare instances, molecule dispersion.

There are two categories of systems in the matrix:

- **Drug adhesive system:** The drug reservoir is created by dispersing the drug into an adhesive polymer, which is then distributed or melted onto a backing layer.
- **Matrix dispersion system:** The drug is evenly dispersed over a matrix made of hydrophilic or lipophilic polymers.(Fig3)

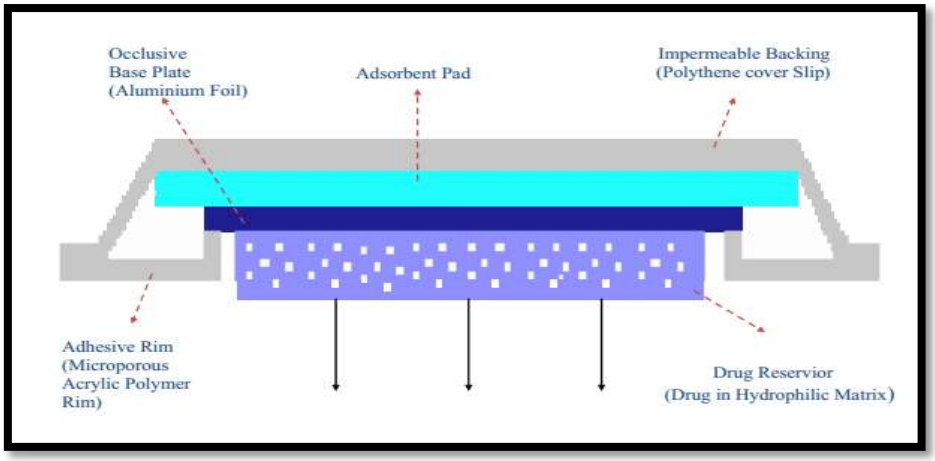

Fig 3: Matrix system

3. Micro reservoir system:

This system combines reservoir and matrix dispersion. To create microscopic spheres that serve as drug reservoirs, the drug is first dissolved in an aqueous solution of a water-soluble polymer and then disseminated in a lipophilic polymer. (Fig4)

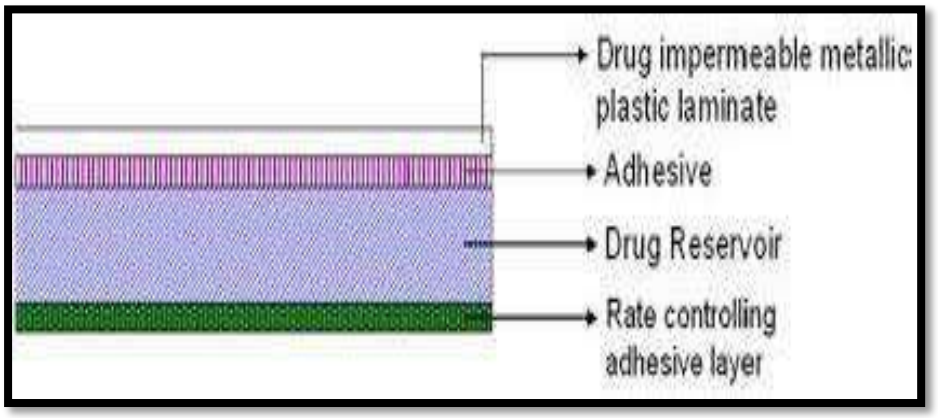

Fig 4: Micro reservoir system

COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS[16-17]

- Drug
- Polymers
- Permeation enhancers
- Backing laminate
- Adhesive polymers
- Plasticizers

The drug's release from the device is managed by the polymer.

- **Drug:** Careful consideration should be given to the drug selection in order to properly build a transdermal drug delivery system.
- Natural polymers such as cellulose derivatives, zein, gelatin, shellac, waxes, proteins, gums and their derivatives, natural rubber, starch, etc. are potential beneficial polymers for transdermal devices.
- Synthetic elastomers, including neoprene, polybutadiene, hydrin rubber, polysiloxane, silicon rubber, nitrile, and acryliconitrile.
- Synthetic polymers, such as polyvinyl chloride, polyvinyl alcohol, polyethylene, polypropylene, polyamide, polyurea, polyvinyl pyrrolidone, polymethyl methacrylate, epoxy, etc.

- **Backing laminate:**

It is a supporting material that is impervious to medications as well as substances that increase permeability. They should be able to coexist chemically with the medication, enhancer, and adhesive as well as other excipients.

Ex: Films made of vinyl, polyethylene, and polyester.

- **Plasticizers:** Dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol.

