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TRANSDERMAL DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT:

A transdermal patch is a medicated adhesive patch applied to the skin to allow a specified drug dose to be absorbed into the bloodstream through the skin. This frequently encourages the healing of a body part that has been hurt. A transdermal patch offers a controlled release of the medication into the patient, typically through either a porous membrane covering a reservoir of drugs or through body heat melting thin layers of medicine embedded in the adhesive. This is an advantage of transdermal drug delivery over other types of medication delivery, such as oral, topical, intravenous, intramuscular, etc. Transdermal medication delivery allows for a constant blood level profile and regulated drug release into the patient, reducing systemic side effects. This review article briefly outlines skin pathways' advantages for transdermal drug delivery systems (TDDS). Various components of a transdermal patch and approaches for the preparation of transdermal patches. Evaluation of transdermal system, general clinical considerations in using TDDS and limitation of TDDS.[1]

KEYWORDS: Transdermal, Permeation pathways. Drug delivery, Matrix system, Reservoir system.

INTRODUCTION:[1,2]

The FDA first approved a transdermal motion sickness patch in 1979 called F of Scopolamine, and nitro-glycerine was the second patch authorised in 1981. There are many patches available today for transdermal usage. Clonidine, Testosterone, Fentanyl, Nicotine, and Hormone patches, among others, are applied for one to seven days, depending on the problem. The most popular method of medication delivery is oral, although there are some significant drawbacks, including poor bioavailability. The first pass effect and the potential for drug levels in the blood to fluctuate.

Anti-analgesic drug topical delivery has become more popular recently because it can deliver concentrated and highly localised pain relief directly to a specific area of the body, as opposed to oral drug delivery, which frequently results in side effects as it travels through the gastrointestinal tract. The outermost layer of human skin, despite having advantages such as tailored and concentrated medication delivery, greatly restricts the use of hydrophobic medicines (stratum corneum).

Transdermal delivery offers regulated, continual medication administration and permits drugs with short biological half-lives to be continuously administered, eliminating the need for pulsed systemic circulation, frequently resulting in unwanted side effects. Thus, several novel drug delivery methods exist, including transdermal drug administration, controlled release, and trans mucosal delivery methods.

Transdermal drug administration has many benefits, including limiting hepatic first-pass metabolism, improving therapeutic effectiveness, and maintaining a constant plasma level. In 1979, the FDA approved Transderm-SCOP, the first transdermal device, to treat motion sickness and nausea brought on by travel. Measurable drug levels in the blood may provide proof of percutaneous drug absorption. Detectable drug and metabolite excretion in the urine and clinical patient response to administered drug therapy.[2]

DEFINITION:[3] A transdermal patch is a medicated adhesive patch placed above the skin to deliver a specific dose of medication through the skin with a predetermined release rate to reach into the bloodstream. Today the most common transdermal system present in the market is mainly based on semipermeable membranes, which are called patches.[3]

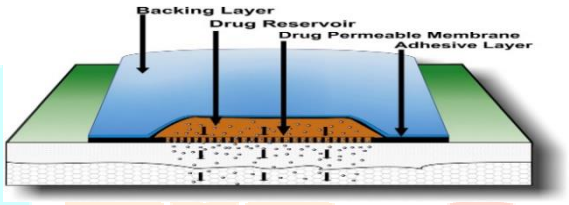

Figure 1: Transdermal patch showing its different components

ADVANTAGES:

1. The drug bypasses the hepatic and pre-systemic metabolism, thereby increasing bioavailability.
2. Consistent serum drug level allowed by steady drug permeation across the skin, which is frequently a goal of therapy.
3. It achieves constant plasma levels, just like intravenous infusion, but it's non-invasive. In addition, if a medicine is provided transdermally and toxicity occurs, the effects may be mitigated by removing the patch.
4. Patients who are queasy or unconscious benefit greatly from it.
5. Because transdermal delivery avoids direct effects on the stomach and intestine, medications that cause gastrointestinal disturbances may be suitable candidates.
6. Topical patches are a non-invasive, painless way to get drugs into the body.
7. Topical patches that distribute medication in a controlled, regular manner over an extended period.
8. Topical patches have fewer adverse effects than supplements or oral medications.
9. Topical patches are an alternative for those who cannot or do not want to take medications or supplements orally.
10. The price of topical patches is reasonable.[4]

Disadvantages:

1. Some medications only partially permeate the skin, which may reduce the effectiveness of the therapy.
2. The ingredients in the TDDS formulation can cause cutaneous erythema, local edema, and irritation.
3. The release rate may be poorly controlled due to damage to a transdermal patch.
4. On the same person, the skin's barrier function varies from one spot to another, person to person, and with age.
5. Higher doses of medicines are not appropriate for use with it.
6. For a chemical with a higher molecular weight, it is inappropriate.
7. Drugs that undergo protein binding in the skin and are metabolised by the skin are inappropriate for TDDS.[5]

Limitations:

1. Drug doses greater than 50 mg/day make transdermal distribution highly challenging; therefore, daily doses of drugs preferred to be less than 20 mg/day must have some physicochemical features to penetrate through the skin.
2. Drugs or other excipients used in the formulations may induce local irritation at the administration site, including itching, erythema, and local edema.
3. Due to system components, some patients get contact dermatitis at the application site.
4. TDDS is unable to deliver ionic drugs.
5. It is restricted to potent drugs.
6. Drug molecules having large molecular sizes (>1000 Dalton) cannot develop for the TDDS.[5]

ANATOMY AND PHYSIOLOGY OF SKIN:

The body's largest organ, the skin, has a surface area of around $2m^2$ on an average adult human. This multi-layered organ receives approximately one-third of all blood circulates through the body. The skin's millimetre-thin thickness isolates the underlying blood circulation system from the external environment. Skin pathways for transdermal drug delivery system: [6]

Human skin comprises three distinct but mutually dependent tissues:

1. The stratified, vascular, cellular called as “epidermis.”
2. The underlying dermis of connective tissues.
3. Hypodermis.

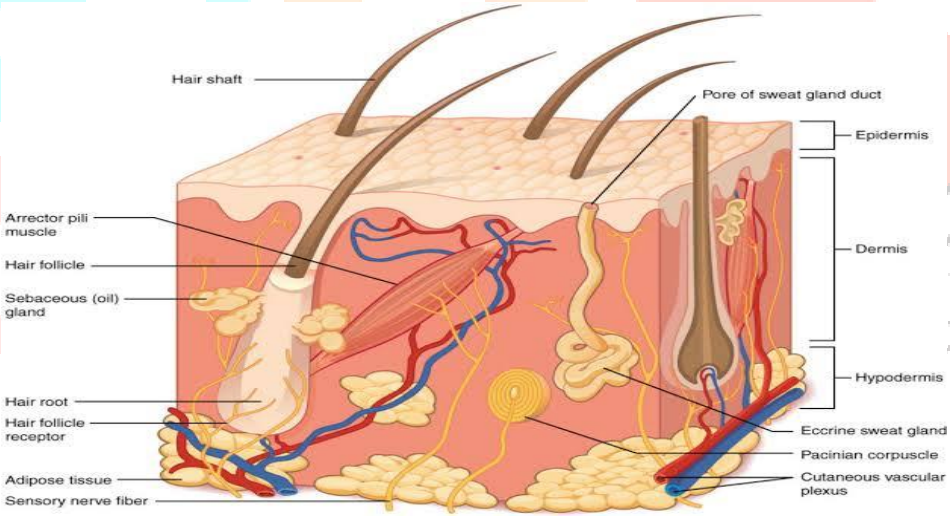

Figure 2: Structure of Human Skin (T.S.)

The epidermis Is about 150 micrometres thick and produced by a basal cell population of active epithelial cells. It is the skin's topmost layer, and differentiation causes cells in the basal layer to move up to the skin's surface. The eventual outcome of this process is the production of the stratum corneum, a thin, stratified, and incredibly durable layer near the skin's surface.

Dermis: This is the skin's outermost layer, commonly known as the horny layer. When fully hydrated, it grows to several times this thickness and is around 10 mm thick when dry. It has 10 to 25 layers of coenocytes, which are dead, keratinised cells that lie parallel to the skin's surface. Although flexible, it is mainly impermeable. The main impediment to penetration is the stratum corneum. The Horney layer's constituents—75–80% proteins, 5–15% lipids, and 5–10% ondansetron material—significantly impact the barrier character. Alpha-keratin makes up the majority of protein fractions (70%), with some beta-keratin (10%) and cell envelope (5%). The bodily site affects the lipid composition (neutral lipids, sphingolipids, polar lipids, cholesterol).

Hypodermis: The dermis and epidermis are supported by the hypodermis or subcutaneous fat tissue. It functions as a place to store fat. This layer offers nutritional support, mechanical protection, and assistance with temperature regulation. Principal blood arteries, nerves, and possibly pressure-sensing

organs are carried there to the skin. In contrast to topical medication administration, where only stratum corneum penetration is necessary, and drug retention in the skin layers is preferred, transdermal drug delivery requires drug penetration through all three layers to enter the systemic circulation.

