ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

Transdermal Drug Delivery System: A Comprehensive Review

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Publication Date: 2026/05/06

Abstract: Transdermal drug delivery systems (TDDS) have emerged as an efficient and non-invasive approach for systemic drug administration through the skin. These systems are designed to deliver drugs at a controlled and predetermined rate, thereby maintaining consistent plasma drug concentrations for prolonged periods. Compared to conventional oral and parenteral dosage forms, TDDS offer several advantages such as avoidance of hepatic first-pass metabolism, reduced gastrointestinal side effects, improved bioavailability, decreased dosing frequency, and enhanced patient compliance. Due to these benefits, transdermal drug delivery has gained significant attention in pharmaceutical research and development. Despite their advantages, the development of effective transdermal drug delivery systems is limited by the barrier nature of the skin, particularly the stratum corneum, which restricts the permeation of many drug molecules. Therefore, careful selection of formulation components including drugs, polymers, plasticizers, and penetration enhancers is essential to achieve optimal therapeutic performance. In addition, formulation and process variables must be properly designed and optimized to ensure adequate drug release, skin permeation, mechanical strength, and stability of the transdermal patches .Evaluation of transdermal drug delivery systems plays a crucial role in determining their physicochemical properties, mechanical characteristics, drug content uniformity, in-vitro drug release behavior, skin permeation performance, and stability. These evaluation parameters ensure the quality, safety, and efficacy of the developed systems. Furthermore, optimization techniques such as factorial design, response surface methodology, and other design of experiments approaches are widely employed to systematically study the influence of formulation variables and to identify the most suitable formulation. This review focuses on the evaluation parameters and optimization strategies involved in the development of transdermal drug delivery systems, highlighting recent advancements, challenges, and future perspectives in this field.

Keywords: *Transdermal Patches; Penetration Enhancers; Evaluation Parameters; Formulation Optimization; Controlled Drug Release; In-Vitro Drug Release; Mechanical Properties; Stability Studies.*

How to Cite: Mehak Sharma; Lovepreet Kaur; Dr. Sanjiv Duggal (2026) Transdermal Drug Delivery System: A Comprehensive Review. *International Journal of Innovative Science and Research Technology*, 11(4), 3275-3291. https://doi.org/10.38124/ijisrt/26apr1601

I. INTRODUCTION

Drugs are available in various dosage forms depending on their route of administration and therapeutic purpose. These include solid dosage forms such as tablets, capsules, and powders; liquid dosage forms like syrups, solutions, and suspensions; semi-solid forms such as creams, ointments, and gels; and advanced drug delivery systems like transdermal patches, injections, and implants. Each dosage form is designed to ensure proper drug delivery, stability, and patient compliance. Among these, transdermal drug delivery systems (TDDS) have gained significant attention due to their ability to deliver drugs through the skin in a controlled and sustained manner. The techniques, formulations, technologies, and equipment utilized to deliver a pharmaceutical substance into the body in order to produce the intended therapeutic effect are collectively referred to as drug delivery systems (DDS) [1]. Any drug delivery system's major goal is to maintain the ideal drug concentration inside the therapeutic window while delivering the medication at a predefined rate, for a predetermined amount of time, and at the intended site of action. Due to variations in plasma drug levels, frequent dosing requirements, and systemic adverse effects, conventional dose forms including tablets, capsules, and injections frequently fall short of these goals. Recent developments in pharmaceutical sciences have resulted in the creation of innovative drug delivery systems with the goal of enhancing patient compliance, safety, and medication efficacy [2]. By offering controlled, sustained, or targeted medication release, these systems are intended to get around the drawbacks of traditional drug delivery methods [3].

Transdermal drug delivery systems (TDDS) are self-contained, discrete dosage forms that, when applied to intact skin, allow the drug to enter the systemic circulation at a regulated rate through the skin. These systems are made to

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

keep plasma drug concentrations steady for a long time, which lessens the swings that come with traditional dosage forms. Drug molecules are transported from the skin's surface through the stratum corneum, viable epidermis, and dermis before entering the systemic circulation. This process is known as transdermal drug delivery. The effectiveness of transdermal drug delivery systems is largely dependent on the stratum corneum, the skin's outermost layer, which serves as the main barrier to drug penetration [4]. Compared to oral and parenteral methods, transdermal drug delivery has a number of benefits, including improved bioavailability, decreased gastrointestinal side effects, avoidance of hepatic first-pass metabolism, and increased patient compliance. TDDS are also safer and more patient-friendly because they make it simple to stop medication therapy in the event of side effects by just taking off the patch [4].

➢ *Difference b/w Conventional Drug Delivery System & Transdermal Drug Delivery System:*

Table 1 Difference between Conventional & Transdermal DDS [5,6]

Parameter	Conventional DDS	Transdermal DDS
Route	Oral,injectable,topical	Applied on intact Skin
1st pass metabolism	Present	Avoided
Drug release pattern	Often fluctuating	Controlled and sustained
Dosing frequency	Multiple dose per day	Reduced dose frequency
Side effects	Higher systemic side effects	Reduced systemic effects
Drug plasma level	Peaks and troughs	Uniform plasma level conc.
Termination of therpy	Difficult	Easy
Patient compliance	Poor	Easy

TDDS helps reduce peak-to-trough fluctuations by preserving constant plasma drug levels. Transdermal drug delivery systems are appropriate for long-term and chronic therapies due to their numerous therapeutic advantages [7]. These systems are especially helpful for medications that have limited therapeutic indices, short biological half-lives, or significant first-pass metabolism when taken orally [8]

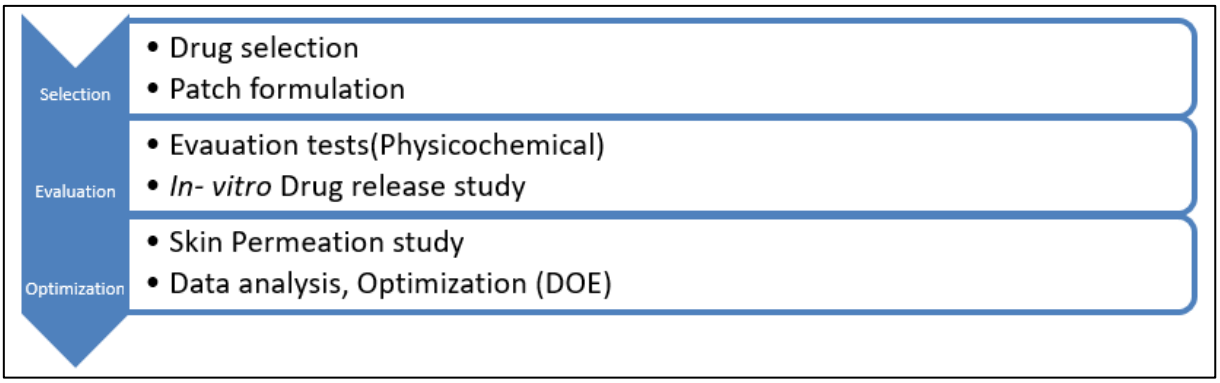

Fig 1 Process of Formulation of Transdermal Drug

An essential first step in determining the effectiveness, safety, and quality of transdermal drug delivery systems is evaluation. To guarantee consistency and dependability of the developed patches, a number of physicochemical, mechanical, and biological parameters are assessed [1]. Evaluation aids in determining whether the formulation satisfies the intended requirements and therapeutic goals [4].

