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Review Article

Transdermal Patch: A Novel Approach for Transdermal Drug Delivery

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Abstract

A self-contained, covert, medicated adhesive patch known as a transdermal patch offers a practical mode of delivery for a range of skin and body problems. Multiple drug administration has several disadvantages including inconvenient administration, the risk of overdose, lack of patient compliance, and drug plasma level fluctuations. Transdermal medication delivery has emerged as a creative means of achieving systemic drug absorption at a predefined rate over an extended period. Its primary benefits are reduced dose frequency, avoiding first-pass metabolism by entering directly into the systemic circulation, suitability for elderly patients who cannot take pharmaceuticals orally, and ability to be self-administered with fewer adverse effects. This review covers general aspects like drug absorption pathways through the skin, the kinetics of drug absorption, different factors affecting the transdermal permeability, various types of transdermal patches, their components, and evaluation parameters. Additionally, some marketed transdermal patches and therapeutic applications of transdermal drug delivery systems have been discussed. Moreover, the article includes various generations of advancements in the transdermal drug delivery system and its future aspect.

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

INTRODUCTION-

Conventional oral dosage forms require many doses to be given at certain intervals and in specific amounts for therapy to be effective. Multiple drug administration has several drawbacks, such as uncomfortable administration, the risk of overdose if delivered before the time interval, poor patient compliance, patients skipping doses, and changes in drug plasma levels.[1-2] Systems for transdermal drug delivery are created to prevent such issues. A transdermal patch is a discrete, self-contained medication patch that offers an easy method of delivery for several skin and body issues.[3]

Researchers will be able to develop ways for enhancing medicine delivery through the skin by better understanding the mechanisms by which substances traverse the skin. The average adult's skin has a surface area of around 2 m^2, and it gets one-third of the body's total blood circulation. There are 200–250 sweat glands and 10–70 hair follicles per square centimetre of skin.[4] A few of the many variables that affect the rate of drug distribution through the skin include the thermodynamic activity of the drug in the formulation, the interaction of the drug and the formulation with the skin, and variations in the skin with age, race, anatomical location, and disease.[5] To maintain the target drug level for an extended length of time, the drug delivered from the transdermal drug delivery system may follow zero (or pseudo-zero-order) or first-order kinetics, or both.[6]

ADVANTAGES- Some advantages of transdermal patch[7-10]

- Patches are simple to apply, painless, and non-invasive.
- The medication can be administered over a long length of time.
- Because a single patch distributes the medication continuously for a longer period, dosage frequency is reduced.
- The drug in the transdermal drug delivery system bypasses first-pass metabolism by entering directly into the systemic circulation, making it suitable for pharmaceuticals that are processed by the liver, gut, or stomach pH.
- There is no drug-food, enzyme-drink, or other Gastrointestinal tract flora interaction.
- Appropriate for elderly individuals who are unable to swallow pills.
- Effective for medications that lessen negative effects and are unpleasant when taken orally.
- Drug delivery can be stopped in the case of toxicity by removing the patch.
- Patches can be self-administered.

DISADVANTAGES- Some disadvantages of transdermal patch[7-10]

- Difficulty in administering large doses (more than 10 mg/day).

- It is difficult to deliver ionic drugs through a transdermal drug delivery system.
- Drugs with a molecular weight greater than 500 Dalton are not suitable for the transdermal drug delivery system.
- High concentrations of drugs may cause skin irritation.
- High plasma drug concentrations are challenging to produce.
- Patients experience discomfort as a result of long-term adherence.
- It is challenging for medications with exceptionally low or high partition coefficients to enter the systemic circulation.[7-10]

ANATOMY AND PHYSIOLOGY OF SKIN-

The Human skin is composed of three main types of tissues.[11]

1. **The Epidermis**- According to cell size and the number of cell layers, the multilayered epidermis' thickness varies, ranging from 0.8 mm on the palms and soles to 0.06 mm on the eyelids. The stratum corneum sometimes referred to as the horny layer, is the skin's outermost layer. It is around 10 mm thick when dry, but when completely hydrated, it swells to a thickness that is several times more. It consists of 10 to 25 layers of corneocytes, which are dead, keratinized cells. It is adaptable and largely impermeable. The stratum corneum layer is the main inhibitor of drug entry. A wall-like structure can be used to represent the horny layer's structure. The lipid fraction contains enough amphiphilic material, including cholesterol and polar free fatty acids, to keep the bilayer structure. The stratum corneum is covered by the viable epidermis, which has a thickness that varies from 0.06 mm on the eyelids to 0.8 mm on the palms. There are many levels as you move inward, including the stratum basal, stratum lucidum, stratum granulosum, and stratum spinosum. The epidermis is continuously renewed by basal layer cells going through mitosis, and this multiplication makes up for the loss of dead horny cells from the skin's surface. The basal layer's cells undergo morphological and histochemical changes as they travel outward, triggering keratinization to produce the stratum corneum's top layer (Figure 1).

