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Next-Generation Transdermal Drug Delivery via Patch Technology

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ABSTRACT:

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to conventional routes of drug administration, offering numerous advantages such as bypassing the gastrointestinal tract, avoiding first-pass metabolism, and providing controlled and sustained drug release. Among these systems, transdermal patches represent a non-invasive and patient-friendly approach that enhances therapeutic efficacy and patient compliance. This review highlights the advancements in next-generation transdermal patch technologies, including the incorporation of novel materials, penetration enhancers, microneedles, iontophoresis, and nanocarrier-based systems to overcome the limitations of traditional patches. Emphasis is placed on the design considerations, mechanism of drug permeation, recent FDA-approved products, and potential future directions. As research progresses, next-generation transdermal patches are poised to revolutionize drug delivery, especially for chronic conditions requiring long-term therapy.

Keywords- Transdermal Patch, Permeability, Polymer Matrix, Rate Controlling Membrane, Permeation Enhancers, in vitro release, in vitro skin permeation.

Introduction: -

One of the main challenges in the constantly changing field of drug therapy is making sure that drugs safely and effectively reach the right location in the body. Although traditional techniques like injections and oral tablets have been used for decades they have serious disadvantages. Because oral medications are frequently metabolized by the liver or broken down in the digestive tract before they can take effect, they frequently have low bioavailability. Other drug administration routes, like intravenous route, can cause pain and need to be administered carefully and sterilely even though they avoid the digestive system [1,2]. To overcome these issues the researchers and pharmaceutical scientists invented the Transdermal patches, this uses transdermal routes to deliver the drugs through the skin to the bloodstream.

The concept of delivering drugs through the skin is not new. It was a common practice in ancient medicine to use herbal ointments and pastes to treat skin conditions. However, this idea didn't take a scientific or technological turn until the late 20th century. The first transdermal patch containing scopolamine, which is used to treat motion sickness, was approved by the US FDA in 1979, marking a significant milestone in this journey. (Br J Pharmacol. 2015 Mar 18;172(9):2179–2209).

A transdermal drug delivery system (TDDS) is a method of topical drug delivery that can provide a controlled systemic effect [3]. Transdermal drug delivery is an alternative way of delivering drugs via the skin layer. The drug is carried through the skin into the bloodstream and circulates systemically in the body before reaching the target site [4,5]. This route can also avoid drug related side effects such as gastric irritation. In transdermal delivery, for this method to be effective, the drug must exhibit specific properties: low molecular weight (ideally <500 Da), lipophilic character, and high potency, since only limited quantities can be absorbed through the skin barrier [6].

A transdermal patch is a medicated patch that can deliver medications at a controlled rate through the layers of the skin into the bloodstream. Because they are non-invasive, the course of therapy can be discontinued at any time and last for a few days, suitable for drugs with short biological half-lives that require frequent dosing, leading to on improving patient compliance. Additionally, this approach can prevent adverse effects or treatment failure that are commonly linked to sporadic dosage for chronic diseases [7]. They come in different sizes and contain multiple ingredients or constituents. When applied to the skin, the patch can deliver active ingredients/constituents into the systemic circulation via diffusion processes [8]. The stratum corneum, which acts as the skin's barrier becomes a barrier to the transdermal patch thus, only drugs with small molecules can easily penetrate the stratum corneum, but this can also be overcome by adding enhancers [9]. Therefore, the amount of medications to be released from the patch matrix and enter the stratum corneum determines how effective a patch is, the drug particles must first be dissolved to form molecules that can diffuse through the matrix, and then the drug will penetrate through the skin [10]. One of the first transdermal patches developed in 1985 was the nitroglycerin patch, this was developed by Gale and Berggren, uses a rate-controlling ethylene vinyl acetate membrane. The duration of drug release also varies depending on the usage, from the

shortest (up to 9h) to the longest (up to 9 days). Transdermal Drug Delivery Systems (TDDS) have certain limits, High molecular weight drugs, peptides, and hydrophilic molecules generally cannot penetrate the skin efficiently. Additionally, skin irritation, dermatitis, and allergic reactions at the application site may affect patient comfort and adherence.

Advantages: -

- TDDS avoids the liver's first-pass effect, which typically diminishes the effectiveness of orally delivered medications, resulting in enhanced bioavailability and more consistent plasma levels.
- In contrast to injections, TDDS patches provide a pain-free way to deliver medication, enhancing patient comfort and minimizing anxiety or reluctance towards treatment.
- Improved Patient Compliance.
- TDDS administers medications at a steady rate for prolonged durations, preventing fluctuations in plasma levels, which helps reduce side effects and improve therapeutic outcomes.
- Patches can be easily used without the need for medical supervision, making them perfect for home treatment and minimizing the necessity for regular hospital visits.
- If side effects arise, the treatment can be easily stopped by taking off the patch, which is a benefit that long-acting injections or oral medications do not offer.
- TDDS patches can be used safely by elderly patients, children, and those with dysphagia, enhancing the accessibility and inclusivity of treatment.
- The continuous usage of the medication ensures stable therapeutic levels in the bloodstream, minimizing variations that could impact its effectiveness or safety.

Disadvantages: -

- Transdermal delivery cannot be done with drugs that have low molecular weight, high potency, and appropriate lipophilicity, as only these characteristics or features allow for effective skin penetration.
- Frequent or prolonged use of patches may lead to irritation, redness, itching, or allergic reactions, which maybe caused due to the adhesives or enhancers used.
- Factors such as the thickness of the skin, moisture levels, age, site of application, and body temperature can also affect how drugs are absorbed; these results in varying drug concentrations.
- Drugs that need a quick onset, like those for acute pain or emergency, are not appropriate for TDDS because it often offers a delayed and prolonged release.
- Compared to oral formulations, transdermal systems are more costly to develop and manufacture due to their intricate design, testing, and quality control requirements.
- The efficacy of medication administration may be diminished by patch detachment brought on by improper adhesion from perspiration, movement, or oily skin.

