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Overview of novel transdermal drug delivery system

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Abstract
The knowledge of a drug's pharmacokinetic and pharmacodynamic behavior has recently made the creation of the ideal drug delivery system more logical. It is now evident that interdisciplinary efforts will play a major role in the success of drug delivery research in the future. These carriers, known as new drug delivery systems (NDDS), keep the drug concentration within the therapeutic range for extended periods of time. With the help of transdermal drug delivery systems (TDDS), it is possible to maintain medication release while lowering the dosage and, consequently, the adverse effects of oral therapy. Transdermal medications come in a discreet, self-contained dose form. It introduces a medication into the systemic circulation at a regulated pace through unbroken skin. Delivery speed is managed. The skin or membrane in the delivery system regulates the rate of distribution. It is a challenging to create drug delivery system that is sophisticated and intricate. It needs certain manufacturing tools and processes.

Keywords: Transdermal drug delivery system, skin, permeation, transdermal patch

Introduction
A novel drug delivery system is one that takes advantage of recent developments in the knowledge of the pharmacokinetic and pharmacodynamic behavior of the drug to provide a more logical method for creating the best possible drug delivery system. The carriers used in innovative drug delivery systems (NDDS) help keep medication concentrations in therapeutic ranges for extended periods of time. Innovative drug delivery methods have a number of benefits over traditional drug delivery methods [1]. There exist a variety of drug delivery methods have been created, and some are currently being developed, with the intention of reducing medication loss, avoiding negative side effects, increasing drug bioavailability, and encouraging and facilitating the drug's accumulation in the necessary bio-zone (Site).

The last several years have seen a resurgence of interest in the creation of innovative drug delivery methods for already-approved pharmaceutical compounds. The creation of a novel delivery method for already-approved medication molecules enhances the drug's performance in terms of safety and efficacy as well as patient compliance and total therapeutic benefit. Transdermal Drug Delivery Systems, or "patches," are self-contained, discrete dosage forms that, when placed to undamaged skin, transfer drugs to the systemic circulation at a controlled rate through the skin. TDDS dose forms are intended to spread a therapeutically effective dosage of medication throughout the skin of a patient [1-2].

Transdermal drug delivery systems aim to administer medications at a preset rate through the skin to the systemic circulation with the least amount of fluctuation between and within patients. Transdermal delivery is now one of the most promising approaches to drug delivery. It lessens the strain that eating orally frequently puts on the liver and digestive system. It improves patient compliance, reduces adverse drug side effects brought on by transient overdoses, and is practical for transdermal medications that only need a single, weak application [2]. Because TDDS prevent first-pass metabolism and improve patient compliance, they are recommended over injectables and oral routes. As the most fruitful novel research area in drug delivery, transdermal delivery has faced competition from oral delivery. This is so because the goal of oral treatment is to achieve and sustain a drug concentration in the body that is within the range that is therapeutically effective.

This is accomplished by administering a fixed dose at regular intervals, which causes the body's drug concentration to follow a peak and trough profile and increases the risk of side effects or therapeutic failure. A significant amount of drug is lost in the region around the target organ, so therapy needs to be closely watched to prevent overdosing [2-3]. When applied to the skin, medicated adhesive patches distribute a therapeutically effective dosage of medication throughout the skin.

In 1981, the first transdermal patch was authorized to treat nausea, vomiting, and motion sickness. The market for transdermal drug delivery. This has made it possible to create active patches that deliver proteins, vaccines, and medications for pain management [3]. Smaller patches with improved adhesion are being produced by passive patch technology. Transdermal drug delivery systems (TDDS) have made a name for themselves as essential components of cutting-edge drug delivery systems.

Transdermal drug delivery system, wherein the drug's bioavailability increases as a result of an increased rate of drug absorption [3-4]. Transdermal medications, which include ointments, creams, gels, micro emulsions, and transdermal patches, are essential for preventing skin infections and preserving the proper health of the skin [4].

Objective

1. The goal is to elucidate the factors that influence transdermal permeation.
2. To go over transdermal delivery system administration routes.
3. To talk about the transdermal delivery system's components.
4. To recognize the parts of a transdermal patch.
5. To talk about how important each component is.
6. To describe the transdermal delivery system's evaluation parameters.