➢ *Ideal Properties of TDDS:*

- The drug should be lipophilic and have a low molecular weight.
- It should be strong and only need a small dosage.
- It must be stable and non-irritating.
- The system should offer sustained and regulated drug release.
- It should be simple to use and stick to the skin well.
- Skin must not be harmed or irritated
- It should facilitate removal and increase patient compliance.

➢ *Advantages of TDDS:*

- Provides controlled and sustained drug release
- Maintains steady drug levels in blood
- Avoids first-pass metabolism
- Non-invasive and easy to use
- Improves patient compliance
- Therapy can be stopped easily by removing patch
- Reduces dosing frequency [9,10]

➢ *Disadvantages of TDDS:*

- Only limited drugs can be used
- May cause skin irritation
- Skin barrier limits drug absorption

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

- Not suitable for high dose drugs
- Environmental and skin factors affect absorption
- Relatively costly [11,12]

Research in this field has accelerated due to the growing need for patient-friendly and controlled drug delivery methods. Transdermal systems have developed over time from basic reservoir-type patches to complex drug-in-adhesive and matrix-based systems. Novel polymers, sophisticated penetration enhancers, and physical enhancement techniques are examples of recent advancements that have increased the variety of medications appropriate for transdermal delivery [1]. Drug penetration can be greatly impacted by changes in skin thickness, blood flow, lipid composition, and hydration level [3, 11]. Variability in transdermal drug absorption is also influenced by factors like age, medical conditions, and the anatomical site of application [13]. Therefore, when designing, assessing, and optimizing transdermal drug delivery systems, a deep comprehension of skin physiology is crucial [14].

II. ANATOMY AND PHYSIOLOGY OF SKIN

➢ *Skin:*

The skin is the largest organ of the human body and serves as a major protective barrier against the external environment. In an average adult, it covers a surface area of nearly 1.7–2 square meters and forms the body's first line of defense.

It protects against microorganisms, harmful chemicals, ultraviolet (UV) radiation, and excessive water loss. Besides protection, the skin also helps in regulating body temperature, enabling sensation, and supporting the production of vitamin D when exposed to sunlight [15-18]

➢ *Structure of Skin:*

Structurally, the skin is divided into three main layers: the epidermis (outer layer), dermis (middle layer), and hypodermis (inner layer) [19]. Each layer has a specific role that contributes to the overall function and health of the skin [20,21].

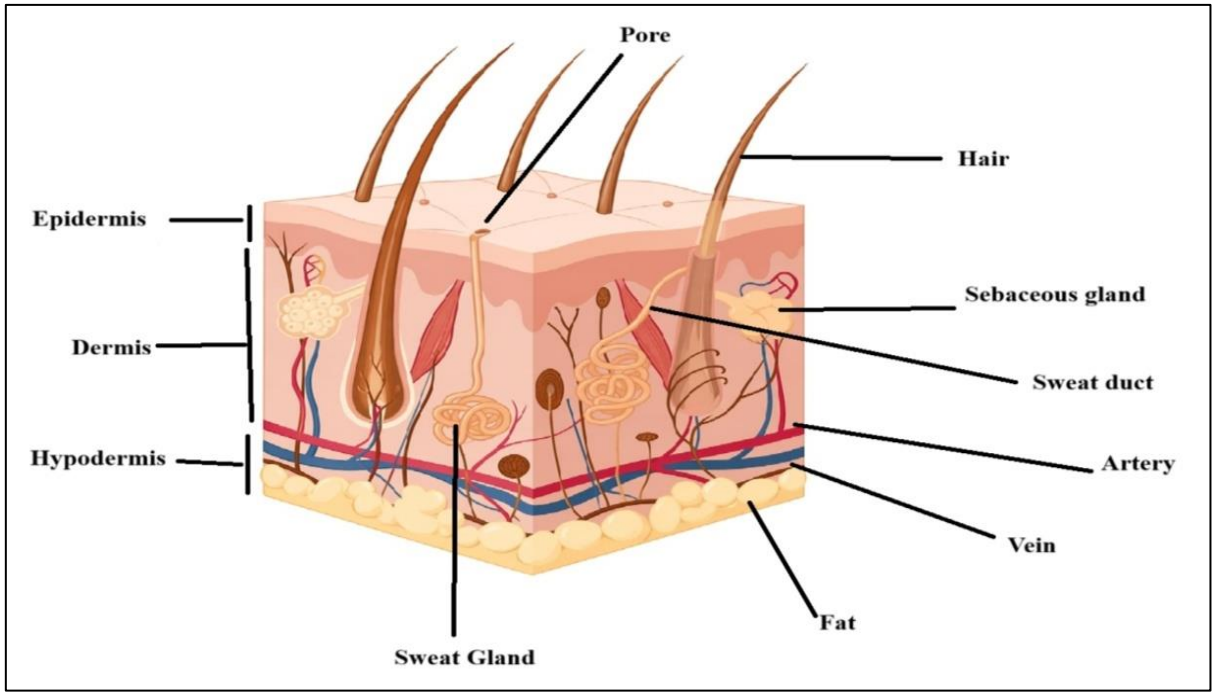

Fig 2 Skin Structure

➢ *Epidermis*

The epidermis is the outermost portion of the skin and acts as the first protective shield [16]. It is thinner than the underlying layers and lacks its own blood supply, receiving nutrients from the dermis below [22]. The majority of cells in the epidermis are keratinocytes, which produce keratin, a tough protein that strengthens the skin and protects it from environmental damage [23]

Table 2 Function of Epidermis [17,19]

Function	Role
Protection	Shields body from microbes, chemicals, & injury
Water barrier	Prevents excessive water loss
UV Defense	Melanin protects against UV rays
Keratin formation	Makes skin tough and resistant
Cell renewal	Produces new skin cells continuously
Immune role	Helps detect foreign substances
Touch support	Contributes to sense of touch

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The thickness of the epidermis differs across body regions. Areas exposed to greater friction, such as the palms and soles, have a thicker epidermis compared to more delicate regions [20]

➢ *Dermis*

The dermis, found beneath the epidermis, is significantly thicker and provides the skin with strength, flexibility, and structural support [15]. It is mainly made up of connective tissue containing collagen and elastin fibers. Collagen contributes to firmness, while elastin allows the skin to stretch and return to its normal shape [18].

Table 3 Function of Dermis [24].

Function	Role
Nutrition	Supplies oxygen and nutrients
Temperature control	Regulates heat via blood vessels & sweat
Sensation	Detects touch, pain,& temperature
Secretion	Produces oil and sweat
Hair growth	Contains hair follicle

➢ *Hypodermis (Subcutaneous Layer)*

The hypodermis is the deepest layer and consists largely of fat cells and loose connective tissue [16]. This layer functions as a thermal insulator, reducing heat loss and helping maintain body temperature [15]. It also acts as an energy storage site and provides cushioning that protects internal tissues and organs from injury [20].