Anatomy and Physiology of the skin:

The skin is the largest organ of the human body, this acts as a barrier between the internal environment and outside environment. Its average thickness ranges from 0.5 mm (eyelids) to 4 mm (palms and soles). The skin has some factors like vast surface area, ability to exchange substances to and for the skin which makes it very suitable for drug delivery. The Transdermal Drug Delivery System (TDDS) utilizes the skin as a way to deliver the drugs through the skin directly into the bloodstream as it bypasses the first pass metabolism.

The skin is made up of 3 layers: - Epidermis, Dermis and Hypodermis.

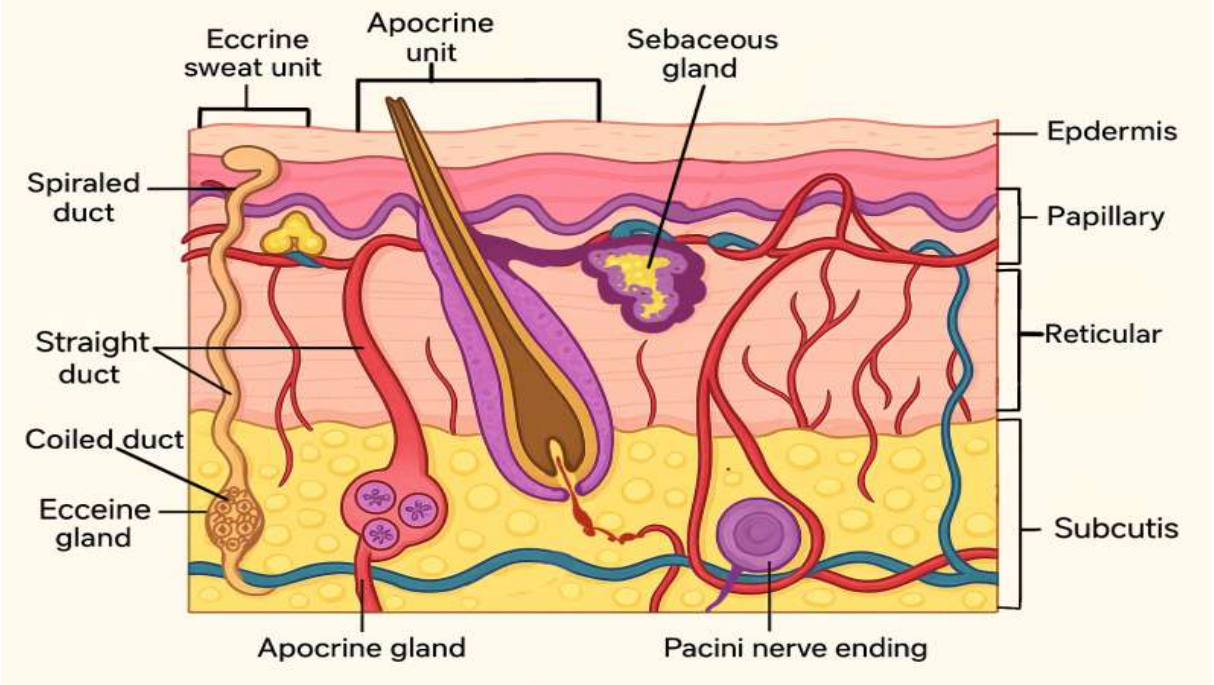
1. Epidermis: - It is the outermost layer of the skin. This is composed of stratified squamous epithelium which is made up of keratinocytes, melanocytes, Langerhans cells, and Merkel cells. Depending on the body site, its overall thickness might range from 50 to 150 micrometers. This layer is around 50-100mm when dry, this acts as a primary barrier to drug penetration. It consists of 10 to 25 layers of corneocytes, which are dead, keratinized cells. The stratum corneum functions as the principal barrier against drug permeation due to the arrangement of flattened corneocytes set in a lipid matrix that primarily consists of ceramides, cholesterol, and free fatty acids. This "brick-and-mortar" structure offers both structural integrity and resistance to water-soluble substances, creating a significant obstacle for transdermal formulations. There are many levels as you move inward, including the stratum basal, stratum lucidum, stratum granulosum, and stratum spinosum.

2. Dermis: - The dermis is the skin's middle layer; it consists of a connective tissue structure that usually has a thickness ranging from 3 to 5 mm. It acts as both a structural and functional base, contains a complex network of nerves, lymphatic vessels, and blood vessels. These factors are vital for preserving the skin's integrity and for the overall homeostasis of the body. A major physiological role of the dermis is thermoregulation. The cutaneous blood supply — which includes arteries, veins, and a vast capillary network — is crucial in regulating body temperature; by modifying blood flow to the skin surface, the body can release excess heat during states of hyperthermia or retain heat when exposed to cold conditions. Aside from regulating temperature, the blood vessels in the skin play a vital role in supplying oxygen and necessary nutrients while also helping to eliminate metabolic waste and harmful toxins from the environment. The microcirculation in the skin operates with impressive efficiency. Capillaries are located merely 0.2 millimeters from the surface of the epidermis, resulting in what is referred to as "sink conditions." These conditions are exceptionally beneficial for the uptake or absorption of drugs or medications that cross the skin's outer layer.

3. Hypodermis: - Beneath the dermis lies the Hypodermis, also referred to as the subcutaneous layer, which is vital for supporting and protecting the overall structure of the skin. This layer offers foundational stability to both the dermis and epidermis, securing the skin to the muscles and bones underneath. One of its main purposes is to store fat, acting as a significant energy reserve that the body can draw on during times of increased metabolic demands. The hypodermis usually varies in thickness from a few millimeters to several centimeters. Thinner areas, like the forearms or the backs of the hands, are often chosen for transdermal therapies because they provide a shorter route for drug diffusion, enhancing systemic absorption. Conversely, thicker hypodermal regions, such as the thighs, abdomen,

It and buttocks, have a longer distance for diffusion, which may slow the absorptionrate and influence the drug's pharmacokinetics.