Advantages

1. It is appropriate for drug candidates with short half-lives and low therapeutic indices.
2. No effect of first pass.
3. A decrease in the number of doses.
4. Reducing the amount of drugs taken each day.
5. Less variation in the drug's plasma concentration.
6. Increases adherence from patients.

Disadvantages

1. Drugs that cause skin irritation or sensitization should not be administered transdermally.
2. The impermeability of the skin naturally limits the amount of drugs that can be delivered transdermally, so only relatively potent medications are appropriate.
3. Technical difficulties with the adhesion of system to different skin type and under various environmental conditions.
4. A lot of medications, particularly those with hydrophilic structures, penetrate the skin too slowly to be useful for therapeutic purposes.
5. Unsuitable for high dosages of drugs.

Skin and Drug permeation

Reviewing the structural and biochemical aspects of human skin, as well as those traits that affect the barrier function and the rate at which drugs enter the body through the skin, is crucial for comprehending the idea of TDDS [4-5].

Anatomically, the skin can be divided in to two layers Epidermis and Dermis or corium

The goal of the TDDS is to apply topical medication on intact skin to reach systemic levels of medication. Thus, when formulating TDDS, consideration should be given to the structural and biochemical characteristics of human skin as well as the elements that influence drug absorption through the skin and barrier function [5].

Several variations exist between the skin's epidermis and dermis layers. One of the largest organs in the human body, the skin covers an area of roughly 2 m² on an average adult. About one-third of the blood that flows through the body is received by this multilayered organ (Guy *et al*., 1987). The epidermis, which is roughly 150 micrometers thick, is produced by a population of active epithelial basal cells [5-6].

It is the skin's outermost layer, and cells migrate from the basal layer towards the skin's surface as a result of differentiation (Flynn, 1985). The epidermis' other layers, known as the stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum, are located beneath this layer [6].

These additional layers come together to form the viable epidermis. Dermis is a mesoderm-derived layer of firm connective tissue that serves as the base for the epidermis. The dermis, also known as the corium, is composed of a dense, felt-like network of connective tissue, primarily composed of bundles of collagenous fibers mixed with a certain amount of elastic tissue at the superficial layers [6-7]. The dermis is home to sebaceous glands, sweat glands, hair follicles, lymphatics, and tiny plexuses of blood vessels.

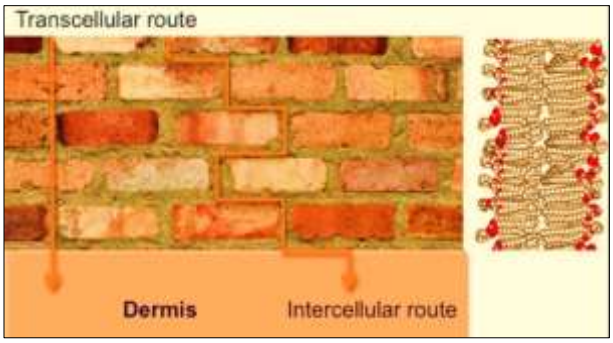

Fig 1: Brick and Mortar Structure with Lipid Bilayer.

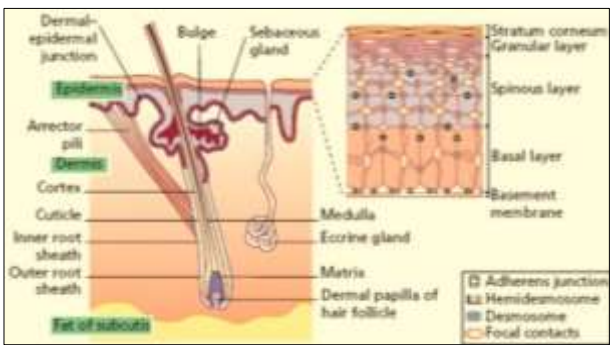

Fig 2: Schematic diagram of different layers of skin

Drug penetration pathways

A drug molecule can cross the intact stratum corneum in three crucial ways: through the skin's appendages (Shunt

routes); through the intercellular spaces between the stratum lucilipiddomains and other layers of the epidermis; or through a transcellular pathway [7]. A given drug is likely to permeate through a combination of these pathways, with the physicochemical properties of the molecule determining the relative contributions of these pathways to the gross flux.