PERMEATION ENHANCERS[18-22]:

Penetration enhancers (also known as sorption promoters or accelerants), which raise the permeability of the SC to achieve higher therapeutic levels of the drug candidate, are one well-established method for increasing TDD. Penetration enhancers interact with the SC's structural elements, altering how the barrier works and increasing permeability. For

medication absorption through the skin, polar, nonpolar, and polar/nonpolar routes are all possible. By changing one of these pathways, enhancers work. Cause protein conformational change or solvent swelling to shift the polar route. Penetration enhancers (also known as sorption promoters or accelerants), which raise the permeability of the SC to achieve higher therapeutic levels of the drug candidate, are one well-established method for increasing TDD. Penetration enhancers interact with the SC's structural elements, altering how the barrier works and increasing permeability. For medication absorption through the skin, polar, nonpolar, and polar/nonpolar routes are all possible. By changing one of these pathways, enhancers work. Cause protein conformational change or solvent swelling to shift the polar route. Modifying the rigidity of the lipid structure and fluidizing the crystalline channel, which significantly improves diffusion, are the keys to changing the nonpolar pathway. The fluidity of the lipid part of the SC is increased by the fatty acid enhancers. Some enhancers (binary vehicles) modify the multilaminate pathway for penetrates, affecting both polar and nonpolar pathways. The techniques used to alter the SC's barrier characteristics in order to improve drug penetration (and absorption) through the skin can be categorized (1) chemical and (2) physical enhancement.

1. Chemical enhancers:

Accelerants, absorption promoters, or penetration enhancers are popular names for chemicals that facilitate the uptake of medications administered topically. When used as a co-solvent, chemical enhancers work by:

- Increasing (and optimising) the drug's thermodynamic activity.
- Increasing the drug's partition coefficient to speed up skin absorption by the body.
- Preparing the SC to facilitate drug diffusion.
- Fostering drug reservoir establishment and penetration in the SC.

The following are some of the most desirable characteristics for penetration enhancers operating on skin:

- They should not be harmful, annoying, or allergic.
- They would respond quickly and have predictable, repeatable activity and duration.
- The penetration enhancers should work unidirectionally, i.e., they should enable therapeutic substances to enter the body while limiting the loss of endogenous material from the body, and they should have no pharmacological effect within the body, i.e., they should not bind to receptor sites.
- Skin barrier characteristics should quickly and completely reappear after removal.
- The penetration enhancers must be suitable for incorporation into various topical treatments and, as a result, ought to get along with both excipients and medications.
- They ought to have a suitable skin "feel" and acceptable cosmetics.

Sulfoxide (DMSO), fatty acids (oleic acid), alcohol (methanol), glycol (propylene glycol), surfactant (anionic surfactant), azone (lauracapran), and others are some of the permeation enhancers that have been the subject of the most research.

2. Physical enhancers:

For improving the diffusion of drug through the skin, physical means of augmentation such as iontophoresis and ultrasound (also known as phonophoresis or sonophoresis) have been used.

Sonophoresis:

An ultrasound device's ability to provide the necessary range of ultrasound frequencies can enhance transdermal medication delivery. Because it enhances drug circulation by establishing an aqueous channel in the disturbed bilayer by cavitations, low-frequency ultrasound is more efficient. In order to create an aqueous route through which the drug can be administered, the drug in question is combined with a specialised coupler, such as a gel or cream that couples ultrasonic waves to the skin and disrupts the skin layers. Ordinarily, drugs move through channels made by applying ultrasonic waves with energies ranging from 20 kHz to 16 MHz.

Additionally, ultrasound raises the localised skin area's temperature and produces a thermal effect that aids in the uptake of drugs. This technique has been used to distribute a variety of medications from various classes, including mannitol and high molecular weight (MW) medications like insulin, regardless of their solubility, dissociation and ionisation constants, and electrical characteristics (including hydrophilicity). However, there are still issues with device accessibility, maximising exposure time and treatment cycles for delivery, and unfavourable side effects, including burns. The precise mechanism of drug penetration using this approach is also not fully understood.

Iontophoresis:

Iontophoresis has been shown to improve skin penetration and increase the release rate of several drugs with poor absorption and permeation profiles by promoting the movement of ions across the membrane under the influence of a small externally applied potential difference (less than $0.5mA/cm^2$). By using an electrochemical potential gradient, this method has been applied to the *in vivo* transport of ionic or non-ionic pharmaceuticals. The polarity, valency, and mobility of the therapeutic molecule, the type of electrical cycle used, and the drug formulation all affect how well iontophoresis works. Contrary to most other drug delivery techniques, medication absorption through iontophoresis is less dependent on biological factors due to its dependence on current. To improve patient compliance, this approach could also incorporate electronic reminders to patients to adjust medications.