For successful transdermal drug delivery, it is essential that the drug molecule first passes through the stratum corneum, epidermis, and dermis before reaching the blood-rich areas of the hypodermis, allowing it to enter the bloodstream. **Fig-1**



[Fig-1 This figure shows anatomy of the skin.]

PATHWAYS OF DRUG ABSORPTION THROUGH THE SKIN: -

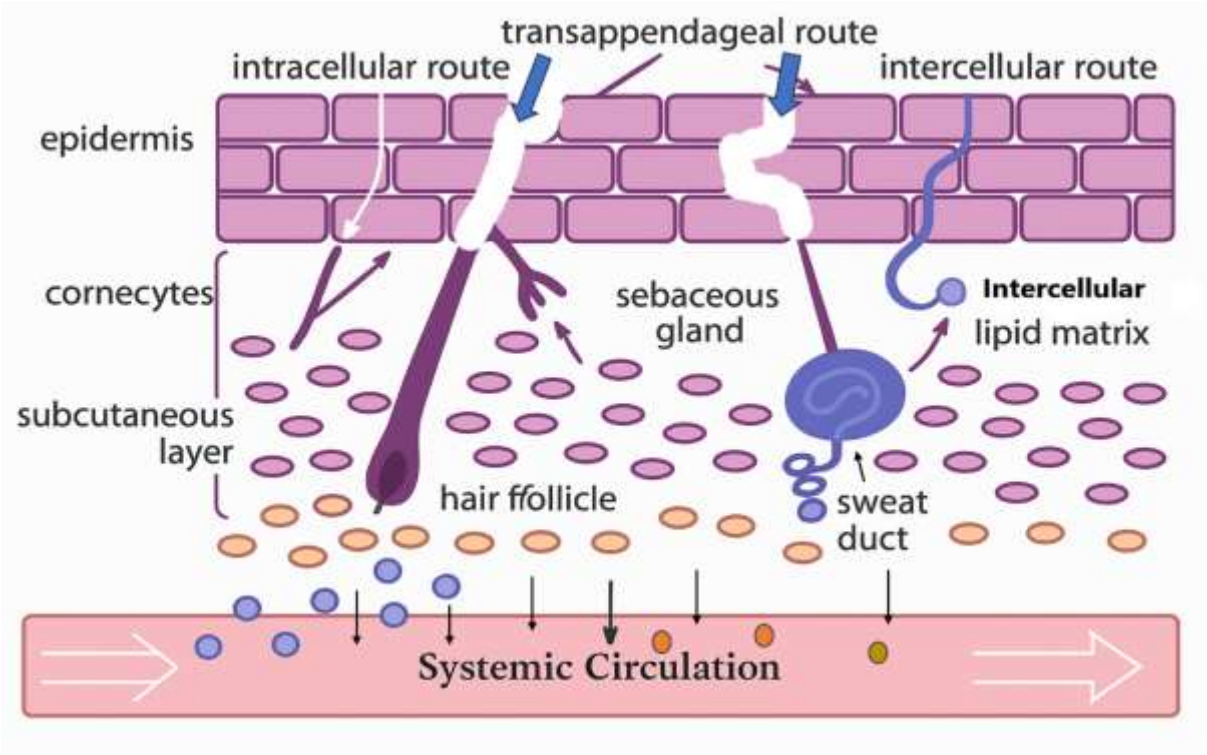
Depending on the drug's physicochemical characteristics, the skin can absorb it through various routes. The skin's upper stratum corneum prevents drug absorption but the presence of various absorption pathways makes it easier for drugs to enter the systemic circulation.

Various drug routes present are as follows: -

1. **Trans-follicular route: -** The trans-follicular route is the fastest approach for a drug to enter the systemic circulation, which offers a wide area for drug diffusion. The skin contains different sweat glands, sebaceous glands, hair follicles, and pores that connect to the skin's outer surface through their ducts. These ducts provide an uninterrupted way for drug transport across the stratum corneum. but various factors like secretion from glands, content and amount of secretion, the size and charge of the molecule, the formulation used, the density and distribution of hair follicles across different body sites, affect the transport of drugs through this route. Although the trans-follicular route offers several potential benefits, its effectiveness can vary from person to person and across different areas of the skin, resulting in varying therapeutic results [11].

2. Transcellular route: - The transcellular pathway for drug absorption involves the direct passage of drug molecules through the cells of the intestinal lining (enterocytes) instead of moving between them. In this process, the drug must first penetrate the apical (outer) membrane, move through the cytoplasm, and then exit through the basolateral (inner) membrane into the bloodstream. Generally, this pathway requires the drug to be lipophilic (fat-soluble) in order to easily traverse the cell membranes, which consist of lipid bilayers. Hydrophilic (water-soluble) drugs generally encounter challenges unless they are facilitated by transporters or carrier proteins. The transcellular route serves as a primary mechanism for the absorption of most drugs that are taken orally [12].

3. Intercellular route: - In the intercellular pathway, the medication moves through the uninterrupted lipid matrix located between the cells. The barrier function of this pathway arises from the complex structure created by corneocytes, requiring the drug to navigate through alternating lipid and aqueous zones by integrating into the lipid bilayer and diffusing inward. Research indicates that water must travel 50 times further via this pathway, making it primarily beneficial for uncharged lipophilic medications [12]. **Fig- 2**