Table 4 Function of Hypodermis [4]

Function	Role
Insulation	Maintain body temperature
Energy storage	Stores fat
Protection	Cushions internal organs
Attachment	Connects skin to underlying tissues

Larger blood vessels and nerves run through this layer and branch into the dermis above. Although sometimes not considered part of the skin itself, the hypodermis plays an essential role in supporting and anchoring the skin while allowing flexibility and movement [17]

➢ *Skin as a Barrier for Drug Permeation:*

The skin acts as a highly effective barrier that limits the entry of foreign substances, including drug molecules,into the body [4]

➢ *Routes of Drug Permeation Through the Skin:*

- *Trans – Appendegeal Route:*

This pathway is also known as the shunt route. In this mechanism, drug molecules penetrate through skin appendages such as: Hair follicles. Sweat glands, Sebaceous glands. [4]

These appendages provide an alternative pathway that partially bypasses the stratum corneum barrier. Although appendages represent only a small fraction of the total skin surface area (approximately 0.1–1%), they play a significant role in the permeation:

Hydrophilic drugs, Large molecules and Peptides and nanoparticles. Drug transport through this pathway depends on factors such as follicular density, follicle opening size, sebum content, and anatomical site of application. This route is particularly important in targeted follicular drug delivery, such as in acne or alopecia treatment.[24]

- *Transcellular Route:*

In the transcellular pathway, the drug passes directly through the corneocytes of the stratum corneum [22]. Lipid-rich cell membranes (lipophilic regions) The molecule must repeatedly partition between: Hydrophilic intracellular keratin & Lipophilic domain [16].

- *This Pathway is Generally Suitable for:*

Small molecules, moderately lipophilic drugs. However, continuous partitioning makes this route complex and energetically demanding [25].

➢ *Intercellular Route:*

This is the most common pathway for drug permeation across the skin. In this route, drug molecules diffuse between corneocytes through the lipid matrix surrounding them [26]. The stratum corneum is often described as a "brick and mortar" structure: Corneocytes = bricks Lipid matrix = mortar [27,28]. Drugs must diffuse through this highly organized lipid domain.

- This pathway is mainly suitable for: Lipophilic drugs & Small molecules [25].

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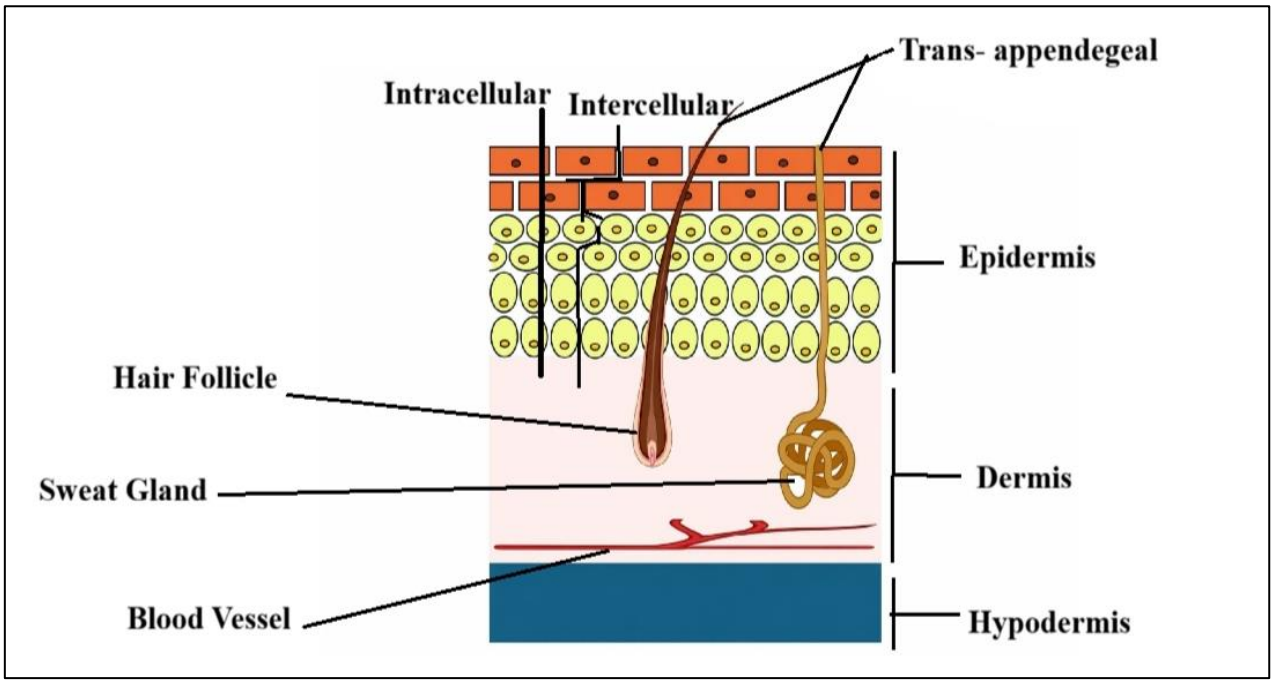

Fig 3 Routes of Drug Permeation [28].

➢ *Functions of Skin:*

Table 5 Functions of Skin [4,16]

Function	Importance in body
Protection	Prevents infection, toxicity, and environmental damage.
Prevention of water loss	Maintains hydration and internal fluid balance.
Thermoregulation	Maintains normal body temperature.
Sensation	Enables interaction with environment and protective reflexes.
Immune defense	Provides early immune response against infections.
Excretion	Assists in removal of metabolic wastes.
Vitamin D synthesis	Essential for calcium absorption and bone health.
Wound healing & regeneration	Maintains skin integrity and repair.
Blood reservoir	Helps regulate blood volume and temperature.
Storage function	Provides insulation and energy supply.
Absorption	Basis for transdermal drug delivery systems.

➢ *Transdermal Drug Delivery System:*

A transdermal drug delivery system (TDDS) is designed to deliver drugs across the skin into systemic circulation in a controlled manner [1]. A typical transdermal patch contains several components that work together to ensure proper drug release, skin adhesion, and stability of the formulation. Each component has a specific function in maintaining the effectiveness and safety of the transdermal patch [3]

- *Basic Components of TDDS:*

Table 6 Components of TDDS [1,29,30]

Component	Example
Drug(Active Pharmaceutical ingredient)	Nitroglycerin, Nicotine, Fentanyl, Scopolamine
Polymer matrix	Hydroxypropyl methylcellulose (HPMC), Polyvinyl alcohol (PVA), Eudragit, Ethyl cellulose
Permeation Enhancers	Ethanol, Oleic acid, Dimethyl sulfoxide (DMSO), Propylene glycol
Backing layer	Polyester film, Polyethylene film, Aluminum foil laminate
Adhesive layer	Polyacrylate adhesive, Silicone adhesive, Polyisobutylene
Release Liner	Silicone-coated polyester film, Fluoropolymer-coated liner
Plasticizers	Glycerol, Polyethylene glycol (PEG), Dibutyl phthalate
Solvent system	Methanol, Ethanol, Chloroform