Electroporation:

This technique involves delivering high-voltage electric pulses to the skin for brief periods of time (ms), resulting in the creation of tiny pores in the SC that increase permeability and facilitate drug diffusion. Electric pulses are administered using closely spaced electrodes in a painless and safe manner. It has been used to demonstrate the successful delivery of both low and high-molecular-weight drugs, including antiangiogenic peptides, oligonucleotides, and the negatively charged anticoagulant heparin. The procedure involves permeabilizing the skin and is extremely painless and safe. Small delivery loads and significant cellular disturbance, including cell death, heating-induced drug destruction, and denaturation of therapeutic proteins and other bio macromolecular molecules, are drawbacks of this approach.

Magnetophoresis[23]:

After increasing applied strength, it was discovered that the magnetic field's influence on the drug substance's diffusion flow was strengthened. Applying a magnetic field with a set intensity helps the medicine penetrate the systemic circulation. A magnetophoretic TDDS patch was used to distribute lidocaine at varying magnetic field intensities of 30, 150, and 300 mT. The magneto kinesis phenomenon facilitates the transport of medication molecules.

Additionally, at 300 mT, magnetophoretic increased the drug's octanol/water partition coefficient from 13.80 to 25.94. Compared to standard nonmagnetic patches, *in vivo* investigations revealed improved and better skin bioavailability. TDDS and devices improve drug distribution by boosting blood flow and absorptive at the level of the skin's blood vessels through the use of a heat-controlled mechanism.

A micro-unit built into the gadget produces chemo reactive oxidative responses that supply the heat in the prescribed quantity and relay time fixed manner. At a 43°C controlled heat application, drug distribution from a nicotine patch applied on the upper arm of 10 healthy non-smokers increased up to 13-fold . When nitro-glycerine patches were exposed to a high ambient temperature, same outcomes were seen. When delivering heat to the skin, the controlled-heat aided drug delivery (CHADD) system/device makes it easier for the medicine to enter the bloodstream. The CHADD systems are made up of a small heating unit that generates heat of a finite intensity and duration through oxidation reactions.

LATEST DEVELOPMENTS IN TRANSDERMAL DRUG DELIVERY SYSTEM[23-27]:

The latest developments in transdermal drug delivery systems are

1. Asymmetric 4-methyl -1-pentane (TPX) membrane method.
2. Mercury substrate method.
3. Circular Teflon mould technique.
4. Glass substrate method.
5. Ethylene vinyl acetate copolymer (EVAC) membrane method.
6. Isopropyl myristate (IPM) membrane method.

1. Asymmetric 4-methyl-1-pentane (TPX) membrane method:

As reported in the literature[23] TDDS are fabricated by Asymmetric TPX membrane method. These are produced using the asymmetric a heat-sealable polyester sheet (type 1009, 3 m) with a concave of 1 cm diameter may be used as the backing membrane for an example patch made for this purpose. A TPX asymmetric membrane is deposited over the concave membrane, which is then filled with the drug sample and sealed with an adhesive applying the dry-wet inversion technique. To create a polymer solution, TPX is dissolved in cyclo hexane, a solvent and non solvent adhesive. Using a garden knife, the polymer solution is cast onto a glass plate at a predetermined thickness after being held at 40°C for 24 hours. The casting film is then evaporated at 50°C for 30 seconds, and the glass plate is then immediately submerged in the bath [Kept the temperature of the coagulation bath at 25°C]. The membrane can be extracted after 10 minutes of soaking and allowed to air dry for 12 hours in a circulation oven at 50°C.

2. Mercury substrate method:

The medication and plasticizer are dissolved in a polymer solution using the mercury substrate technique. In order to prevent solvent evaporation, the aforementioned solution must be agitated for ten to fifteen minutes to ensure a homogenous dispersion before being placed onto a mercury surface that has been levelled.

3. **Circular teflon mould technique**:

In this technique, solutions with different ratios of polymers are used in an organic solvent. Half of the same organic solvent is used to dissolve the calculated amount of medication. The second half of the organic solvent is used to dissolve the enhancers in a number of concentrations before adding more. As a plasticizer, di-butylphthalate is added to medication

chemical compound resolution. The entire mixture must be mixed for 12 hours before being placed into a Teflon mould with a circle shape. In order to regulate solvent vaporisation in a very streamline flow hood model with an air speed of 0.5 m/s, the moulds must be put on a level surface and coated with an inverted funnel. For 24 hours, the solvent is allowed to evaporate. The dried films must be hold on for a further 24 hours at 25 0.5°C in a silica gel-filled desiccators before examination to reverse the effects of ageing. The type of films must be assessed within a week of their production.