DRUG PENETRATION PATHWAYS:

A drug molecule can penetrate the intact stratum corneum in three fundamental ways: through the skin's appendages (shunt pathways), the intercellular spaces between the stratum lucilipid domains and the other layers of the epidermis. A specific drug will likely enter the body by a combination of these pathways, with the proportional contributions of each path to the overall flux determined by the physicochemical characteristics of the drug's molecule.[7]

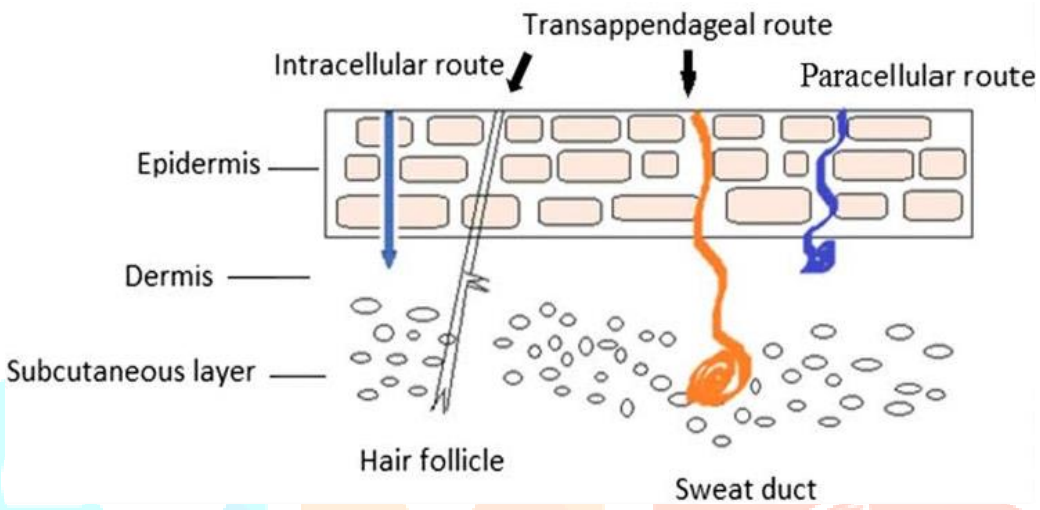

Figure 3: Routes of Drug Permeation

1. The appendageal route:
   Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by several factors. The surface area occupied by hair follicles and sweat ducts is small (typically 0.1% of skin surface area), limiting the space for direct contact with the applied drug formulation.
2. Transcellular route:
   Drugs that penetrate the skin transcellular pass via corneocytes. Because corneocytes have highly hydrated keratin, they can pass hydrophilic medicines in an aqueous environment.
3. Intercellular route:
   The medication diffuses across the continuous lipid matrix in the intercellular course. This path is a significant challenge for two reasons. The interdigitating nature of the corneocytes produces a complex conduit for intercellular drug absorption, in contrast to the comparatively direct path of the transcellular route, which brings to mind the "bricks and mortar concept of the stratum corneum. In the intercellular domain, bilayers with different structures alternate.

FACTORS INFLUENCING TRANSDERMAL DRUG:

Effective transdermal drug delivery can be formulated by considering three factors as Drugs. Skin, and the vehicles. So the factors affecting this can be divided into biological and physicochemical factors.[8]

- **Biological factors:**

1) Skin conditions -Acids, alkalis, and several solvents, including chloroform and methanol, harm skin cells and encourage penetration. The patient's illness affects their skin's condition. Although the skin is a better barrier when it is intact, the factors mentioned above affect penetration

2) Skin age- Younger skin is more porous than older skin, and children are more susceptible to toxin absorption through the skin. Therefore, skin age is one of the factors affecting the drug's penetration in TDDS.

3) Blood supply- As blood supply changes in peripheral circulation can affect transdermal absorption

4) Regional skin site- Differences include appendage density, stratum corneum type, and skin thickness. These elements have a significant impact on penetration.

5) Skin metabolism-The skin processes steroids, hormones, chemical carcinogens, and medicines. Therefore, the efficacy of a medication that has penetrated the skin is determined by skin metabolism.

6) Species differences- The penetration is affected by the skin's thickness, density, and keratinisation, which differ from species to species.

- **Physiological Factors:**

1) Skin hydration- The skin's permeability rises dramatically when it comes into touch with water. The most crucial aspect in promoting skin permeability is hydration, and the use of humectants in transdermal administration is thus made.

2) Temperature and pH - Drug permeability multiplies ten times with temperature change, and the diffusion factor falls as the temperature drops. Depending on the pH, weak bases and acids separate. The percentage of unionised drugs influences the number of medications on the skin. So, temperature and pH play a significant role in medication permeation.

- **Diffusion coefficient** - Drug diffusion coefficient affects drug penetration. Keeping the temperature steady, the relationship between a drug's diffusion coefficient, the diffusion medium, and their interactions.
- **Drug concentration**- The flux is proportional to the concentration gradient across the barrier, and the concentration gradient will be higher if the attention of the drug is more across the border.
- **Partition coefficient**– The ideal K. partition coefficient is necessary for effective action. High K drugs are not yet ready to leave the skin's lipid layer. Additionally, drugs with low K levels won't permeate.
- **Molecule size and shape**- Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, molecular size's effect is unknown.