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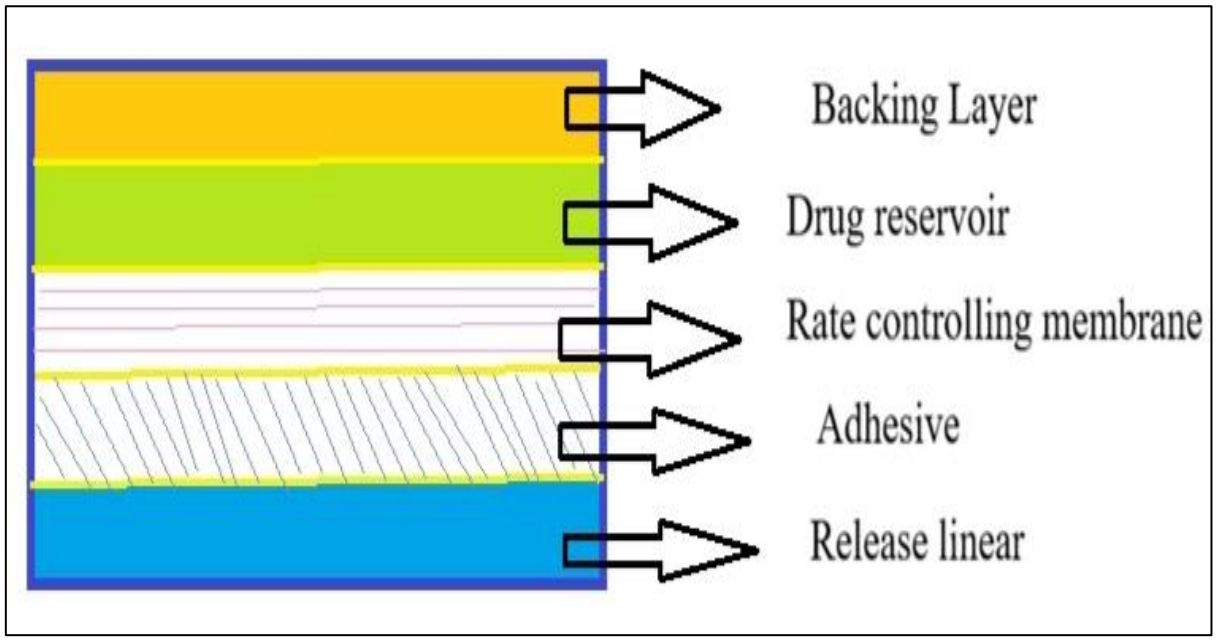

Fig 4 Layers of Transdermal Patch

III. DRUGS USED IN TDDS

Transdermal patches are used to deliver drugs through the skin directly into the bloodstream [31].Only specific drugs with suitable physicochemical properties can effectively penetrate through the skin and produce the desired therapeutic effect [32].

➢ *Common Drugs Used in TDDS*

- Nicotine: Nicotine patches are widely used to help individuals quit smoking. These patches provide a controlled release of nicotine, reducing withdrawal symptoms [32].
- Nitroglycerin: It is used in the treatment of angina pectoris (chest pain). Transdermal patches provide continuous drug release, preventing sudden attacks [33].
- Fentanyl: Fentanyl patches are used for severe and chronic pain management. It is a potent opioid and is suitable for transdermal delivery due to its high potency.[4]
- Estradiol: Used in hormone replacement therapy, especially in postmenopausal women. It helps maintain hormonal balance. [34]
- Scopolamine: Used to prevent motion sickness. It provides prolonged action when delivered through a patch. [35]
- Clonidine: Used in the treatment of hypertension (high blood pressure). It provides a steady release, improving patient compliance [36].
- Lidocaine: A local anesthetic used to relieve pain. Transdermal delivery helps in targeted pain relief [11].

➢ *Polymers used in TDDS:*

Polymers are one of the most important components of transdermal patches[4]. They form the structural framework (matrix or reservoir) of the patch and play a major role in controlling drug release [31]. The selection of polymer greatly influences the performance, stability, and effectiveness of the transdermal system [37]

- *Types of Polymers*

✓ *Hydrophilic Polymers (Water-Loving Polymers):*

These polymers have the ability to absorb water and swell [37]. This swelling increases the diffusion of drug molecules, leading to faster drug release [31].

✓ *Examples:*

Hydroxypropyl methylcellulose (HPMC), Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP) [4]

✓ *Hydrophobic Polymers (Water-Repelling Polymers):*

Hydrophobic polymers do not absorb water easily and form a dense structure [31]. This slows down the movement of drug molecules and provides controlled or sustained release [37].

✓ *Examples:*

Ethyl cellulose (EC), Eudragit, Silicone rubber [32] These polymers are suitable for controlled and prolonged drug release systems.

➢ *Functions of Polymers in TDDS*

- Control the rate of drug release
- Provide mechanical strength and flexibility
- Maintain the structure and integrity of the patch
- Protect the drug from environmental conditions
- Improve the stability and shelf-life of the formulation [4,31,37]

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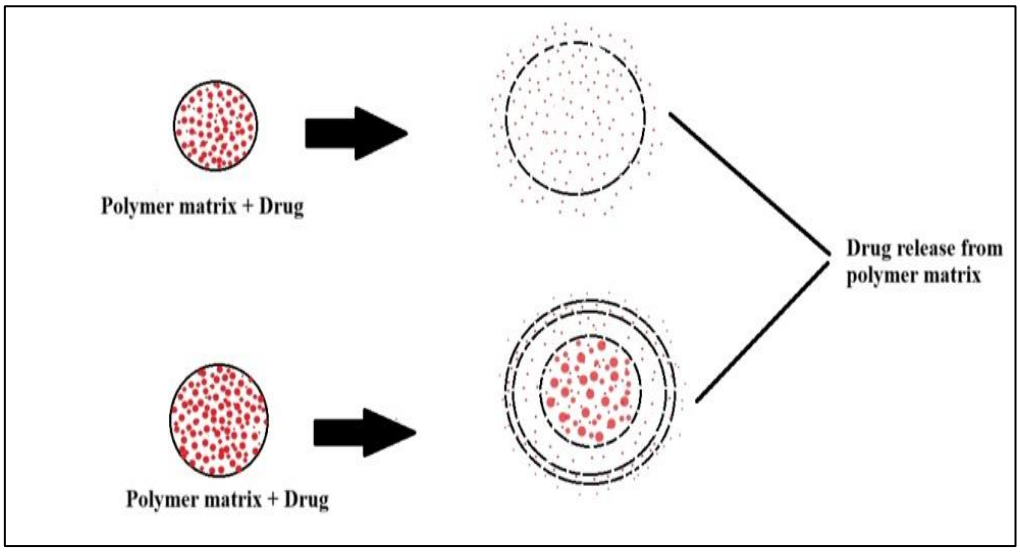

Fig 5 Drug & Polymer Complex

➢ *Types of Transdermal Drug Delivery Systems:*

- *Single-Layer Drug-in-Adhesive Patch:*

In this type of transdermal patch, the drug is directly mixed with the adhesive polymer layer. This adhesive layer performs two functions: it holds the drug and also helps the patch stick to the skin. A backing layer is placed on the outer side of the patch to protect the drug layer and provide support.

✓ Example: Daytrana® patch containing methylphenidate.

- *Multilayer Drug-in-Adhesive Patch:*

This type of patch contains two or more adhesive layers. One layer contains the drug while the other layer helps control the release of the drug. These layers allow the drug to be delivered in a controlled manner over a longer period of time. A backing layer and protective layer are also present in this system to support the patch structure.

✓ Example: Nicotine transdermal patches.

- *Vapor Transdermal Patch:*

Vapor patches release active ingredients in the form of vapors instead of delivering the drug directly through the skin. These patches usually contain essential oils or aromatic substances that slowly evaporate after application. The vapors provide therapeutic effects such as relief from congestion or relaxation.

✓ Example: Nicoderm CQ® vapor patch.

- *Membrane-Moderated Reservoir Patch:*

In this system, the drug is stored in a separate compartment known as the drug reservoir. A special polymer membrane controls the rate at which the drug is released from the reservoir to the skin. The membrane ensures a constant and controlled drug release over a long period of time.

✓ Example: Transderm-Nitro® patch containing nitroglycerin.