4. Glass substrate method:

After allowing the polymeric solutions to expand, the necessary amount of plasticizer and drug solution are added, and stirred for 10 minutes. It is then poured into a clean, dry petriplate after being set aside for a while to release any trapped air. By inverting a glass funnel over the petriplate, the rate of solvent evaporation can be adjusted. The dry films are removed in the next day and kept in desiccators.

5. Ethylene vinyl acetate copolymer (EVAC) membrane method :

1% carbopol reservoir gel, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) membranes can be employed as rate control membranes to prepare the target transdermal treatment system. Propylene glycol is used to make gel when the medication is not soluble in water. The drugs are dissolved in propylene glycol then add carbopol resin to the aforementioned solution and neutralize it. A sheet of backing material covering the designated area is placed on top of the medicine (in gel form). To create a leak-proof device, a rate-regulating membrane is positioned over the gel, and the borders are heated to seal them.

6. **Isopropyl myristate (IPM) membrane method:**

This approach involves mixing the medicine with water and propylene glycol to dissolve it, then stirring the mixture for 12 hours in a magnetic stirrer. Triethanolamine is to be added in order to neutralize the dispersion and make it viscous. If the drug's solubility in aqueous solution is particularly poor, buffer pH 7.4 can be employed to create solution gel. The IPM membrane will incorporate the gel produced.

EVALUATION OF TRANSDERMAL PATCHES[29-34]:

A. Evaluation of parameters:

1. Thickness:

A travelling microscope, dial gauge, screw gauge, or micrometre is used to measure the transdermal patch's thickness at three different points on the patch. The patch's thickness is then calculated as the average of the three measurements; a patch that is uniformly thick will have the same thickness throughout. The thickness fluctuation, both within and between patches, can be calculated.

2. Weight uniformity:

Before the patches are weighed, they are dried at 60 °C. The weight homogeneity of a transdermal patch is evaluated, and the weight variance is measured by cutting and weighing a 1 cm^2 piece of three patches. The weight of the patch is determined by taking the mean of the three values. An individual's weight must not deviate too far from the average weight.

3. Folding endurance:

A strip of patch or film is gradually folded in the same position until it breaks or folds up to 300 times. This is how folding endurance is measured. The number of folds a patch can withstand without breaking is its folding endurance. The transdermal patch's flexibility can be determined in part by its folding endurance.

4. Tensile strength:

The tensile strength is calculated using the average weight of three patches. On a glass plate, a small film strip (4 x 1 cm) is cut using a sharp blade. When the film is put in the film holder, one end is attached between adhesive tapes to provide stability. To keep the strip straight while stretching, another end of the film is fastened between the adhesive tapes with a tiny pin sandwiched between them. Near the pin, a tiny hole is created in the adhesive tape, and a hook is inserted. A small pan is attached to one end of the thread that is linked to the hook, passed over the pulley, and used to retain the weights. The thread that passes over the graph paper fixed to the base plate has a little pointer connected to it. A pulley system is used to pull the film in order to test its tensile strength. To progressively raise the pulling power until the film is shattered; weights were gradually added to the pan. By measuring the pointer's movement on the graph paper prior to the film breaking, the elongation is calculated. The break force is defined as the amount of weight needed to split the film. The following formula is used to get the tensile strength:

Tensile strength = Tensile load at break/a.b. $(1+ \Delta L/L)$

Where a, b, and L are width, thickness, and length of strip respectively, and ΔL is the elongation at break.

Break force = weight requires to break the film (kg)

Elongation at break = IB–IO/IO x 100

Where,

IO = original length of film.

IB = length of film breaks when stress applied.

5. Percentage moisture content:

The films must be weighed separately and maintained at room temperature in desiccators with fused calcium chloride for 24 hours. The films must be reweighed after 24 hours in order to calculate the percentage moisture content using the formula below.

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

6. Percentage moisture uptake:

To maintain 84% RH, the weighed films must be stored in the desiccators for 24 hours at room temperature with a saturated potassium chloride solution. The films must be reweighed after 24 hours to calculate the percentage moisture uptake using the procedure below.

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

7. Percentage moisture loss:

Weighed $4cm^2$(area) patch stored in desiccators with calcium chloride at the room temperature for 24 hours. After three days, the weight of the patch is determined. The percentage moisture loss is calculated by the following formula

% Moisture loss = [Initial weight – Final weight / Final weight] x 100.