TYPES OF TRANSDERMAL PATCHES:

1. Single-layer drug adhesive
2. Multilayer drug in adhesive
3. Vapour patch
4. Reservoir system
5. Matrix type
    a) Drug-in-adhesive system
    b) Matrix-dispersion system
6. Micro reservoir-controlled TDDS

1. **The single-layer drug in adhesive**- In this form, the medicine is included in the sticky layer. The treatment is released to the skin by the adhesive layer, which also clings the several layers together. There is a backer and a temporary liner around the adhesive layer.
2. **Multilayer drug in adhesive**- This type is comparable to the single layer. Still, it includes an immediate drug-release layer in addition to the adhesive layer, which makes it different from other layers that will have a controlled release.
3. **Vapour patch**- The adhesive layer's function in this patch goes beyond simply holding the various layers together. It also serves as a market, frequently used to release essential oils during decongestion. Many other kinds of vapour patches on the market enhance sleep quality and lessen the effects of smoking.
4. **Reservoir system**- The drug reservoir is embedded between a waterproof backing layer and a rate-controlling membrane. The drug releases only through the rate-controlling membrane, which can be microporous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. The hypoallergenic adhesive polymer can be applied as an outer surface polymeric membrane compatible with Drugs.

5. **Matrix system -** A matrix patch is an adhesive patch on which medication has been dispensed.
   a) Drug-in-adhesive system- In this type, the drug reservoir is created by first dispersing the medication in an adhesive polymer and then applying the medicated adhesive polymer to a waterproof backing layer by solvent casting or melting. On the top of the reservoir, unmediated adhesive polymer layers are used for protection. (Drug reservoir in adhesive)
   b) Matrix-dispersion system- A hydrophilic or lipophilic polymer matrix has a uniform medication distribution in this type. This drug-containing polymer disc is housed in a compartment made from a drug-impermeable backing layer and bonded to an occlusive base plate. The adhesive is distributed around the outside of the drug reservoir rather than on its face, creating a strip of the adhesive rim.
6. **Micro reservoir controlled TDDS-**
   This drug delivery method combines matrix-dispersion and reservoir systems. To create the drug reservoir, the drug is first suspended in an aqueous solution of a water-soluble polymer before being uniformly dispensed in a lipophilic polymer to create millions of microscopic, inaccessible drug reservoir spheres.[9]

COMPONENTS OF TDDS:

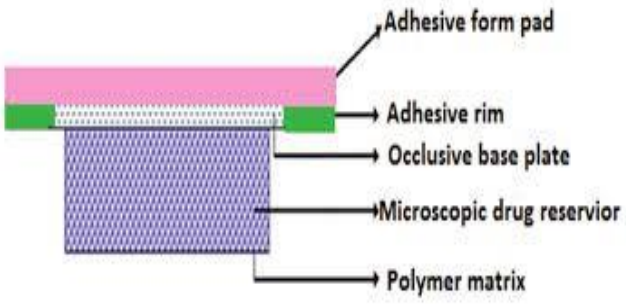

Figure 4: Microreservoir-controlled TDDS

1) Polymer matrix
2) Drug substance
3) Permeation enhancers
4) Pressure sensitive adhesives(PSAs)
5) Backing membrane
6) Release liner

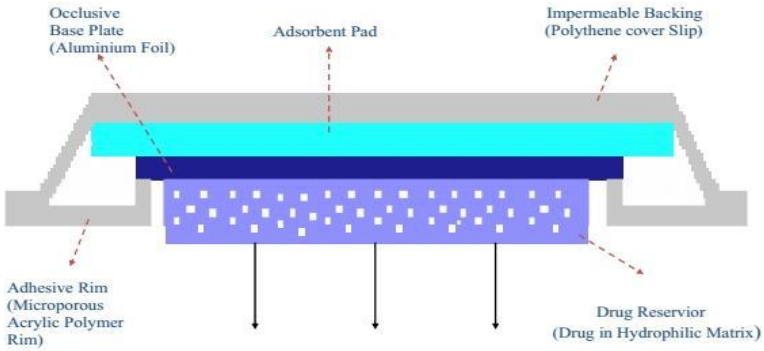

Figure 5: Components of TDDS

1. **Polymer matrix-** A polymer is an essential and crucial part of the transdermal drug delivery system. Systems for transdermal delivery are made of multi-layered polymeric laminates, which have two polymeric layers sandwiching a drug reservoir or drug-polymer Matrix between them. The outer impermeable backing layer prevents drug loss through the backing surface, and the inner polymeric layer serves as an adhesive or rate-controlled membrane.

✓ Ideal properties of a polymer to be used in a transdermal system –

- The polymer's molecular weight, glass transition temperature, and chemical functionality should all be chosen so that the drug can diffuse and be released through it effectively.
- The polymer should be stable.
- The polymer should be non-toxic.
- The polymer should be easy of manufactured.
- The polymer should be inexpensive.
- The polymer and its degradation product must be non-toxic or non-antagonistic to the host.
- Large amounts of the active agent are incorporated into it.