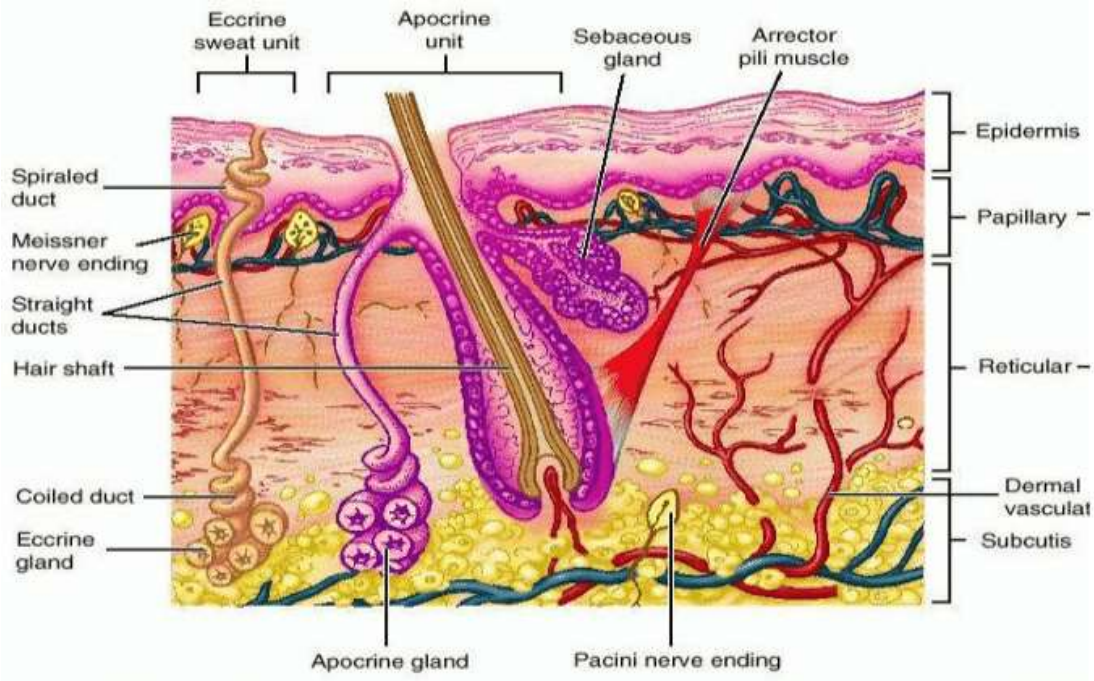


Figure 1: Structure of the skin[11]

2. **The Dermis**- The dermis is a layer of connective tissue that is 3 to 5 mm thick and is made up of nerves, lymphatic vessels, and blood vessels. An essential component of controlling body temperature is the cutaneous blood supply. While eliminating waste and pollutants, it also nourishes and oxygenates the skin. The skin's surface is within 0.2 mm of capillaries, which offers sink conditions for the majority of molecules that cross the skin barrier. Because of the blood supply, a permeate dermal concentration is kept extremely low, and the ensuing concentration gradient across the epidermis is crucial for transdermal permeation.
3. **The Hypodermis**- The dermis and epidermis are supported by it. It serves as a place to store fat. This layer aids in maintaining body temperature, providing dietary support, and providing mechanical protection. Major blood vessels and sensory organs for pressure may be present.

While topical medication delivery only involves penetration through the stratum corneum and then requires drug retention in the skin layers, transdermal drug delivery often entails the penetration of the drug through all three layers and into the systemic circulation.