- *Micro-Reservoir Transdermal Patch:*

The micro-reservoir system is a combination of reservoir and matrix systems. In this type of patch, the drug is suspended in very small microscopic reservoirs which are dispersed in a polymer matrix. This structure helps in maintaining a constant drug release and improves the stability of the drug within the patch.

✓ Example: Nitrodisc® patch containing nitroglycerin.

- *Matrix System (Drug-in-Adhesive System):*

In the matrix system, the drug is uniformly mixed within a polymer matrix or adhesive material. The medicated polymer layer is spread on a backing layer and the drug is released gradually through diffusion when the patch is applied to the skin. This system is widely used because of its simple design and easy manufacturing process.

✓ Example: Nicotine matrix patches.

- *Matrix-Dispersion System:*

In this system, the drug is evenly dispersed within a polymer matrix which may be hydrophilic or lipophilic. The drug-containing matrix is attached to an impermeable backing layer, while adhesive is applied around the edges to keep the patch attached to the skin. The drug is slowly released from the matrix and diffuses through the skin over time.

✓ Example: Estradiol transdermal patch. [38-42].

- *Methods for Preparation of Transdermal Patch:*

Different techniques are used to prepare transdermal patches depending on the drug and desired release. These methods mainly focus on making a smooth film and controlling drug release through the skin.

- *Asymmetric Membrane Method:*

In this method, a special uneven membrane is prepared, and the drug is placed inside it. This membrane controls how fast or slow the drug comes out. It Helps in controlled drug

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release. The Membrane structure is different on both sides [43].

- *Circular Teflon Mold Method:*

Here, drug and polymers are dissolved in a solvent and poured into a circular mold. The solvent evaporates slowly, leaving behind a thin patch. Simple and commonly used method. It Produces uniform films.

✓ Example: Used to prepare basic skin patches like diclofenac (pain relief) patches[44].

- *Mercury Substrate Method:*

The drug-polymer solution is spread over a smooth mercury surface to form a uniform layer. After drying, a thin film is obtained. It Gives very smooth and even films**.** Mostly used in research work.

✓ Example: Used in labs for preparing experimental transdermal films.[45].

- *IPM (Isopropyl Myristate) Membrane Method:*

In this method, a chemical called IPM is added to improve drug penetration through the skin. It Enhances drug absorption. The drug is mixed with polymer and then formed into a membrane. Useful for drugs with poor skin permeability.

✓ Example: Used for drugs that cannot easily cross the skin barrier.[46].

- *EVAC Membrane Method:*

The drug is mixed with EVA polymer and dissolved in a solvent. After drying, a membrane is formed that controls drug release. It Provides controlled and sustained release**.** It is Stable and widely used in industry.

✓ Example: Nicotine patches for smoking cessation.[47]

- *Aluminium Backed Adhesive Film Method:*

Drug is mixed with adhesive and spread onto an aluminium backing layer. It Protects from moisture and light.This protects the drug and helps in easy application. It Provides strong support.

✓ Example: Used in patches containing sensitive drugs like hormones [48].

- *Proliposome Method:*

Drug is mixed with lipids to form proliposomes, which convert into liposomes when applied on skin, improving drug absorption. It Enhances penetration and also improves stability.

✓ Example: Used in antifungal or anti-inflammatory patches [49,50].

- *Free Film Method:*

The drug and polymer solution is poured and allowed to dry freely to form a thin film without initial backing. It is Easy and cost-effective. This method Mainly used for testing.

✓ Example: Used during early-stage development of new patches. [51]

➢ *Evaluation of Transdermal Patch:*

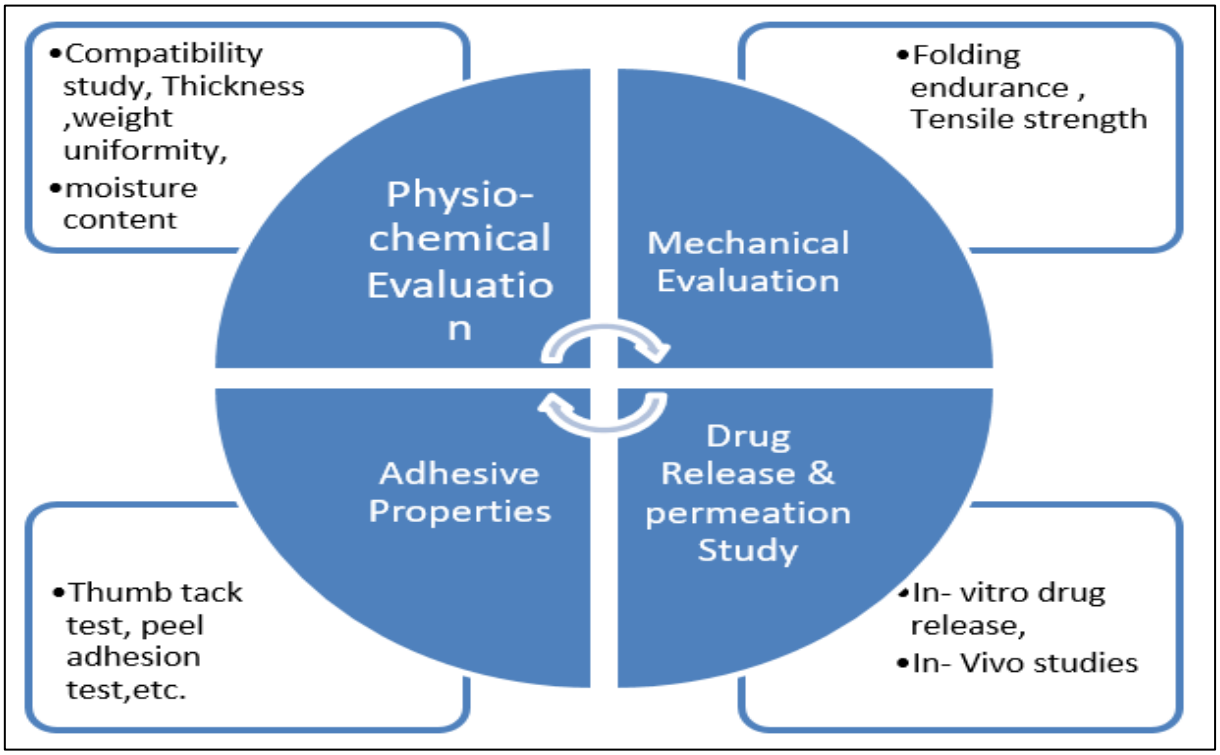

Fig 6 Classification of Evaluation

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- *Physicochemical Method:*

✓ *Compatibility Study:*

Before making a patch, it is important to check whether the drug and polymers are compatible. If they react, the drug may lose its effect or degrade. Techniques like FTIR, UV spectroscopy, or thermal analysis are used. [52]

✓ *Thickness:*

A transdermal patch's thickness can be measured using a traveling microscope, dial gauge, screw gauge, or micrometer, among other instruments. Measurements taken at three different locations on the patch are averaged to determine the patch's thickness. On a patch that is consistently thick, every measurement point will display the same thickness. [53]

✓ *Weight Uniformity:*

Before the patches are weighed, they are dried at 60°C. Three patches are cut into 1 cm^2 pieces, each of which is weighed separately to determine weight uniformity. By calculating the weight variation, it is ensured that the individual weights do not differ appreciably from the average weight. The patch's weight is determined by averaging the three pieces' weights [54].