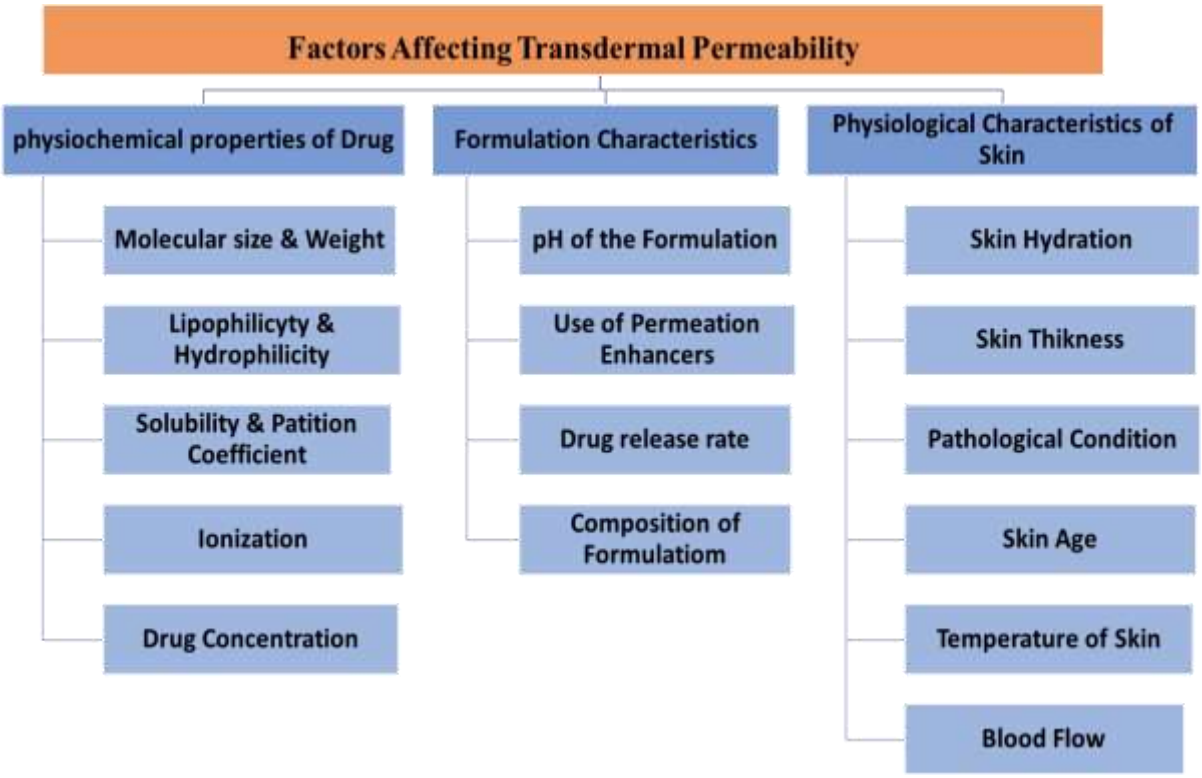


[Fig-2- This figure shows different pathways of drug absorption]

FACTORS AFFECTING TRANSDERMAL PERMEABILITY SKIN PERMEATION:

The skin, the largest organ in the human body, acts as a vital barrier to keep out environmental threats. In addition to its physiological and structural roles, the skin serves as a dynamic surface that can absorb and transfer chemicals into the bloodstream. The process by which a chemical enters the skin's layers and either has local effects or enters the systemic circulation is known as skin permeation. Understanding skin permeation is essential in diverse fields such as **dermatology, pharmaceutical sciences, cosmetics, and toxicology**. Effective transdermal delivery systems, cosmetic formulations, and risk assessments for dermal exposure rely heavily on the principles of skin permeation. **Table-1**

Table-1



FACTORS AFFECTING TRANSDERMAL ROUTE:

1. **Physiochemical properties of drug;**

   I. **Molecular weight & size**: Drug molecular size and weight in terms of physiochemistry: molecules weighing less than 500 Daltons have a higher chance of successfully passing through skin.

   II. **Hydrophilicity and lipophilicity:** Finding the perfect balance between lipophilicity (fat solubility) and hydrophilicity (water solubility) is crucial.

   III. **Partition Coefficient and Solubility:** The ideal molecules for transdermal dispersion have a Log P that is modest, typically between 1 and 3.

   IV. **Ionization:** Unlike ionized molecules, non-ionized (neutral) molecules penetrate the skin more easily.

2. **Formulation Characteristics**

   I. **Formulation pH:** Because non-ionized molecules penetrate the lipid-rich stratum corneum more easily than ionized molecules, the pH should ideally favor the non-ionized form of the drug. To avoid irritation or damage to the barrier function, the pH should be consistent with skin physiology, which ranges between pH 5 and 6.

   II. **Permeation enhancers:** These enhancers promote molecular transport by altering protein conformations or increasing lipid bilayer fluidity. For example, consider sodium lauryl sulphate, EDTA, Polyacrylates

   III. **Formulation composition:** The active ingredient's ability to permeate the skin can be directly impacted by the solvent or vehicle used to dissolve it. Vehicles can work by solubilizing the drug and maintaining its permeability.

   - Altering the barrier properties via interacting with the skin's lipids.
   - Altering the thermodynamic effect of the medication. oleic acid.

3. **Physiological Features of skin: -**

   - Keeping the skin hydrated alters the tightly organized structure of the stratum corneum, enhancing its permeability. This idea is frequently utilized in both transdermal medication delivery and cosmetic products.
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- **Pathological Conditions:** When the barrier function is compromised, skin that is injured, diseased (like psoriasis or eczema), or inflamed can exhibit significantly increased permeability.
- **Skin Age**: The permeability patterns may sometimes vary due to the diminished barrier and reduced lipid levels found in older skin in comparison to younger skin.
- **Skin Temperature**: Elevated skin temperatures increase permeability by making lipid structures more fluid and speeding up the rates of molecular diffusion.
- Blood Flow: While preserving a noticeable concentration gradient, increased cutaneous blood flow encourages greater systemic absorption of penetration medications.

Transdermal Patch:

A transdermal patch is a transdermal carrier system that enables drugs to enter the bloodstream through the skin. The patch can minimize systemic side effects and increase a treatment's therapeutic efficacy by controlling the medication's release. This is one benefit of using this route as opposed to oral, intravenous, and intramuscular medication administration techniques. Distributing the medication into the systemic circulation through the skin at a predetermined rate with minimal variation among individuals is the main objective of the transdermal drug delivery system [13].