Table 1: Types of polymer

Natural Polymers	Synthetic Polymers	Synthetic Elastomers
Cellulose Derivatives	Poly Vinyl Alcohol	Hydration Rubber
Gelatin	Poly Vinyl Chloride	Silicone Rubber
Waxes	Polyethylene	Polybutadiene
Proteins	Polypropylene	Nitrile
Gum	Polyamide	Acrylonitrile
Natural Rubber	Acetal Copolymer	Neoprene
Starch	Polystyrene	Chloroprene
Chitosan	Epoxy	Polysiloxane

2. **Drug substance:** The drug should be chosen with great care for developing a transdermal drug delivery system.

a. Physiochemical properties -

- The drug's molecular weight should be under 1000 Daltons.
- The medication should be able to bind to both the lipophilic and hydrophilic phases.
- Extreme partitioning properties do not support effective drug delivery via The skin.
- The medication needs to have a low melting point (200°).
- The drug should be potent, have a short half-life and be non-irritating.

b. Biological properties-

- The drug should have a high potency with a daily dosage of just a few mg.
- The medication needs to have a brief biological half-life (10 h or less)
- The medicine shouldn't irritate or cause skin allergies in people.
- When in touch with the skin, the medication needs to remain stable
- They shouldn't cause the skin to mount an immunological response.
- Near zero order release profile of the medicine must prevent the development of tolerance to it.
- The recommended dose is less than 10 mg daily and less than 50 mg daily.
- The subcutaneous tissue shouldn't become permanently bound with the medication, and the skin shouldn't undergo a significant amount of medication metabolism.

3. **Penetration enhancers**-These are the compounds that promote the penetration of topically applied drugs and are commonly referred to as absorption promoters, accelerants, or penetration enhancers.
   - ✓ Ideal properties –
     - Reversible and controlled boosting action
     - Compatibility with medication and other pharmaceutical excipients in chemistry and physics. The enhancer shouldn't bring on loss of bodily fluids, electrolytes, or other endogenous substances.
     - It needs to be non-toxic, non-irritating, and non-allergic.
     - It should be inert pharmacologically.
     - Odourless, colourless, affordable, and acceptable from a cosmetic standpoint.
   - ✓ Classification of penetration enhancers–
     i. Terpenes (Essential oils): e.g. Nerolidol, menthol, 1 8 cineol, limonene, carvone etc.
     ii. Pyrrolidone: e.g. N-methyl-2-pyrrolidone (NMP), ozone etc. Fatty acids and esters: e.g. oleic acid, linoleic acid, lauric acid, capric acid etc.
     iii. Sulfoxides and similar compounds: e.g. Dimethyl sulfoxide (DMSO), N, N dimethyl Form amide Alcohols, Glycols, and Glycerides: e.g. Ethanol, Propylene glycol, Octyl Alcohol etc.
     iv. Various enhancers: e.g. Phospholipids, Cyclodextrins, Amino acid derivatives. Enzymes etc.
4. **Pressure-sensitive adhesive:**

   Pressure Sensitive Adhesive (PSA) is a material that helps maintain intimate contact between the transdermal system and the skin surface.

   Properties –
   - It should not be irritant
   - It should be easily removed
   - It should not leave an unwashable residue on the skin.
   - It should have excellent contact with the skin.

5. **Backing membrane:**
   a. They are adaptable, offer a solid attachment to the medication reservoir, and keep the medication from escaping the dosage form through the top.
   b. It shields the item with a waterproof membrane while being applied to the skin.
   c. Must be compatible with formulation (non-adsorptive), E.g., Metallic plastic laminate, plastic backing with adsorbent pad, adhesive foam pad.
6. **Release liners-**
   a. During storage, the patch is covered by a protective liner that is removed and discharged immediately before applying the patch to the skin.
   b. Part of primary packaging.
   c. The base layer -Non-occlusive (e.g. Paper fabric) or occlusive (e.g. Polyethylene, polyvinylchloride).
   d. Release coating layer silicon or Teflon.[10]

IDEAL CHARACTERISTICS OF TDDS.[11]

PARAMETERS	PROPERTIES
Dose	Should Be Low (Low Than 20mg/Day)
Half-Life	10 Or Less (H)
Molecular Weight	< 400 Da
Partition Coefficient	Log P (Octanol –Water) Between 1.0 And 4.0
Skin Permeability Coefficient	$>0.5\times10^{-3}$ Cm/H
Lipophilicity	10< K o/w <1000
Oral Bioavailability	Low
Therapeutic Index	Low
Melting Point	< 200°C
pH	Between 5.0 And -9.0

METHOD OF PREPARATION OF TDDS:

1. **Asymmetric TPX membrane method:**

A prototype patch can be fabricated for this. A heat-sealable polyester film (type 1009, 3m) with a concave 1cm diameter will be used as the backing membrane. The drug sample is dispensed into the hollow membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