✓ *Drug Content Uniformity:*

A suitable solvent, such as methanol or phosphate buffer at pH 7.4, is used to dissolve the film, which has a specific area and weight, before it is filtered. The drug content is ascertained using UV or HPLC (High-Performance Liquid Chromatography) techniques, utilizing a standard curve, following the creation of appropriate dilutions. This analytical procedure aids in determining the drug's concentration in the film sample. If a patch is labeled 10 mg, it should contain close to that amount [55].

✓ *Moisture Content:*

After weighing each patch separately, they are put in desiccators with fused calcium chloride at a particular temperature for a full day. Following this time, the patches are weighed again, and the weight difference before and after the desiccation process is used to determine the percentage moisture content. This technique aids in figuring out how much moisture is in the patches. [54]

✓ *Moisture Uptake:*

After 24 hours in a desiccator, the weighed films are exposed to 84% relative humidity, which is accomplished by using potassium chloride in a different desiccator. Until the films achieve a consistent weight, they are periodically reweighed. This procedure makes it possible to ascertain how the films take in and hold onto moisture under particular humidity levels, giving important details about their performance and stability [53,54]]

✓ *Water Vapour Permeability:*

The amount of water vapour permeated through the patch is determined by applying hot air to it and weighing it both before and after it has dried for a full day [56].

✓ *Flatness Test:*

After cutting the patch into three longitudinal strips (right, left, and middle), measure the patch's length to determine its initial and final lengths.

▪ *Formula for Calculating Percentage Constriction:*

$$\% \text{ Constriction} = (\text{Initial length} - \text{Final length})/\text{Initial length} \times 100$$

100% flatness is indicated if the percentage constriction is 0%, which means that the patch keeps its smooth surface over time without experiencing any constriction. [57]

- *Mechanical Properties:*

These Properties check strength, flexibility, and durability.

✓ *Folding Endurance:*

A strip of the patch or film is folded repeatedly at a designated location until it breaks or is folded up to 300 times in order to measure folding endurance. The patch's folding endurance is determined by how many times it can be folded without breaking. This measurement shows how flexible the patch is. [53]

✓ *Tensile Strength:*

Measured using a tensiometer, this shows how much force is needed to tear the patch. [58].

✓ *Percentage Elongation Break Test:*

This measures how much the patch stretches before breaking [59].

- *Adhesive Properties:*

These tests check how well the patch sticks to skin.

✓ *Peel Adhesion Test:*

The force needed to remove the patch from a surface is measured in this test. After applying the patch to a steel plate, it is removed from the surface at a 180-degree angle. The adhesive strength of the patch is determined by measuring the force required to separate it.

▪ Example: Nicotine patch should peel off easily without leaving residue [53]

✓ *Shear Adhesion Test:*

This test is used to evaluate the adhesive polymer's cohesive strength. This technique involves applying an adhesive-coated patch to a smooth surface and hanging a certain weight from it parallel to the surface. The strength of the adhesive bond is indicated by the shear adhesion property, which is measured by the time it takes to remove the patch from the surface [53].

✓ *Thumb Tack Test:*

The force required to remove a thumb or any other object from an adhesive surface is a measure of tackiness [53].

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✓ *Rolling Ball Tack Test:*

This test involves rolling a 7/16-inch-diameter steel ball down an inclined plane with the adhesive surface exposed and the patch positioned horizontally facing upward. On the patch, the ball rolls down and covers a predetermined horizontal distance. The ball's travel distance reveals details about the adhesive patch's tackiness or tack property. The ability of an adhesive to quickly stick to a surface upon contact is measured by its tackiness. [60]

- *Drug Release and Permeation Studies:*

✓ *In- Vitro Drug Release:*

A USP dissolution apparatus is used in the in vitro release test at 37°C and 50 rpm. An adhesive is used to attach a transdermal film to a glass slide, which is then immersed in a dissolution medium that contains 900 milliliters of pH 7.4 phosphate buffer. Over the course of 24 hours, 5 ml samples are taken out and replaced with an equivalent volume of buffer in the dissolution medium. Following spectrophotometric analysis of these samples, the cumulative drug release is computed using the information gathered. [61]

✓ *In-Vitro Skin Permeation:*

An in vitro permeation study can be done using a diffusion cell. Full-thickness abdominal skin from male Wistar rats weighing 200–250 g is used. The hair on the abdominal area is carefully removed using an electric clipper. The dermal side of the skin is then cleaned with distilled water to remove any attached tissues or blood vessels.

Before starting the experiment, the skin is kept in dissolution medium or phosphate buffer (pH 7.4) for about one hour to equilibrate. The diffusion cell is placed on a magnetic stirrer with a small magnetic bead to ensure uniform mixing of the solution. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater.

The prepared rat skin is placed between the two compartments of the diffusion cell, with the epidermal side facing the donor compartment. At regular time intervals, a fixed volume of sample is taken from the receptor compartment and replaced with an equal amount of fresh medium. The collected samples are filtered and analyzed using a UV spectrophotometer or HPLC.

The flux is calculated from the slope of the graph plotted between the steady-state amount of drug permeated (mg/cm²) and time (hours). The permeability coefficient is then calculated by dividing the flux by the initial drug concentration. [61]

✓ *In-Vivo Studies:*

In vivo studies involve testing the transdermal patch on living organisms, usually animals or human volunteers. These tests are done after successful in-vitro (lab-based) evaluations to confirm real-world performance.

- *Animal Studies:*

The most popular animal species for assessment Transdermal drug delivery systems include hairless rats, mice, rabbit, guinea pig, hairless dog, and hairless rhesus monkey etc.

- *Human Volunteers:*

The last phase of a transdermal device's development includes gathering pharmacokinetic and pharmacodynamic information after the patch is applied to volunteers who are human. There have been clinical trials to evaluate the effectiveness, risk, adverse effects, and patient compliance, etc. [61,62]

- *Biological and Stability Studies:*

✓ *Skin Irritation & Sensitization:*

Tests for skin irritation and sensitization can be conducted on healthy rabbits weighing between 1.2 and 1.5 kg on average. The rabbit's dorsal surface (50 cm2) needs to be cleaned, hair removed by shaving, and the surface cleaned using rectified spirit. The skin can then be treated with the corresponding formulations. After 24 hours, the patch must be taken off, and the skin must be examined and categorized into five grades based on the extent of the skin damage [53]

✓ *Stability Studies:*

The stability of the optimized formulations was examined under accelerated circumstances (40 ± 0.5˚C and 75 ± 5% relative humidity) in an environmental test chamber that can be programmed for six months. This demanding testing setting replicated harsh storage conditions to evaluate the formulations' stability and long-term durability. The samples were thoroughly assessed for moisture content, tensile strength as well as the drug release percentage. [61]

IV. OPTIMIZATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

Optimization of transdermal drug delivery systems (TDDS) is a crucial step in the formulation and development of effective drug delivery patches. It refers to the process of selecting the most suitable combination of formulation variables and process conditions in order to achieve the desired performance of the transdermal patch. [63]

In TDDS, many formulation factors such as polymer type, drug concentration, plasticizer amount, penetration enhancers, and solvents system [64].

➢ *Formulation Variables:*

The design and development of TDDS depend on careful selection of formulation variables. These variables influence drug release kinetics, mechanical properties, stability, and patient acceptability.[65]

- *Polymer Type and Concentration:*

Polymers act as the backbone of the transdermal patch and form the matrix or reservoir that holds the drug. They play a major role in controlling drug release and maintaining the structural integrity of the patch.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

Hydrophilic polymers such as HPMC (Hydroxypropyl Methylcellulose) and PVA (Polyvinyl Alcohol) absorb water and swell, allowing faster drug diffusion. In contrast, hydrophobic polymers such as ethyl cellulose slow down drug release by forming a dense barrier.