Different Types of Transdermal Patches:

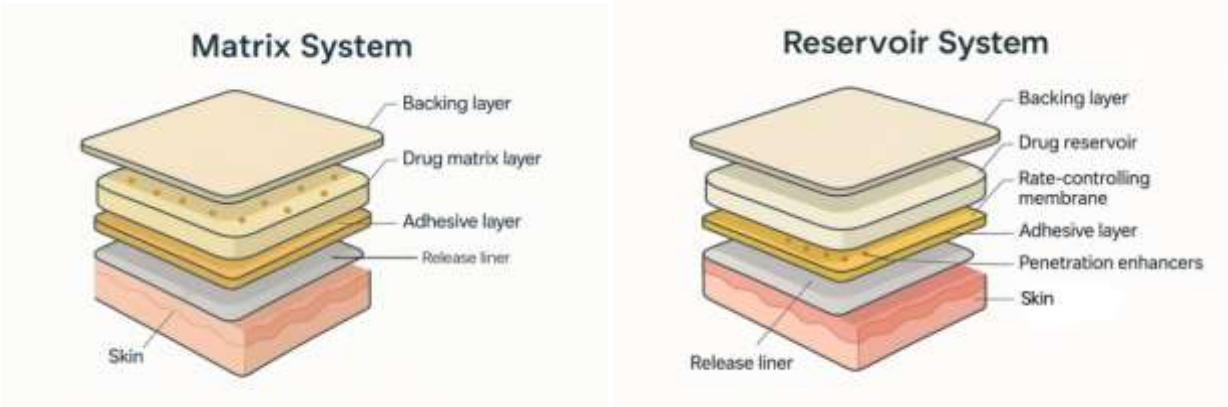
a) **Single layer drug in adhesive**: - In this category, the layer of adhesive incorporates the medication. This adhesive layer functions to bond the different layers, it is also responsible for delivering the drug to the skin. It is enclosed by a temporary liner and a backing [14]

b) **Multi-layer Drug-in-Adhesive:** -A multi-layer drug-in-adhesive patch is a specific kind of transdermal system that, similar to its single-layer counterpart, employs adhesive layers not just for securing the patch to the skin but also for the delivery of the medication. This design contains two different adhesive layers, one is designed for instant drug release to provide quick therapeutic benefits, and the other is created to manage and extend the drug's release over a longer period of time, acting as a reservoir system. The multi-layer design includes an extra adhesive layer which contains the drug, it is typically divided by a polymeric membrane which controls the movement of the drug among layers—although, in some cases, a membrane might be unnecessary. Additionally, this patch features a temporary protective liner that is taken off prior to application and a lasting backing layer which safeguards the patch from environmental factors such as moisture and physical damage [14].

c) **Reservoir**: - The reservoir transdermal system has a separate drug layer. The drug reservoir is placed between the backing layer and a rate controlling membrane. The drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix.

d) **Matrix system:** - The matrix system is a prominent approach for transdermal drug delivery in which the drug is evenly distributed within a polymer matrix. In this arrangement, there is no separate reservoir; instead, the medication and polymer are combined to form a single solid layer. When the patch is put to the skin, the medication diffuses out of the matrix and into the bloodstream. The release rate is mostly determined by the type of polymer employed and the concentration of the medication in the matrix. This device is easier to produce than reservoir systems and frequently provides greater patient comfort. Matrix patches are widely used to deliver medications that don't require precise control over release rates [15].

e) **Vapour Patch**: - In this type of patch, the adhesive layer has an additional function i.e. to release vapour. Vapor patches are a recent addition to the market, and they can dispense essential oils for as long as 6 hours. These vapour patches emit essential oils and are primarily utilized for decongestion. There are also controller vapor patches available that enhance sleep quality. Additionally, there are vapor patches that help reduce the number of cigarettes smoked each month on the market. For e.g. Nicotine patches [16]. **Fig-3**



[Fig- 3 – these three figures indicated different types of patches for drug delivery]

Components of a Transdermal Patch:

1. **Drug**- The medication to be used also affects how well TDDS development goes. Transdermal patches, for instance, have several benefits for medications with a limited therapeutic window, high first pass metabolism, or short half-lives that result in nonadherence from frequent dosing. The drug solution should be in direct contact with the release liner. **Table-2**

Physiochemical properties-

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

Biological properties-

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

Table-2 It indicates ideal properties of the drug for transdermal patch

IDEAL PROPERTIES OF THE DRUG FOR TRANSDERMAL PATCH	
Parameters	**Properties**
Dose	<20mg/day
Half-life	<10 hours
Molecular weight	<500 Dalton
Partition Coefficient (Lipophilicity)	Moderate (Log P between 1-3)
Hydrophilicity	>1mg/ml
Melting point	<200°C
pH	5.0 - 9.0
Skin reaction	Non-irritating and non-sensitizing
Therapeutic Index	Low

2. **Drug reservoir / Polymer Matrix;**

The TDDS polymer regulates the drug's release from the patch. As a result, the polymers employed in TDDS need to be chemically and biocompatible with medications and other system elements like PSA and filtration enhancers. In addition, polymers need to deliver drugs consistently and effectively. Natural and synthetic polymers are the two categories into which polymers are separated according to their source.

Table-3-The following table lists some examples of polymers that are frequently utilized in transdermal preparations.