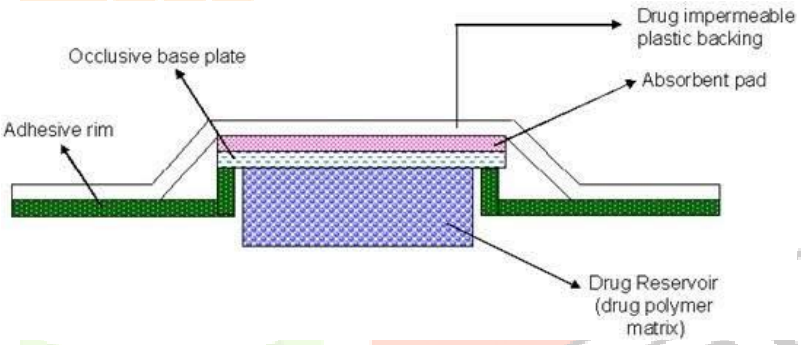

Figure 6: Asymmetric TPX membrane method

[(Asymmetric TPX membrane preparation)]:

These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and non-solvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs. And cast on a glass plate to a predetermined thickness with a gardener knife. After that, the casting film is evaporated at 50°C for 30 seconds, and then the glass plate is immersed immediately in a coagulation bath [maintained at 25°C]. After 10 minutes of immersion, the membrane can be removed and air dry in a circulation oven at 50°C for 12 hrs.].

2. **Circular Teflon mould method:**

Solutions containing polymers in various ratios are used in an organic solvent. The calculated amount of the drug is dissolved in half the quantity of the same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and added. Di-N-butyl phthalate is added as a plasticiser into the drug-polymer solution. The total contents are stirred for 12 hrs. And then poured into a circular Teflon mould. The moulds are to be placed on a levelled surface and covered with an inverted funnel to control solvent vaporisation in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs, at 2540.5°C, in a desiccator containing silica gel before evaluation to eliminate aging effects. The type of films is to be evaluated within one week of their preparation.

3. **Mercury substrate method:**

   In this method, the drug is dissolved in a polymer solution along with a plasticiser. The above explanation is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured into a levelled mercury surface, covered with an inverted funnel to control solvent evaporation.

4. **By using "IPM membranes" method:**

   In this method, the drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs. in a magnetic stirrer. The dispersion is to be neutralised and made viscous by adding triethanolamine. Buffer pH 7.4 can be used to obtain solution gel if the drug solubility in an aqueous solution is very poor. The formed gel will be incorporated into the IPM membrane.

   Using the "EVAC membranes" method: To prepare the target transdermal therapeutic system, 1% Carbopol reservoir gel. Polyethylene (P.E.) and ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used to prepare the gel. The drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralised using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of a backing layer covering the specified area. A rate-controlling membrane will be placed over the gel, and the edges will be sealed by heat to obtain a leak-proof device.

5. **Preparation of TDDS by using Proliposomes:**

   The proliposomes are prepared by carrier method using the film deposition technique. From the earlier reference drug and lecithin in the ratio of 1:2 can be used as an optimised one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask, which is kept at a 60-70°c temperature, and the flask is rotated at 80-90 rpm and dried the mannitol is at a vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture. An Aliquot of 0.5ml of the organic solution is introduced into the round bottom flask at 37°C; after complete drying second aliquot (0.5ml) of the key is to be added. After the last loading, the flask containing proliposomes is connected to a lyophilised. Subsequently, drug-loaded mannitol powders (proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at a freezing temperature until characterisation.

6. **By using the free film method:**

   A free film of cellulose acetate is prepared by casting it on a mercury surface. A polymer solution of 2% w/w is to be ready by using chloroform. Plasticisers are to be incorporated at 40% w/w of the polymer weight. 5 ml of the polymer solution was poured into a glass ring placed over the mercury surface in a glass petri dish. The solvent's evaporation rate is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated and stored between the sheets of wax paper in a desiccator until use. Free movies of different thicknesses can be prepared by changing the volume of the polymer solution.[12]

EVALUATION PARAMETER: The evaluation methods for transdermal dosage form can be classified into the following type[13]

1. Physicochemical evaluation
   a. Interaction studies
   b. The thickness of the patch
   c. Weight uniformity
   d. Folding endurance
   e. Percentage moisture content
   f. Percentage moisture uptake
   g. Water vapour permeability (VWP)evaluation
   h. Drug content
   i. Content uniformity test
   j. Polariscope examination
   k. Shear adhesion test
2. In vitro evaluation
3. In vivo evaluation
4. Stability studies

1**) Physicochemical evaluation:**

a) Interaction studies-

Excipients are essential to practically all pharmaceutical dose forms. The compatibility of the medicine with the excipients is one of the elements that affect a formulation's stability. To create a stable product, the drug and excipients must be compatible. As a result, it is essential to identify any potential physical or chemical interactions because they may affect the bioavailability and stability of the drug. The compatibility studies are crucial for formulating new excipients that have never been used in formulations containing the active ingredient. By contrasting their physicochemical properties, interaction investigations are frequently conducted using thermal analysis, FT-IR, U.V., and chromatographic techniques.

b) Thickness of the patch-

The thickness of the patch is measured at different points using a digital micrometre. It determines the average thickness and standard deviation for the same to ensure the consistency of the prepared patch.