DRUG ABSORPTION PATHWAYS THROUGH THE SKIN-

The medicine can be absorbed via the skin in a variety of ways depending on its physicochemical makeup. Different methods of absorption are used for drugs that are hydrophilic and lipophilic. Drug entrance and transport to the systemic circulation are facilitated by the availability of several absorption pathways, which circumvent the upper stratum corneum of the epidermis and restrict drug absorption (Figure 2).[1]

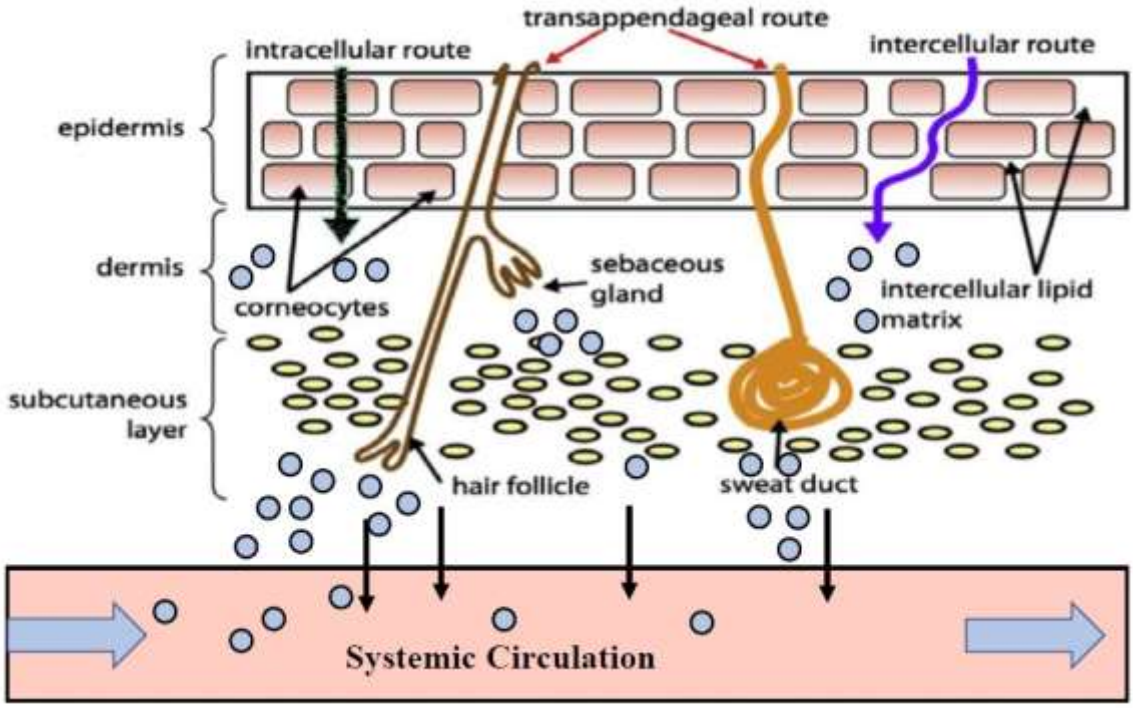


Figure 2: Drug absorption pathways through the skin [12]

The following are the three main drug absorption pathways-

1. **Trans-follicular pathway**- The trans follicular channel offers a broad area for drug diffusion and is the quickest mechanism for a medication to enter the systemic circulation. The skin has a large number of pores, sweat glands, oil glands, hair follicles, and ducts that allow them to open to the skin's surface. Drug transport through these ducts is continuous across the stratum corneum, although it is impacted by several variables, including gland secretion, the kind and volume of secretion, and others. However, the trans appendageal pathway contributes less because it only takes up 0.1% of the skin's surface.
2. **Trans-cellular pathway**- Through this system, drugs are administered from corneocytes, which have a hydrophilic pathway and contain highly hydrated keratin. Lipids that surround and connect corneocytes. A drug, therefore, needs several partitioning and diffusion processes. It is the route that many different kinds of medications most frequently take. The transcellular method allows the medicine to pass through the cytoplasm (matrix) of the cells. Hydrophilic medicines are suited for this approach. The highly hydrated keratin provides an aqueous route for hydrophilic drugs.
3. **Inter-cellular pathway**- The continuous lipid matrix that is present between the cells serves as the conduit through which medicines diffuse in this channel. The barrier nature of this pathway is due to the tortuous structure created by corneocytes, and the medication must diffuse to the inner side and partition into the lipid bilayer to pass through the alternating lipid and aqueous domain. It is preferred mostly for uncharged lipophilic medicines because it has been shown that water flows 50 times more quickly by this route.