Category	**Polymer**
Natural Polymer	Sodium Alginate Chitosan Gelatine Gum Tragacanth
Semi-Synthetic Polymer	Methylcellulose Carboxymethyl Cellulose Hydroxypropyl Methylcellulose
Synthetic Polymer	Polyvinyl Alcohol Polyvinyl Chloride (PVC) Polypropylene Glycol Polyethylene

3. Membrane:

In a multilayer patch, the membrane regulates the discharge of drugs from the reservoir. The membrane's diffusion characteristics are employed to regulate the skin's accessibility to medications and/or excipients. Polyurethane, silicone rubber, and ethylene vinyl acetate are a few examples. These function as a membrane to control the release of drugs. (14) Rate-controlling membranes regulate how quickly a medication is released from a dose form. A range of synthetic and natural polymers are used to create rate-controlling membranes. For instance, poly2-hydroxyethyl methacrylate with chitosan [17,18].

4. Permeation Enhancers:

In order to achieve the intended therapeutic level, enhancers work to increase skin permeability. Non-toxic, non-allergic, non-irritating, controlled and reversible enhancing action, pharmacological inertness, the capacity to act precisely for a predictable amount of time, chemical and physical compatibility with medications and other pharmaceutical excipients, and colourless and odorless are the ideal qualities of enhancers [13].

5. Pressure Sensitive Adhesive (PSA):

PSA is a substance that sticks to the substrate—in this example, leather—when applied lightly and removes without leaving any residue. Polyacrylate, polyacrylate, polyisobutylene, and silicon-based adhesives are PSA polymers that are frequently utilized in TDDS. In transdermal patches, the adhesive's primary function is to keep the skin in touch for an extended amount of time. Selection criteria for patches include adhesive properties, patch type, and patch design. It needs to be easy to remove, safe for skin and excipients, and non-irritating. Polyacrylate, poly-iso-butadiene, and silicon-based adhesive polymers are a few types of adhesives [19].

6. Backing films:

Backing films are chosen based on their flexibility, appearance, and occlusion requirements. Thus, it is crucial to take the material's chemical resistance into account while creating a backing layer. Furthermore, excipient compatibility should be taken into account since extended interaction between the excipient and the backing layer may result in the excipient's detachment from the backing layer or in the diffusion of the drug, enhancer, or excipient through the layer. Vinyl, polyethylene, polyester, aluminium, and polyolefin films are some examples of these materials [13,20].

It supports and protects the transdermal patches from the external environment. To prevent drug loss, the backing membrane must be elastic, flexible, and impermeable to drug diffusion. It must be compatible with the polymer, excipients, and drug. It is made of aluminum foil, polyethene, polyester, polyvinyl chloride, heat-sealed layers, polyurethane, and contains an adhesive foam pad [17,21].

7. Release liner:

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

For example-

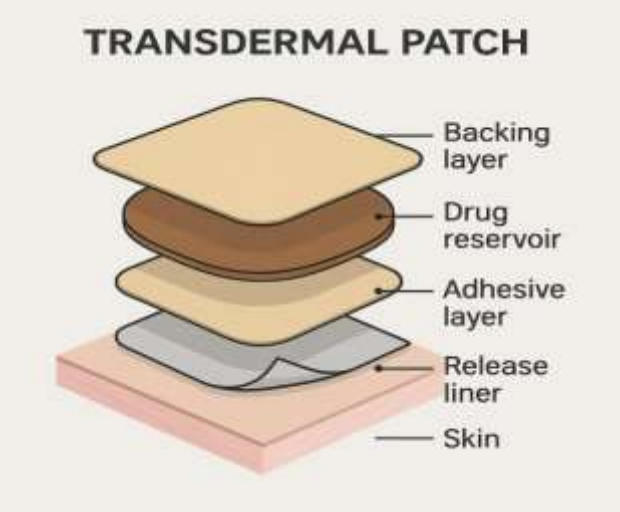
- Occlusive- polyethene or Polyvinyl chloride
- Non-occlusive (paper fabric)- polyester foil and metallic foil [22].

8. Other Excipients:

a) Plasticizers: These substances make polymers more brittle and flexible. These change the polymer's mechanical and physical characteristics when they are applied. For instance, alcohols, phthalic acid esters, sebacic acid esters, oleic acid esters, and glycerol derivatives.

It decreases tensile stress, hardness, electrostatic charge ability, and glass transition temperature while increasing polymer elongation at break, toughness, and flexibility [23].

b) Solvents: chloroform, methanol, acetone, isopropanol, and dichloromethane are used to manufacture drug reservoirs.



[Fig-4 this figure indicates different layers of transdermal patches]

Different Mechanism of Drug Release: -

A transdermal patch's drug release mechanism typically consists of three basic processes: diffusion, dissolution, and osmosis. These techniques can be used alone or in combination, depending on the patch's formulation and design.

- **Diffusion: -**

Diffusion is the most essential process for the release of medication from a transdermal patch. In this process, drug molecules move from an area of high concentration within the patch's matrix or reservoir to an area of low concentration on the skin. This movement is governed by Fick's First Law of Diffusion, which states that the rate of drug diffusion is directly related to the concentration gradient between the patch and the skin. After the patch is applied, the drug diffuses through the polymer layers of the patch and then penetrates the stratum corneum, which is the main barrier of the skin. The medication can reach the skin through intercellular pathways, transcellular pathways, or through appendageal routes such as hair follicles and sweat glands.

- **Dissolution: -**

Dissolution plays a crucial role in the drug release process when the medication is in a solid or semi-solid form within the patch. For diffusion to occur, the drug must first dissolve in a suitable medium within the patch, typically found in a polymeric or gel matrix. Several factors, including the drug's solubility, the properties of the polymer, and the patch's hydration level, affect the dissolution of drug molecules. Once dissolved, the drug is prepared to diffuse through the layers of the patch and into the skin. The rate of dissolution can be a limiting factor, particularly for drugs with limited solubility.

- **Osmosis: -**

Osmosis is integral to the release of pharmaceuticals in certain transdermal delivery systems, especially in patches designed with an osmotic driving mechanism. These patches contain a reservoir filled with a concentrated drug solution and osmotic agents. Upon application to the skin, moisture generates an osmotic pressure gradient. This gradient helps in the influx of solvent, especially water into the drug reservoir, resulting in the solubilization of the drug, this is then subsequently expelled through a semi-permeable membrane at a controlled rate. This osmotic-driven release strategy enables sustained and consistent drug delivery over an extended period.