Polymer concentration is also very important. A higher concentration of polymer results in a thicker and denser matrix, which slows down drug diffusion. On the other hand, lower polymer concentration may lead to faster drug release but can reduce the strength of the patch [63].

➢ *Plasticizer Concentration:*

Plasticizers are added to improve the flexibility, elasticity, and handling properties of the patch. Common plasticizers include polyethylene glycol (PEG), propylene glycol, and dibutyl phthalate. If the amount of plasticizer is too low, the patch becomes hard and brittle, making it difficult to handle. If the amount is too high, the patch becomes too soft and sticky, which may affect adhesion and patient comfort. [66].

➢ *Drug Load:*

Drug load refers to the amount of drug incorporated in the patch. It directly affects the therapeutic effectiveness and release profile of the drug. A high drug load may cause an initial burst release, which can lead to toxicity. On the other hand, a low drug load may not provide sufficient therapeutic effect. Therefore, an optimum drug concentration is required to maintain a balance between efficacy and safety [63].

➢ *Penetration Enhancers:*

The skin, especially the stratum corneum, acts as a strong barrier to drug permeation. Penetration enhancers are added to improve the permeability of the skin.

Common penetration enhancers include oleic acid, menthol, terpenes, and dimethyl sulfoxide (DMSO). These substances temporarily alter the lipid structure of the skin, allowing the drug to pass through more easily. However, excessive use of penetration enhancers can cause skin irritation, redness, or sensitization. Therefore, concentration must be optimized carefully.[66,67]

➢ *Solvent System:*

Solvents are used during the preparation of transdermal patches to dissolve the drug and polymers and to facilitate film formation. The choice of solvent affects drug distribution, drying rate, and uniformity of the patch. Common solvents include ethanol, acetone, isopropyl alcohol, and water.

Fast-evaporating solvents may produce porous or brittle patches, while slow-evaporating solvents may result in sticky patches. Therefore, proper selection of solvent system is essential for producing a uniform and stable patch.

➢ *Formula for Solvent System:*

Drug release from a transdermal patch prepared using solvent system mainly follows diffusion principle, which can be explained by:

- *Fick's Law of Diffusion:*

$$J = D \times K \times C \div h$$

Where:

J = drug flux (rate of drug permeation)
D = diffusion coefficient
K = partition coefficient
C = drug concentration
h = thickness of the membrane [68]

➢ *Patch Thickness:*

Patch thickness plays an important role in controlling drug release. It determines the diffusion path length of the drug. Thicker patches slow down drug release due to increased diffusion distance, while thinner patches may release the drug quickly, sometimes causing a burst effect. Uniform thickness is essential to ensure consistent drug delivery and reproducibility of the formulation.[63]

- *Effect of Polymer Concentration on Drug Release:*

Table 7 Effect of Polymer Conc.

Polymer	Concentration (%)	Drug Release (%)	Interpretation
HPMC	2%	High	Faster drug release due to hydrophilic nature.
HPMC	4%	Moderate	Controlled release
Ethyl cellulose	2%	Low	Slower release
Ethyl cellulose	4%	Very low	Very slow release due to dense matrix.

➢ *Techniques of Formulation Optimization:*

- *Experimental Method (OFAT – One Factor at a Time):*

This is the simplest optimization technique where one variable is changed at a time while keeping all other variables constant. For example, polymer concentration can be varied while keeping drug load and plasticizer constant.

✓ *Advantages:*

- Easy to perform
- Useful for initial screening

✓ *Limitations:*

- Time-consuming
- Cannot study interaction between variables

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

- May not give the best formulation

This method is usually used in the early stages of formulation development.[63]

- *Statistical Method (Design of Experiments – DoE):*

Statistical design of experiments is an advanced method used to study multiple variables simultaneously. It helps in understanding the relationship between formulation variables and the response.

➢ *Types of Statistical Designs:*

- *Factorial Design:*

This method studies the effect of two or more variables at different levels. For example, a 2^2 design studies two variables at two levels.

- *Response Surface Methodology (RSM):*

This method helps in understanding the relationship between variables and responses such as drug release and adhesion strength.

- *Central Composite Design (CCD):*

This is a type of RSM used for studying complex formulations and nonlinear relationships.

✓ *Advantages:*

- Reduces number of experiments
- Identifies interaction between variables
- Provides accurate and reliable results
- Helps in predicting optimal formulation [66]

✓ *Optimization Process:*

- Selection of formulation variables
- Preparation of transdermal patches
- Evaluation of patches
- Data analysis using statistical tools
- Optimization of formulation
- Final optimized transdermal patch [67,68]

➢ *Penetration Enhancement Techniques:*

The skin acts as a natural protective barrier and prevents the entry of harmful substances into the body. The outermost layer of the skin, known as the stratum corneum, is mainly responsible for this barrier function. Because of this, many drugs cannot easily penetrate through the skin.

To overcome this problem, different penetration enhancement techniques are used in transdermal drug delivery systems (TDDS). These techniques temporarily reduce the barrier property of the skin and allow drugs to pass through more easily and effectively.

- *Penetration Enhancement Techniques are Mainly Classified into:*

✓ Chemical techniques
✓ Physical techniques

Both methods are used depending on the type of drug and the required therapeutic effect.

- *Chemical Penetration Enhancement Techniques:*

Chemical techniques involve the use of substances called penetration enhancers, which increase the permeability of the skin.

➢ *Types of Chemical Enhancers with Examples*

- *Sulfoxides:*

Example: Dimethyl sulfoxide (DMSO) It is a strong enhancer that reduces skin resistance and increases drug penetration.

- *Fatty Acids:*

Example: Oleic acid It disturbs the lipid packing of the skin and increases permeability.

- *Terpenes / Essential Oils:*

Example: Menthol, eucalyptus oil These natural enhancers improve drug diffusion by altering skin lipids.

- *Glycols:*

Example: Propylene glycol, PEG They act as solvents and improve drug solubility and penetration.

- *Pyrrolidones:*

Example: N-methyl-2-pyrrolidone These increase drug absorption by improving solubility and partitioning.[69,70].

➢ *Physical Penetration Enhancement Techniques:*

Physical techniques use external energy or devices to increase drug penetration through the skin.

V. METHODOLOGIES

➢ *Electrically Based Techniques:*

- *Iontophoresis:*

In this method, a small electric current is applied to push charged drug molecules through the skin.

✓ Example: Lidocaine patches [71]

- *Electroporation:*

This technique uses high voltage electrical pulses to create temporary pores in the skin.

✓ **Use**: Delivery of large molecules like proteins and peptides [72]

- *Sonophoresis (Ultrasound Technique):*

Ultrasound waves are used to disturb the skin structure and increase permeability.

✓ Example: Delivery of anti-inflammatory drugs [73].

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

➢ *Structure Based Techniques:*

- *Microneedles:*

Microneedles are very small needles that create tiny channels in the skin without causing pain.