DRUG ABSORPTION KINETICS- Passive diffusion of drugs through the skin is the main mechanism by which drugs are absorbed through the skin. It means that the drug is absorbed according to the concentration gradient because there is a higher concentration of drug on the skin than inside the skin, so drug molecules diffuse from the reservoir to systemic circulation through the skin. Fick's law of diffusion governs the rate of drug absorption via passive diffusion.[1]

The permeation rate is given by:

$$dQ/dt = P_s [C_d - C_r] \quad (1)$$

Where-
C_d represents the concentration of the drug in the donor phase, i.e., on the skin's surface
C_r represents the concentration of the drug in the receptor phase, i.e., inside the skin in the systemic circulation.
Pr is the overall permeability constant and can be calculated using the following equation:

$$P_r = (K_s D_{ss} / h_s) \quad (2)$$

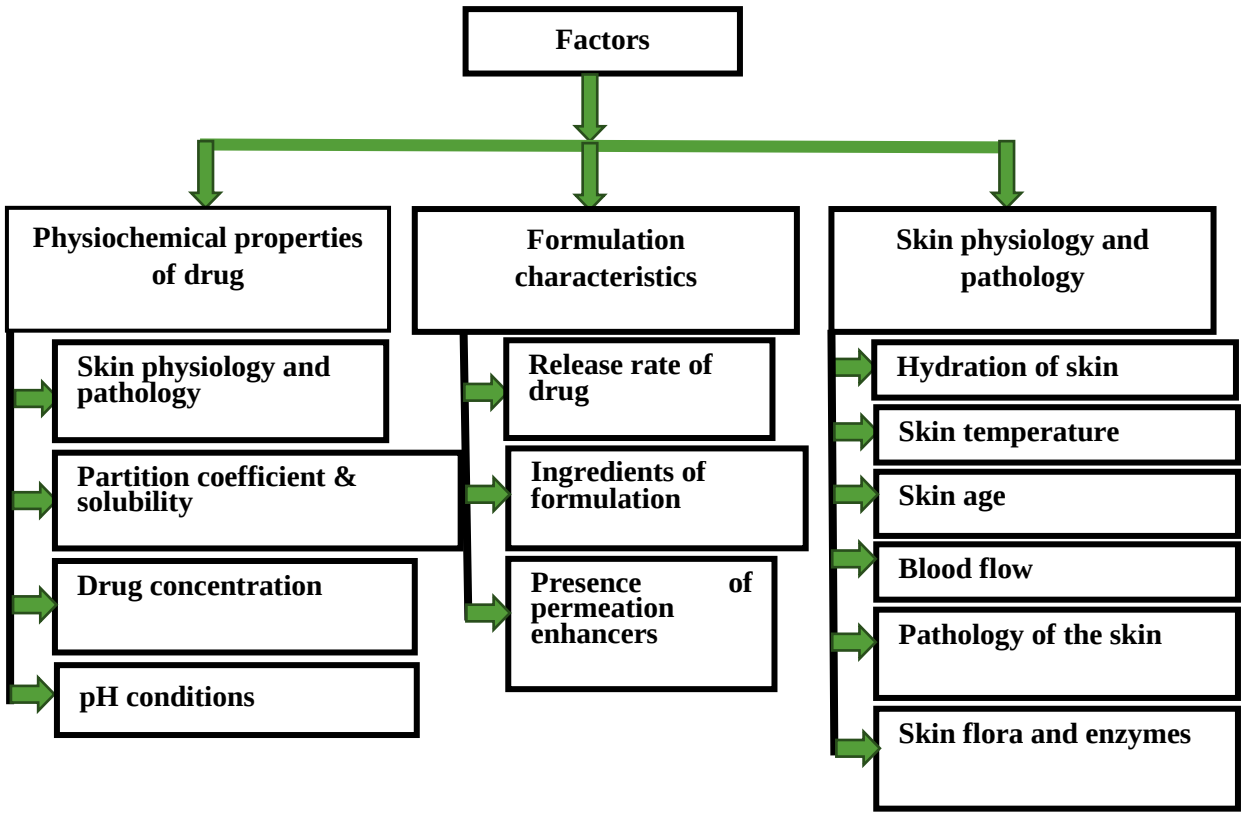
Where-
K_s is the drug's partition coefficient
D_{ss} is the apparent diffusivity of the drug,
h_s is the skin thickness.
Because K_s, D_{ss}, and h_s (from equation 2) are constant under certain conditions, the permeability constant Ps can be considered constant. If $C_d > C_r$, a constant rate of diffusion is achieved.
As a result, the diffusion rate dQ/dt in equation 1 can be reduced to:

$$dQ/dt = P_s . C_d \quad (3)$$

C_d value should be constant throughout the permeation process across the skin to keep the permeation rate (dQ/dt) constant. To keep C_d constant, the drug release rate (R_r) should always be greater than the absorption rate (R_a), i.e., (R_r) > (R_a).
As a result, the concentration of drug on the skin surface is always greater than the drug's saturation solubility in the skin (C^e_s), i.e., $C_d > C^e_s$, and a maximum skin permeation rate (dQ/dt) m is obtained:

$$(dQ/dt)_m = P_s . C^e_s \quad (4)$$

FACTORS AFFECTING TRANSDERMAL PERMEABILITY [13-17]-



TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM PATCHES-

1. **Reservoir system**- A rate-regulating microporous or nonporous membrane and an impermeable backing laminate surround the medicine in reservoir systems. To create a paste, the medication is uniformly disseminated in a solid polymer matrix and suspended in a viscous liquid medium. The abrasion rate, permeability, diffusion, and thickness of the membrane all affect how quickly the drug is released. The release rate of the reservoir system is a zero-order process. An impermeable metallic backing holds the entire system together. [18-19]
2. **Matrix diffusion system**- In a matrix diffusion system, the drug is uniformly disseminated in a hydrophilic or lipophilic polymeric substance. The rate of drug release is determined by the rate of polymer erosion, layer thickness, and film surface area. The matrix system doesn't contain any additional rate-regulating membranes. Monolithic systems are another name for matrix diffusion systems. The adhesive layer is applied to the polymer disc's perimeter rather than the patch's surface.[20-21] By injecting the medicine directly into the adhesive layer, the Matrix drug delivery mechanism can be altered. Both a single-layer drug and a multi-layer drug in an adhesive system can be manufactured for use with this.
3. **The drug in the adhesive system**- In this approach, the medication is disseminated in the adhesive layer of the patch. The adhesive layer controls the pace of drug distribution to the skin in addition to adhering the patch's components to the skin. The sticky layer is encircled by the liner. In a single-layer patch, there is just one drug present in the adhesive layer; however, in a multilayer patch, there are two layers: one for immediate drug release and the other for regulated drug release.[22]
4. **Micro reservoir system**- It consists of a matrix and reservoir system. In the micro reservoir system, the medication is first suspended in an aqueous solution of a hydrophilic polymer (such as Polyethylene glycol), and then the aforementioned suspension is combined with a lipophilic polymer (such as silicon) by a high shear mechanical stirrer. The micro reservoir system is stabilized by the in-situ cross-linking of polymer chains, resulting in the formation of a medicated polymer disc with a specific area and thickness. [23, 24]

COMPONENTS OF TDDS-

1. **Drug**- The drug solution should be in direct contact with the release liner.

Physiochemical properties-

- The drug's molecular weight must be under 1000 Daltons.
- The medication needs to be able to bind to both lipophilic and hydrophilic phases.
- A low melting point is required for the medication.

Biological properties-

- The medication must be effective at a dose of only a few mg per day.
- The drug must have a short half-life (t½).
- There must be no allergic response produced by the drug.
- Drug tolerance must not form due to the transdermal patches' nearly zero-order release profile.

2. **Polymer**- Polymer is the main component of transdermal delivery systems (Shown in Table 1).

Polymer used in transdermal patches should have the following characteristics-

- The polymer should have specific molecular weight, and chemical functionality so that the diffusion of the drug occurs properly and can be released through it easily.
- The polymer must meet the following criteria: stability, nontoxicity, and affordability.
- The polymer's degradation byproduct must not be harmful to the host.
- The medicine and excipients should be compatible with the polymer.

Table 1: Types of polymer and examples

S. No.	Types of Polymers	Examples	References
1.	Natural Polymer	Gelatin, Shellac, Protein, Chitosan, Natural rubber, Starch, Waxes	25-29
2.	Synthetic Polymer	Polyvinyl chloride, Polyvinyl alcohol, Polyurea, Polyethylene, Polypropylene, Polyacrylate	
3.	Synthetic Elastomer	Silicon Rubber, Acetonitrile, Neoprene, Hydrin rubber, Polyisobutylene	
4.	Biopolymers	Collagen, Xanthan, Gellan, Elastin, Polylactic acid	

3. **Backing Layer**- It supports and protects the transdermal patches from the external environment. To prevent drug loss, the backing membrane must be elastic, flexible, and impermeable to drug diffusion. It must be compatible with the polymer, excipients, and drug. It is made of aluminium foil, polyethene, polyester, polyvinyl chloride, heat-sealed layers, polyurethane, and contains an adhesive foam pad. [30-31]

4. **Rate Controlling Membrane**- The rate at which a drug is delivered from a dosage form is determined by rate-controlling membranes. A rate-controlling membrane is made from a variety of natural and synthetic polymers. For example- chitosan and poly2-hydroxyethyl methacrylate .[32-33]