Formulation of Transdermal Patch:

Patch architectures are classified into four categories: drug-in-adhesive, reservoir (membrane-controlled), matrix (monolithic), and micro-reservoir systems. They differ in how the medicine is stored and released. The majority of commercial patches (for pain, smoking cessation, or hormone therapy) use reservoir or matrix designs.

To create a transdermal patch the first step is to choose a suitable drug and excipients. The drug must have specific physicochemical characteristics to make sure delivery through the skin is quite effective. An ideal drug for transdermal administration should have a molecular weight under 500 Daltons, show a good balance of lipophilicity and hydrophilicity with a log P value ranging from 1 to 4, should have strong pharmacological effects that require a small daily dosage, and be non-irritating or sensitizing to the skin. Furthermore, the drug should maintain stability and be able to penetrate the stratum corneum barrier. Some drugs that have been successfully administered via transdermal patches include fentanyl, nicotine, clonidine, and estradiol [24].

After selecting the drug, the excipients are then selected to serve different functional purposes in the patch formulation. The polymer acts as the matrix or adhesive, it ensures the mechanical stability and regulating drug release. Some frequently utilized polymers are Eudragit, hydroxypropyl methylcellulose (HPMC), and ethyl cellulose. The flexibility and processing of the polymeric film is enhanced by using plasticizers such as polyethylene glycol (PEG) and propylene glycol. To enhance the drug's absorption through the skin some penetration enhancers like oleic acid, dimethyl sulfoxide (DMSO), and isopropyl myristate are usually added [25].

The next step involves the preparing of the mixture of drug and polymer or drug and adhesive. For matrix-type patches, the drug is first dissolved in an appropriate volatile solvent like ethanol or chloroform then a suitable polymer is subsequently added into the drug solution and it is stirred until a uniform mixture is formed. During this process, a plasticizer and (if necessary), penetration enhancers are added to the formulation. Now continuous stirring of the solution is done to achieve consistency [26]. In the case of drug-in-adhesive patches, the drug is directly blended into the adhesive solution, which may consist of silicone or acrylic adhesives. It is important to carefully avoid trapping air bubbles during mixing, as these can cause issues in the final patch [27].

Now after achieving a uniform dispersion, the next step is to cast the formulation. Now the drug-polymer or drug-adhesive solution is gently poured onto a smooth, inert surface like a glass plate or a release liner. A film applicator, for e.g. Like a doctor’s blade is used to evenly distribute the solution into a thin film. The thickness of the wet film is controlled according to need usually between 100 to 500 microns to ensure consistency in dosing in the final patches. Here care must be taken during this procedure so as to prevent the formation of air bubbles or any irregularities in the film.

After the casting is completed, the film is now dried to eliminate the solvent/moisture part and solidify the structure. This film is then allowed to dry at room temperature or in a controlled oven at 40-60°C to evaporate the solvent and form a solid matrix. By Controlled drying it guarantees that the solvent is completely removed without causing thermal damage to the drug. Inadequate drying may result in variable drug release profiles and compromise the stability of the final product [28].

Evaluation Of Transdermal Patches:

A. Physicochemical Evaluation-

Thickness: The thickness of the transdermal patch is determined by taking three separate measurements with a travelling microscope, dial gauge, screw gauge, or micrometer. The average of the three measurements is then used to determine the patch's thickness; a uniformly thick patch will have the same thickness all over. It is possible to compute the variance in thickness within and between patches [29,30].

Weight uniformity: Prior to being weighed, the patches are dried at 60°C. The weight homogeneity of a transdermal patch is evaluated by cutting and weighing a 1 cm2 section of three patches, after which the weight variance is calculated. The weight of the patch is determined by averaging the three values. An individual's weight cannot deviate appreciably from the average weight [31,32].

Folding endurance: A strip of patch or film is folded gradually in the same spot until it breaks or folds up to 300 times to test folding endurance. The amount of times a patch can be folded without breaking is known as its folding endurance. The transdermal patch's flexibility is determined in part by its folding endurance [33].

Drug content: A suitable solvent, such as methanol or phosphate buffer pH 7.4, is used to dissolve a film of the right area and weight, which is then filtered. Following the appropriate dilutions, the UV or HPLC method uses a standard curve to assess the drug content [34,35].

Percentage moisture content: To calculate the percentage moisture content, separately weighed patches are kept in desiccators with fused calcium chloride for a whole day at room temperature. After a day, the patches are weighed again, and the following formula is used to calculate the patches' percentage moisture content: (Initial weight - Final weight/Final weight) x 100 is the percentage moisture content [36,37].

The shear adhesion test: is used to assess the sticky polymer's cohesive strength. After positioning the adhesive patch on a level surface, the required weight is suspended straight from the patch. The time it takes to remove the patch from the surface indicates its shear adhesion.

The peel adhesion test: determines how much force is required to remove a patch from a surface. The patch is positioned on the surface of a steel plate and then pulled 180 degrees away from it. The amount of force required to remove the patch is measured.

Roll ball track test: A 7/16-inch-diameter steel ball is rolled down and tilted in the rolling ball tack test, which involves placing a patch horizontally on the adhesive surface with the patch facing up. How tacky the sticky patch depends on how far the ball flies [38,39].

Stability research: To ascertain how long the patch will be viable and usable, a stability study is conducted. According to standards from the International Conference of Harmonization (ICH), stability is assessed for six months at 40°C / 75 percent relative humidity since the medicine rapidly deteriorates in unstable patch formulations. Stability tests are performed on samples at 0, 30, 60, 90, and 180 days [40].