✓ Example: Insulin patches, vaccine delivery systems [74]

➢ *Velocity Based Techniques:*

- *Jet Propulsion:*

In this method, drug is delivered into the skin using a high-speed jet stream without using needles. [75]

➢ *Some other Enhancement Techniques:*

- *Thermal Enhancement:*

This method uses heat to increase skin permeability. Heat makes the skin lipids more fluid, allowing the drug to pass easily. It also increases blood flow, which improves drug absorption. [4,76]

- *Magnetophoresis:*

In this technique, a magnetic field is used to enhance drug movement through the skin. It helps in increasing the penetration of drug molecules without damaging the skin. [77]

- *Laser Ablation:*

Laser is used to remove or disrupt the outer layer of the skin (stratum corneum). This creates small pathways for drug entry and improves drug absorption.[78]

- *Radiofrequency (RF) Technique:*

Radiofrequency energy creates tiny microchannels in the skin. These channels allow drugs to pass through more easily and increase permeability.[79]

- *Hydration Technique:*

In this method, the skin is hydrated (moisturized), which causes swelling of the stratum corneum. This swelling opens up pathways and enhances drug penetration.[90]

- *Recent Advances in TDDS:*

Table 8 Advances in TDDS [24, 69-75]

Advances In TDDS	Advantages	Disadvantages	Example
Iontophoresis	1. Aids in the distribution of charged or neutral compounds through topical and transdermal routes. 2. Small peptides have traditionally been delivered by iontophoretic delivery.	1. A more significant current intensity or the characteristics of the drug molecule can sometimes produce erythema or skin irritation.	Dupel® iontophoresis system
Electroporation	1. Relatively safe and painless method that has been shown to administer LMW medicines successfully. 2. The transdermal penetration rate and extent may be controlled by adjusting the electroporation settings.	A lot of cell disruption, including cell death and damage to heat-liable medicines is seen.	MedPulser® Electroporation System
Ultrasound	1. Delivers drugs in a low-frequency range. 2. Enhanced delivery through the transdermal route. 3.Increase delivery of high and low molecular weight drugs 4. Controlled dispersion. 5.Patient compliance	1. Sophisticated technique. 2.Energy consuming 3.Time consuming 4. Irritation and burning sensation.	SonoPrep system (lidocaine delivery)
Suction Abrasion	Eliminates the discomfort due to dermal invasion.	1. Prolonged period to reach a blister. 2. Can cause epidermal infections (less severe).	Cell patch
Skin Puncture	Suitable for transferring drugs like insulin. Faster action	1. Excessive bleeding, if not used properly. 2.Lightheadedness 3. Scarring (occurs when there have been multiple punctures in the same area).	Dermaroller®

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

Needle-Free injection	1. Self administration is possible. 2.Quicker drug delivery 3.No skin puncture 4.Improves vaccine response	1. Not suitable for I.V. administration. 2.Time consuming 3.Proper training needed	Ped-O-Jet
Radio-Frequency	1.Painless,safe and Effective 2. Improve drug penetration. 3. Substitute for S.C. Vaccines.	Maintenance of high-frequency alternating current (~100 kHz)	ViaDerm® system
Magnetophoresis	1. Induction of structural changes. 2. Enhancement in permanent Flux.	Alters the properties of SC	Magnetophoretic transdermal patch
Photomechanical Waves	1.Delivers macromolecules, 2.deeper penetration into tissue 3. Increase permeability.	Poor mechanism understanding , No human clinical data	Laser-induced photomechanical wave system
Transferosomes	1.High deformability 2. Enhance drug bioavailability.	1.chemical instability 2. high cost 3.skin irritation	Jet injector
Niosomes	1.Biodegradable & Non – toxic, good for hydro & lipophilic drug	1.storage issues 2. limited drug loading 3.oxidation of compound	Ketoconazole, doxorubicin

➢ *Marketed Products:*

Table 9 Marketed Products

Product Name	Drug	Dose (Release rate)	Indication
Alora	Estradiol	0.025 – 0.1 mg/ day	Post menstrual syndrome
Androderma	Testosterone	2 - 4 mg/ day	Hypogonadism in males
Captapres-TTS	Clonidine	0.1 – 0.3 mg/ day	Hypertension
Climaderm	Estradiol	0.025 – 0.1 mg/day	Post menstrual syndrome
Climara	Estradiol	0.025 – 0.1 mg/ day	Post menstrual syndrome
Combipatch	Nore thindrone	0.14 – 0.25 mg/ day	Hormone replacement therapy
Deponit	Nitroglycerin	5 – 15 mg / day	Angina pectoris

- *Challenges in TDDS Development:*

Even though TDDS has many benefits, there are several problems that must be solved to make it safe and effective.

✓ *Skin Barrier:*

The outer layer of the skin (stratum corneum) acts like a strong protective wall. It prevents most substances from entering the body. Only small and fat-soluble (lipophilic) drugs can easily pass through it. [81]

- Large, water-loving (hydrophilic), or charged molecules cannot pass easily.
- To solve this, scientists use special methods like chemicals or tools to improve drug penetration.

- *Example:*

Nicotine works well in patches because it is small and lipophilic, but insulin cannot be delivered through skin easily because it is large and hydrophilic. [82]

- *Skin Irritation and Sensitivity:*

Some ingredients used in patches (like drugs, polymers, or enhancers) can irritate the skin. This may cause redness, itching, or allergic reactions.

✓ Strong chemicals can damage the skin barrier.
✓ Long-term use of patches can make the skin more sensitive.

- *Example:*

Some people using pain relief patches may develop redness or itching after repeated use. [82]

- *Dose Limitation:*

Only a small amount of drug can pass through the skin. Because of this, TDDS is suitable mainly for drugs that work in low doses.

✓ Drugs needing high doses cannot be delivered effectively through patches.
✓ Advanced systems can improve this, but they make the design more complex.

- *Example:*

Hormone patches work well because they need small doses, but antibiotics usually cannot be given through patches [4]

- *Patch Adhesion:*

The patch must stick properly to the skin to work correctly. If it does not stick well, the drug delivery becomes uneven.

✓ Sweat, movement, or temperature can affect adhesion.
✓ Too much stickiness can damage the skin when removing the patch.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1601

- *Example:*

A patch may fall off during exercise due to sweating, leading to reduced drug effect. [4,93]

- *Drug Stability:*

Some drugs can break down when exposed to heat, light, moisture, or air.

✓ This can reduce effectiveness or even produce harmful substances.
✓ Proper packaging and stabilizers are needed to protect the drug.

- *Example:*

A patch stored in high temperature may lose its effectiveness before use. [94]

VI. CONCLUSION

Transdermal Drug Delivery Systems (TDDS) have become an important and advanced method for delivering drugs through the skin into the bloodstream. These systems provide many benefits compared to conventional methods, such as controlled and sustained drug release, improved bioavailability, and better patient compliance. However, to achieve these advantages, proper evaluation and optimization of the transdermal patch are essential.

Evaluation plays a key role in ensuring the quality, safety, and effectiveness of TDDS. Various evaluation parameters such as physical properties, drug content uniformity, mechanical strength, in-vitro drug release, and skin permeation studies help in assessing the performance of the patch. In addition, tests like skin irritation and stability studies ensure that the formulation is safe for long-term use and remains stable under different environmental conditions. These evaluations help in identifying any problems in the formulation and provide useful data for further improvement.

Optimization is equally important in the development of an effective transdermal system. It involves selecting the most suitable drug, polymers, plasticizers, and penetration enhancers in the right proportions. Optimization techniques help in improving drug release rate, enhancing skin permeability, and maintaining the stability of the patch. Methods such as trial-and-error and experimental design approaches are commonly used to achieve the best formulation. By optimizing formulation and processing conditions, a balance can be achieved between effectiveness, safety, and patient comfort.

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