5. **Adhesive**- The main role of the adhesive in transdermal patches is to maintain contact with the skin for a prolonged period. Patch type, patch design, and adhesive characteristics are selection factors for patches. It must be non-irritating, suitable for skin and excipients, and simple to remove. Some examples of adhesives are silicon-based adhesive polymers, polyacrylate, and, polyisobutadiene.[34]

6. **Release liner**- The release liner, which is a part of primary packaging, guards against both drug loss from the polymer matrix and external environment contamination of the patch during storage and shipping. At the time of use, it is peeled off. For example-

- Occlusive- polyethene or Polyvinyl chloride
- Non-occlusive (paper fabric)- polyester foil and metallic foil.[35]

7. **Plasticizers**- Plasticizers increase the flexibility and brittleness of the polymer. When these are added, they alter the physical and mechanical properties of the polymer. For example- Glycerol derivatives, phthalic acid esters, sebacic acid esters, oleic acid esters, and alcohols-

- Increase polymer elongation at break, toughness, and flexibility.
- Reduces tensile stress, hardness, electrostatic charge ability, and glass transition temperature.[36]

8. **Other excipients**- Permeation enhancers are used to dissolve the drug and polymers. Examples- methanol, chloroform, triethyl citrate, polyethene glycol, and propylene glycol (Shown in Table 2).[37]

Table 2: Types of permeation enhancers

S. No.	Class of permeation enhancers	Examples	Reference
1.	Fatty acids	Oleic acid, Short fatty acids	38
2.	Surfactants	Na-lauryl sulfate, Polyoxyethylene-9-lauryl ether	
3.	Positively charged polymer	Chitosan salts, Trimethyl chitosan	
4.	Chelating agents	EDTA, Polyacrylates	
5.	Cyclodextrins	α-, β- and γ cyclodextrins, Methylated β cyclodextrins	

SOME MARKETED TRANSDERMAL PATCHES- Shown in Table 3.

Table 3: Marketed transdermal products [39]

Brand Name	Drug	Manufacturer	Indications
Alora	Estradiol	Thera Tech/Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoS mithKline	Hypogonadism in males
Catapres TTSR	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/B erlex Labs	Postmenstrual syndrome
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic R	Fentanyl	Alza/Janssen Pharmaceutical	Moderate/severe pain
Estraderm	Estradiol	Alza/Novartis	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Matrifen R	Fentanyl	Nycomed	Pain relief patch
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm R	Nicotine	Alza/GlaxoSmithK line	Smoking cessation
NicotinellR	Nicotine	Novartis	Pharmacological smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Neupro R	Rigotine	UCB and Schwarz Pharma	early-stage idiopathic Parkinson's disease
NuPatch 100	Diclofenac diethylami ne	Zydus Cadila	Anti-Inflammatory
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
OrthoEvraTM	Norelgostromin/ Ethinyl Estradiol	ORTHO-McNEIL	Postmenstrual syndrome
Oxytrol R	oxybutynin	Watson Pharma	Overactive bladder
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTSR	Testosterone	Alza	Hypogonadism in males
Transderm-Nitro R	Nitroglycerin	Alza/Novartis	Angina pectoris
Transderm-Scop R	Scopolamine	Alza/Novartis	Motion sickness

EVALUATION OF TRANSDERMAL PATCHES-

A. Physicochemical Evaluation-

- **Thickness**- The transdermal patch's thickness is measured using a travelling microscope, dial gauge, screw gauge, or micrometre at three different points on the patch; the patch's thickness is then calculated as the average of the three measurements; a uniformly thick patch will have the same thickness throughout. Calculations can be made for the thickness variation both inside and between patches.[40,41]
- **Weight uniformity**- The patches are dried at 60°C before being weighed. By chopping and weighing a 1 cm^2 piece of three patches, the weight homogeneity of a transdermal patch is assessed, and the weight variance is then estimated. By taking the mean of the three values, the patch's weight is calculated. The weight of an individual must not significantly depart from the average weight. [42,43]
- **Folding endurance**- Folding endurance is determined by gradually folding a strip of patch/film in the same position until it breaks or folds up to 300 times. The folding endurance of a patch is determined by the number of times it can be folded without breaking. The folding endurance helps to determine the flexibility of the transdermal patch.[44]
- **Drug content:** A suitable solvent, such as methanol or phosphate buffer pH 7.4, is used to dissolve a film of the right area and weight, which is then filtered. After the proper dilutions, the drug content is measured using a standard curve by the UV or HPLC method.[45,46]
- **Percentage moisture content**- Individually weighed patches are stored in desiccators with fused calcium chloride at room temperature for 24 hours to determine the percentage moisture content.[47,48] The patches are reweighed after 24 hours, and the percentage moisture content is determined using the formula below:

Percentage moisture content = (Initial weight - Final weight/ Final weight) x 100

- **Percentage moisture uptake**- Films that have been weighed are subjected to 84 per cent relative humidity using potassium chloride after spending 24 hours in a desiccator. The films are reweighed once their weight has stabilized.[47-49]

Percentage moisture uptake = (Final weight - Initial weight/Initial weight) x 100

- **Shear adhesion test**- The cohesive strength of the sticky polymer is evaluated using this test. The patch with the adhesive is placed on a flat surface, and the necessary weight is then suspended from the patch in a straight line. The patch's shear adhesion is determined by how long it takes to remove it from the surface.
- **Peel adhesion test**- This test is used to calculate the force needed to remove a patch from a surface. A steel plate's surface is used to position the patch, which is then dragged 180 degrees away from it. It is measured how much force is needed to remove the patch.
- **Rolling ball tack test**- In this test, a steel ball with a 7/16-inch diameter is rolled down and inclined while having a patch put horizontally on the adhesive surface facing

upward. The length the ball travels determines how tacky the sticky patch. [50,51]

- **Stability study**- A stability study is performed to determine how long the patch will be viable and usable. Since the drug gradually degrades in unstable patch formulations, stability is tested for 6 months at 40 ^{0}C/75 % Relative Humidity according to an international conference of Harmonization (ICH) guidelines. Samples are collected and tested for stability at 0, 30, 60, 90, and 180 days.[52]

B. In-vitro Evaluation-

- **In vitro release study**- Utilizing a United States of Pharmacopeia (USP) dissolve equipment at 50 rpm and 37°C, in vitro release is assessed. An adhesive is used to attach the transdermal film to a glass slide, which is then submerged in a dissolution medium that contains 900 ml of phosphate buffer with a pH of 7.4. For 24 hours, a 5 ml sample is taken out and an equivalent volume of buffer is added to the dissolution medium. The cumulative drug release is calculated after spectrophotometric analysis of the sample.[53]
- **In vitro skin permeation study**- A vertical diffusion cell with two chambers that are divided by the skin of a male Wistar rat is used to conduct in vitro skin permeation research. On the skin of the rat, the transdermal film is applied and linked to the diffusion cell positioned between the donor and receptor compartments. Samples are taken regularly, and a new medium of the same volume is substituted. Flux is calculated by spectrophotometric analysis of the samples.[54]
- **Skin irritation study**- In an in vitro skin permeation investigation, albino rats, mice, or rabbits are used for skin irritation testing. There are six animals in each of the five categories of animals. Group I is the control group, Group II is treated with commercially available adhesive tape (USP official adhesive tape), Group III is treated with a transdermal patch without medication, Group IV is treated with a transdermal patch with medication, and Group V is treated with a standard irritant, % v/ v formalin solution. Animal skin hairs are removed, and depending on their group, the animals receive treatment for 7 days. Animals are rated daily depending on the appearance of discomfort and their ability to scratch and develop scars.

C. In-vivo Evaluation-

- **Animal model**- Since human studies require a significant amount of time and resources, therefore, small-scale animal studies are preferred. The mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, and guinea pig are the animal species that are most frequently used to test transdermal drug delivery systems. Numerous studies have demonstrated that in both in vitro and in vivo trials, hairless animals are preferred over hairy animals. One of the best models for analyzing transdermal medication distribution in humans is the Rhesus monkey.[55]
- **Human model**- The application of the patch to human volunteers resulted in a collection of pharmacokinetic and pharmacodynamic data at the end of the transdermal device development process. Clinical trials have been conducted to assess the effectiveness, hazards, side effects, patient compliance, and other factors. Phase I clinical trials are used to assess safety largely in volunteers, whereas phase II clinical trials are intended to assess safety and efficacy in patients over the short term. While phase IV trials during post-marketing surveillance are conducted to detect adverse drug reactions, phase III trials demonstrate the safety and efficacy of marketed patches in a vast number of patient populations.[56-60]