B. In-vitro Evaluation-

In vitro release study: In vitro release is evaluated using a United States of Pharmacopeia (USP) dissolve apparatus set to 50 rpm and 37°C. The transdermal film is applied with an adhesive to a glass slide, which is subsequently immersed in a dissolving medium containing 900 milliliters of 7.4 pH phosphate buffer. A 5 ml sample is removed and added to the dissolving medium along with an equivalent volume of buffer for a 24-hour period. Following the sample's spectrophotometric analysis, the cumulative drug release is computed [41].

In vitro skin permeation study: This type of investigation is carried out using a vertical diffusion cell that has two chambers separated by the skin of a male Wistar rat. The transdermal film is placed to the rat's skin and connected to the diffusion cell that sits between the donor and receptor compartments. Regular samples are collected, and a fresh medium with the same volume is used in their place. Spectrophotometric examination of the samples is used to calculate flux [42].

Skin irritation study: Albino rats, mice, or rabbits are utilized to test for skin irritation in an in vitro skin penetration study. Each of the five animal categories contains six animals. Group V receives a standard irritant, % v/v formalin solution, Group III receives a transdermal patch without medication, Group IV receives a transdermal patch with medication, Group I serves as the control group, and Group II receives commercially available adhesive tape (USP official adhesive tape). The animals undergo treatment for seven days, depending on their group, after the skin hairs are removed. Animals are graded every day based on how uncomfortable they seem, as well as how easily they can scratch and leave scars.

C. In-vivo Evaluation-

Animal model: - Small-scale animal studies are therefore preferable since human studies demand a substantial investment of time and resources. The most common animal species used to evaluate transdermal drug delivery devices include mice, hairless rats, hairless dogs, hairless rhesus monkeys, rabbits, and guinea pigs. Numerous studies have shown that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. The Rhesus monkey is among the best models for examining the distribution of transdermal medications in people [43].

Human model: At the conclusion of the transdermal device development phase, pharmacokinetic and pharmacodynamic data were gathered from the patch's application to human volunteers. To evaluate the efficacy, risks, adverse effects, patient compliance, and other aspects, clinical trials have been carried out. While phase II clinical trials aim to evaluate safety and efficacy in patients over the short term, phase I clinical trials are mostly used to evaluate safety in volunteers. Phase III trials show the safety and effectiveness of marketed patches in a large number of patient populations, whereas phase IV trials are carried out during post-marketing surveillance to identify adverse medication reactions [44].

Application of Transdermal Patch: - [45]

1. Pain Management: -

Transdermal patches are the most commonly used methods for managing both chronic as well as acute pain. Medications such as lidocaine, fentanyl and buprenorphine are administered via patches to give prolonged pain relief without any gastrointestinal side effects which are usually linked to oral painkillers. Fentanyl patches are frequently recommended for patients dealing with cancer-related discomfort and post-surgical pain who are already accustomed to opioids.

2. Hormone Replacement Therapy (HRT): -

Transdermal patches are widely used as hormone replacement therapy for postmenopausal women. Estradiol and progesterone patches promote hormonal balance, lowers the risk of osteoporosis, and also relieve symptoms including hot flashes and mood swings. Transdermal patches provide more stable plasma hormone levels than oral formulations because they bypass the hepatic first-pass metabolism.

3. Cardiovascular Disorders: -

To treat angina pectoris, drugs such as nitroglycerin are administered using transdermal patches. The regulated drug delivery helps to maintain the drug therapeutic levels, improves blood flow to the heart and reduces chest pain. Transdermal clonidine patches are also used to treat hypertension, giving constant blood pressure management over several days.

4. Smoking Cessation: -

Nicotine transdermal patches are readily accessible over the counter (OTC) and play an important part in the nicotine replacement treatment (NRT). These patches provide a controlled amount of nicotine to people who seek to stop smoking, reduce withdrawal symptoms and cravings. They offer a safer alternative to smoke and boost cessation success rates.

5. Neurological and Psychiatric Disorders: -

Transdermal drug delivery of rivastigmine is approved for the treatment of Alzheimer's disease, this provides an effective alternative for the patients who have trouble for swallowing the drugs or do not adhere to oral therapy. Similarly, selegiline transdermal patches are used to treat severe depressive disorder, which reduces the negative effects associated with oral administration.

6. Contraception: -

The transdermal contraceptive patch, which contains ethinyl oestradiol and norelgestromin, provides an alternative to daily oral contraceptives. It is given once a week and works to prevent the ovulation and modify the uterine lining. It improves the user's compliance and it ensures consistent hormone supply

7. Motion Sickness and Nausea: -

Scopolamine transdermal patch is used to treat travel-related motion sickness and nausea. It delivers continuous drug delivery for 72 hours and it is especially useful for long travels or for patients undergoing chemotherapy

8. Parkinson's Disease: -

Rotigotine is a dopamine agonist. It is administered through transdermal route to treat Parkinson's disease and restless leg syndrome. This patch maintains steady-state plasma drug levels, which is crucial for regulating the motor fluctuations and also enhancing symptoms control in Parkinson's patients.

Conclusion

Next-generation transdermal patch technology represents a significant advancement in drug delivery, offering a non-invasive, effective, and patient-compliant alternative to conventional administration routes. By incorporating innovative materials, drug carriers, and enhancement strategies such as microneedles and nanotechnology, these modern systems are overcoming earlier limitations like poor skin permeability and restricted drug compatibility.

Transdermal drug delivery offers clear advantages, notably bypassing the gastrointestinal tract and first-pass metabolism, making it particularly suitable for hormones, analgesics, and cardiovascular drugs. The increasing research interest in transdermal drug delivery systems (TDDS) has spurred the development of advanced formulations with improved therapeutic outcomes and the potential for personalized medicine.

To ensure continued progress, it is critical that formulations do not disrupt normal skin physiology. A thorough understanding of skin anatomy, physiology, and the interaction between polymers and skin components is essential for the successful design and optimization of future patches. With ongoing research and technological innovations, next-generation transdermal systems are well-positioned to revolutionize pharmacotherapy in the years ahead.

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