c) Weight uniformity test-

Before testing, the prepared patches must dry for four hours at 60 degrees Celsius. A predetermined patch area must be divided into various patches and weighed in the balance. The average weight and standard deviation values should be computed using individual weights.

e) Percentage moisture content -The produced films must be weighed separately and stored for 24 hours at room temperature in desiccators with fused calcium chloride. The movie must be reweighed after 24 hours to calculate the percentage moisture content using the formula below. Moisture content as a percentage is equal to

[Initial weight- final weight/final weight]*100.

f) Percentage moisture uptake –

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

[Final weight- Initial weight/Initial weight]*100 = % moisture uptake.

g) Water vapour permeability (WVP) Evaluation –

A natural air circulation oven is used in place of an air-forced range to measure water vapour permeability. The following formula can be used to calculate the

WVP=W/A

Where **WVP** is expressed in gm/m per 24 hrs.

W is the amount of vapour permeated through the patch expressed in gm /24hr, and A is the surface area of the exposure sample expressed in m^2.

h) Drug content- A predetermined patch area must dissolve in a predetermined volume in an appropriate solvent. After that, the solution must be filtered through a filter medium, and the drug content must be determined using the proper methodology (U.V. or HPLC technique). Each number is the average of three distinct samples.

i) Content uniformity test- 10 patches are chosen, and each patch's material is determined separately. Transdermal patches pass the test for content uniformity if 9 out of 10 patches have content ranging from 85% to 115% of the given value and one patch from 75% to 125% of the specified value. But if three patches test positive for drug content between 75% and 125%, 20 more patches are examined. The transdermal patches pass the test if the range of these 20 patches is between 85% and 115%.

j) Polariscope examination- This test will examine the drug crystals from the patch by polariscope. To determine if the drug is present in the patch in crystalline form or amorphous form, a specific section of the piece must be kept on the object slide and examined for drug crystals.

2) In vitro evaluation:

a) **In vitro drug release studies-**

You can evaluate the drug release from the produced patches using the paddle-over disc method (USP equipment V). A glass plate must be covered with dry films of defined thickness, cut into a specific form, weighed, and fastened with an adhesive. The device was then brought to an equilibrium temperature of 32 + 0.5°C before submerging the glass plate in 500 mL of the dissolution liquid or phosphate buffer (pH 7.4). The paddle was turned on at 50 rpm while placed 2.5 cm away from the glass plate. At suitable intervals of up to 24 hours, samples (5 ml aliquots) can be taken out and examined using a U.V. spectrophotometer or HPLC.

b) **In vitro skin permeation studies-**

A diffusion cell can be used to conduct in vitro permeation research. Male Wister rats weighing 200–250g have full-thickness abdomen skin. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels. Before beginning the experiment, the subject was equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 and placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. A heater with a thermostatic control was used to keep the cell's temperature at 32°C plus or minus 0. 5°C.The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. At regular intervals, a sample volume of a specific volume is to be taken out of the receptor compartment, and an equal volume of fresh medium is to be replaced. Samples must pass through a filtering medium before being examined spectrophotometrically or using HPLC. The permeability coefficients were calculated by dividing the flux by the initial drug load mg cm, and flux can be calculated directly as the slope of the curve between the steady-state values of the amount of drug penetrated mg cm2 vs. time in hours.

c) Horizontal Type skin permeation studies-

This has been extensively used to assess medication penetration via skin. The cell is separated into donor and receptor compartments, each with a tiny membrane area and a modest solution volume (3.5ml) (0.64cm2). A matched set of star-head magnets rotating at a 600rpm speed continuously stirs them. Through a water jacket enclosing the two chambers, thermostated water controls the system.

d) Franz diffusion cell-

Donor and receptor compartments make up the cell. The receptor compartment has an effective surface area of 1–5 cm2 and a 5–12 ml capacity. A magnetic bar continuously stirs the diffusion buffer at 600 rpm. The water jacket around the receptor compartment is filled with thermo-stated water, which regulates the temperature in most of the solution.

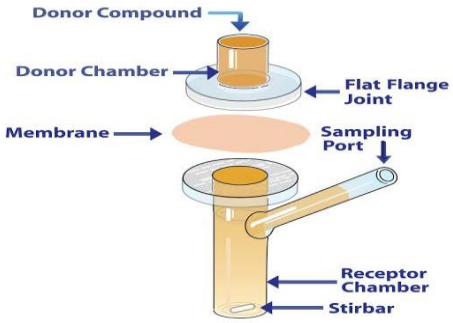

Figure 7: Franz diffusion cell

e) Flow through Diffusion cell -

The benefit of using flow via diffusion cells is that they can be employed when the drug's solubility in the receptor compartment is reduced. This cell is immediately connectable to HPLC and is fully automatable. They have a large donor chamber to allow for proper compound loading and a small (0.3ml) receiver chamber to guarantee quick penetrant removal at relatively slow pumping rates.