THERAPEUTIC APPLICATIONS

Table 4: Therapeutic applications of TDDS

Drug Name	Application in TDDS	Ref
Diclofenac sodium and celecoxib	Formulated in TDDS may overcome the gastric lesions associated with oral dosing.	61
Captopril, verapamil, terbutaline sulfate, and propranolol	Formulated as TDDS to achieve prolonged steady-state plasma concentration.	
Prazosin Hydrochloride	Formulated in membrane-controlled TDDS, deliver the drug in sufficient quantities to maintain the MEC while avoiding the hypotension associated with high initial oral dosing.	
Indomethacin	Provide better anti-inflammatory activity and lower ulcer indices with polyvinylpyrrolidone polymer.	
Diclofenac sodium	Formulated as ion pairs with oppositely charged enhancers to improve transdermal delivery over non-ion paired forms.	
Nimesulide in sodium alginate transdermal gel	Provide better analgesia and anti-inflammatory activity while avoiding the side effects associated with long-term oral dosing.	
Terbutaline sulfate	Incorporated into the magnetic TDDS to provide a driving force to escape the applied magnetic field and improve diffusion across the skin.	
Zidovudine	Formulated in TDDS, may overcome the toxic effects of frequent higher oral doses.	

1. **Advancement in transdermal drug delivery system**- Human civilization has employed chemicals for cosmetic and medical purposes for thousands of years. However, the twentieth century saw the recognition of the skin as a drug delivery pathway. There are some limitations of skin when it comes to drug delivery and cannot be used for all drug candidates. As science and technology continue to progress, the transdermal drug delivery system is increasingly desired and practical for the majority of medications. Based on transdermal drug delivery system developments, transdermal delivery is classified into three generations.[62]

- **First-generation**- It contains classic patches with a more straightforward design. These include matrix adhesive methods and straightforward reservoir patches. These consist of a straightforward backing layer, a membrane that regulates the flow rate, a laminate, and an adhesive system.

- **Second-generation**- Simple patches are combined with permeability enhancers in second-generation patches. The rate and quantity of tiny lipophilic drug molecules transported through the skin are increased by these permeation enhancers. The skin is irritated, damaged, or disrupted by the permeation enhancer, which lessens the skin's barrier function.

- **Third-generation**- Large hydrophilic medicinal molecules are intended to penetrate third-generation patches. Only the most advanced techniques, such as iontophoresis, sonophoresis, electrophoresis, magneto phoresies, microneedle technology, etc., can administer hormones via a skin patch. These permeation promoters can push drug molecules through the skin or physically harm it.

2. **The future aspect of the transdermal drug delivery system**- In the future, regulated doses, reduced frequency of dosing, and increased patient compliance will make transdermal drug administration the preferable method. To quit smoking, nicotine patches for transdermal application were created twenty years ago. After that, various medications were developed as transdermal patches, including nitroglycerin for angina, estradiol for estrogen insufficiency, and fentanyl for pain. Researchers have been inspired to create medications in novel and palatable dose forms as a result of patent periods expiring. Transdermal delivery methods are becoming more and more common as technology and design advance. The top pharmaceutical corporations are working on Transdermal drug delivery systems, and numerous transdermal delivery methods have been patented and are currently being developed for effective use. Innovative delivery methods like liposomes, Niosome, nanoparticles, microspheres, and microemulsions are utilized to manufacture Transdermal drug delivery systems to enhance absorption and increase the solubility of insoluble medications. Other permeation enhancement methods are also being developed, such as the application of mechanical energy to change the physiology of the skin or to speed up drug molecules to increase drug flux over the skin. Electrophoresis, iontophoresis, sonophoresis, and magnetophoretic are some more methods that have been researched for enhancing drug distribution over the skin for high molecular weight medications as well as insoluble drugs. The skin is now the safest and most acceptable method of medication administration for systemic circulation when compared to the oral route.

CONCLUSION-

Transdermal drug delivery is the most secure and effective method of drug delivery. Many drugs, including hormonal therapy, a wide range of analgesics, and drugs for heart disease, have been developed in Transdermal drug delivery systems form to avoid Gastrointestinal tract effects and first-pass metabolism. Transdermal drug delivery systems are gaining popularity and attracting the attention of researchers, there will be the formulation of many new drugs in a transdermal form. While designing a transdermal drug delivery system, it should be kept in mind that the formulation may not alter the physiology of the skin. A better understanding of the physiology and anatomy of skin would help us to improve the future advancement of transdermal patches. However, a thorough understanding of the interactions of various polymers and skin components is required to design and optimize transdermal delivery.

CONFLICT OF INTEREST-

The author declared that there is no conflict of interests regarding the publication of this paper.

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