8. Drug content:

In an appropriate solvent, a predetermined patch area must dissolve in a predetermined volume. After that, the fluid must pass through a filter media to analyse the medication. Using the appropriate technique (UV or HPLC technique). Each number is the average of three various samples.

2. *In vitro* evaluation studies:

- ***In vitro* release studies:**

To describe the drug dissolution profile of a controlled release dosage form and, therefore, there in vivo performance, it is vital to understand the drug release mechanisms and kinetics of the dosage form. The best fit is produced to characterise the drug release process after the dissolution data is fitted to these models. The drug release rate of TDDS can be determined using a variety of approaches.

- ***In vitro* skin permeation study :**

The amount of medication released from the polymeric transdermal films has a significant impact on how much is available for absorption into the systemic pool. The medication enters the skin surface and then travels through the epidermis and between the epidermis cells via skin appendages to the dermal microcirculation. The constructed transdermal patch with rat skin or a synthetic membrane is often placed between the donor and receptor compartments in a vertical diffusion cell, such as the Franz or Keshary-Chien diffusion cell, to conduct permeation investigations. The lipophilic side of the membrane is in contact with the receptor fluid when the transdermal system is placed in the diffusion cell and applied to the hydrophilic side of the membrane. The receiver compartment is continually swirled at a fixed pace and kept at a set temperature (often 32°C for skin). At regular intervals, samples are taken out, and the same amount of buffer is replaced. After properly diluting the samples, the absorbance is calculated spectrophotometrically. The drug permeation rate per centimetre square is then computed for each time interval. The release of the medicine can be impacted by a number of factors, including system design, patch size, skin surface area, thickness, temperature, and others. So, the steps in a permeation study include preparing the skin, mounting it on a permeation cell, adjusting experimental parameters including temperature, stirring, and sink conditions, extracting samples at various time intervals, analysing the samples, and calculating the flux, or the amount of medicine that permeates per cm^2 per second.

a. *In vivo* evaluation studies:

The most accurate representation of a drug's performance is found *in vivo* tests. *In vivo* investigations can completely examine the variables that cannot be considered during *in vitro* experiments. The following methods can be used to evaluate TDDS *in vivo:* animal models.

- **Animal models:**

Since doing human studies requires a lot of time and money, small-scale animal studies are favoured. The most typical Animals including the mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig, and others are used to test transdermal medication delivery systems. Numerous studies have shown that hairless animals perform better in both *in vitro* and *in vivo* experiments than hairy animals. One of the most trustworthy animal models for testing transdermal medication administration in humans *in vivo* is the rhesus monkey.

Marketed products in transdermal drug delivery system[28]:

An effective alternative to traditional medication delivery methods including injection and oral administration is a TDDS. But only a few medications can be properly carried across the skin at the actual pace, hence the commercial application of a TDDS is constrained. However, a number of transdermal devices improve medication delivery across healthy skin. The first transdermal medication, Transderm Scop®, was released in 1979 and was used for 3 days to alleviate motion sickness at sea. Additionally, it was contrasted with oral delivery, demonstrating a better outcome in terms of minimising the negative effects. A transdermal patch containing clonidine called Catapress-TTS® was approved in 1984 as an alternative to the transdermal scopolamine medication. In 1986 and 1990, respectively, further transdermal products like Estraderm®, Harbitrol®, and Duragesic® were created and put on the market. From 1991 through 2004, hormones such as oestradiol, testosterone, ethynyl estradiol, norelgestromin, and levonorgestrel were developed for transdermal devices. This suggests that transdermal products were initially intended primarily for the transportation of hydrophobic medicines, which are made of sterols. (Table: 1).

During 2005 and 2013, a number of pharmacological classes—including selegiline (Emser®), methylphenidate (Daytrana®), fentanyl (Ionsys®), diclofenac epolamine (Flector®), a mixture of menthol and methylsalycylate (Salonpas®), and sumatriptan (Zecuity®)—were included in a transdermal product. Two transdermal products, Secuado® (asenapine for schizophrenia) and Twirled® (ethinyl estradiol and levonorgestrel), have just received FDA approval in 2019 and 2020, respectively.

Table 1: Marketed products of TDDS

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

Conclusion:

Successful transdermal application needs to address various drawbacks. Among which they stratum corneum is the main barrier to drug transport. There is a need to alter the barrier property of the skin temporarily by employing various types of permeation enhancers so that we can develop more effective TDDS for new drugs. TDDS is more popular method in recent

years due to rapid development drug technologies. The properties of the drug states of the patient skin are also play a key role for success safe and effective drug delivery.

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