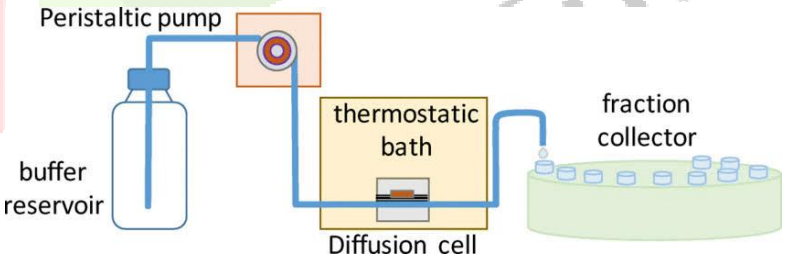

Figure 8: Flow through diffusion cell

3) In Vivo evaluation studies:

In vivo evaluations are the accurate depiction of the drug's performance. The variables that cannot be considered during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using the following:

Animal models

Human volunteers

Biophysical models

- **Animal models-**
  Small-scale animal research is preferable since human studies require a lot of time and resources. The most often utilised animal species for testing transdermal drug delivery systems include the mouse, hairless rat, hairless dog, rhesus monkey, rabbit, and guinea pig. Numerous studies have shown that hairless animals perform better in both vitro and vivo experiments than hairy animals. The rhesus monkey is one of the most trustworthy animal models for assessing human transdermal medication distribution in vivo.

- **Human model-**
  After applying the patch to human volunteers, the transdermal device's final stage of development entails gathering pharmacokinetic and pharmacodynamics data. Clinical studies have been carried out to evaluate a treatment's effectiveness, risks, side effects, patient compliance, etc. Phase I clinical trials are carried out to determine the safety of volunteers, and phase II clinical trials are carried out primarily to determine patients' short-term safety and effectiveness. Phase III studies demonstrate safety and efficacy in a vast patient population, while phase IV studies are conducted for marketed patches during post-marketing surveillance to identify adverse medication reactions. Although they cost a lot of resources, human studies are the best for evaluating the effectiveness of a medicine.

- **Biphasic model-**
  After applying the patch to human volunteers, the transdermal device's final stage of development entails gathering pharmacokinetic and pharmacodynamics data. Clinical studies have been carried out to evaluate a treatment's effectiveness, risks, side effects, patient compliance, etc. Phase I clinical trials are carried out to determine the safety of volunteers, and phase II clinical trials are carried out primarily to determine patients' short-term safety and effectiveness. Phase III studies demonstrate safety and efficacy in a vast patient population, while phase IV studies are conducted for marketed patches during post-marketing surveillance to identify adverse medication reactions.

FDA-APPROVED TRANSDERMAL MARKETED PRODUCTS:

Drug	Indications	Approval Year
Scopolamine	Motion Sickness	1979
Estradiol	Menopausal Symptoms	1986
Fentanyl	Chronic Pain	1990
Nicotine	Smoking Cessation	1991
Lidocaine	Post-Hepatic Neuralgia	1999
Rivastigmine	Dementia	2007
Sumatriptan	Migraine	2013
Diclofenac epolamine	Acute Pain	2007

FUTURE TECHNOLOGIES AND APPROACHES:

- Thermal Poration is the formation of aqueous pathways across the stratum corneum by applying pulsed heat; this approach has been used to deliver conventional drugs and extract intestinal glucose from human subjects.
- Jet injectors are receiving increased attention nowadays, opening doors for improved device design for controlled, needle-free injection of drug solutions across the skin and into deeper tissue.

- A small needle is inserted a few millimetres into the skin, and drug solution is flowed through the hand into the skin at controlled rates using a micro infusion pump contained within a large patch affixed to the skin; morphine has been delivered to humans utilising this approach.
- During the past decade, several theories have been put forward in addressing the combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound.
- TransPharma is focused on products for which our technology will provide clear benefits over existing therapies. Such benefits include improving safety and compliance through a drug patch or enhancing efficacy with the help of sustained-release patch formulation, among others.

CONCLUSION:

Drug delivery methods that use transdermal patches have been proven to be secure and efficient. The world is using its potential for the controlled release of outstanding achievers in science. Transdermal delivery is an incredibly efficient route of administration when a drug's physical chemistry and pharmacology are adequately balanced. Many fresh studies are being conducted today to incorporate newer medications via the system because of the TDDS' significant benefits. Transdermal medication delivery is becoming the most frequently acknowledged method of drug delivery because of recent technological advancements and the ability to include the drug at the site of action without disrupting the skin barrier. This article is a helpful resource for understanding the formulation and assessment of transdermal medication delivery systems.

The information above demonstrates that TDDS has significant potential since it can create promising deliverable medications from hydrophobic and hydrophilic active substances. More knowledge of the various biological interactions and polymer mechanisms is needed to optimise this drug delivery technology. The next generation of drug delivery systems, TDDS, is a practical application.

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