The Appendageal Route

A continuous passageway directly through the stratum corneum barrier is provided by skin appendages. Nevertheless, a number of factors make their impact on drug penetration less effective. The area available for direct contact of the applied drug formulation is limited due to the small surface area occupied by sweat ducts and hair follicles, which typically make up 0.1% of the skin's surface area [7-8].

Transcellular Route

Medication that enters the skin through the transcellular pathway passes through corneocytes. Hydrophilic medications can pass through the aqueous environment that corneocytes, which are composed primarily of hydrated keratin, provide. A drug's transcellular diffusion pathway necessitates several partitioning and diffusion steps [8].

Intercellular Route

The drug diffuses through the continuous lipid matrix as part of the intercellular pathway. There are two main reasons this route is a significant challenge. The interdigitating nature of the corneocytes produces a convoluted pathway for intercellular drug permeation, which contrasts with the relatively direct path of the transcellular route, reinforcing the "bricks and mortar" model of the stratum corneum [9]. The domain separating cells is made up of bilayers with alternating structures. As such, a medication needs to repeatedly diffuse through lipid and aqueous domains and partition into them one after the other. It is widely acknowledged that this pathway accounts for the majority of small, uncharged molecules that enter the skin [9-10].

Factors Influencing Transdermal Drug

Three factors can be taken into consideration when formulating an effective transdermal drug delivery system: the drug, the skin, and the vehicles. Thus, biological and physicochemical factors can be used to categorize the influencing factors.

Biological Factors

Skin Conditions

Although the intact skin serves as a barrier, numerous substances such as acids and alkali can pass through the skin's barrier cells and open the intricate, dense horny layer structure. Lipid fraction is removed by solvents like methanol and chloroform, creating artificial shunts that allow drug molecules to move freely through [10].

Skin Age

Younger skin is more porous than older skin. Children are more vulnerable to toxins absorbing through their skin. Compared to mature adult skin, the skin of fetuses and infants is more permeable. As a result, children absorb topical steroids through the skin more quickly than adults do, but both groups absorb water equally [10-11]. Age of the skin is therefore one of the variables influencing drug penetration in TDDS.

Blood Supply

Transdermal absorption may be impacted by modifications to the peripheral circulation.

Regional Skin Site

Site-specific differences include skin thickness, stratum corneum type, and appendage density. These elements have a big impact on penetration.

Skin Metabolism

Chemokines, hormones, steroids, and certain medications are all metabolized by the skin. Therefore, the effectiveness of a drug absorbed through the skin is determined by skin metabolism.

Species Difference

Anatomical variations in the skin of different mammalian species include variations in the SC's thickness, the quantity of sweat glands, and the density of hair follicles per unit surface area.

The thickness, density, and keratinization of skin differ among species, which influences the penetration [11].

Physiochemical Factors

Skin Hydration

Skin becomes much more permeable when it comes into contact with water. The most crucial element boosting skin penetration is hydration. Humectants are therefore used in transdermal delivery.

Temperature and PH

Drug penetration increases tenfold as temperature changes. With a drop in temperature, the diffusion coefficient falls. The dissociation of weak bases and acids is contingent upon the pH and pKa or pKb values. The amount of unionized drug in the skin determines the drug concentration [11-12]. As a result, two critical variables influencing drug penetration are pH and temperature.

Diffusion coefficient

Drug penetration is based on the drug's diffusion coefficient. The properties of the drug, the diffusion medium, and their interactions all affect the drug's diffusion coefficient at constant temperature.

Drug Concentration

The gradient of concentration across the barrier determines the flux, and a higher concentration gradient indicates a higher drug concentration across the barrier.

Partition Coefficient

The drug is soluble in both lipids and water. Good action necessitates the ideal K partition coefficient. Medication with a high K content isn't ready to leave the skin's lipid layer. Drugs with low K content won't permeate either [12].

Molecular Size and Shape: Transdermal flux is inversely correlated with the drug's molecular size. For transdermal delivery, a drug molecule's ideal size and shape are less than 400.

Types Of Transdermal Patches

Transdermal patches come in the following types: Three fundamental design principles (a specialized design constitutes the fourth) can be used to characterize the developed patch-type TDDS:

1. Drug in reservoir (membrane type).
2. Drug in matrix (monolithic type).
3. Drug in adhesive (matrix).
4. Drug in micro reservoir (reservoir in adhesive matrix).

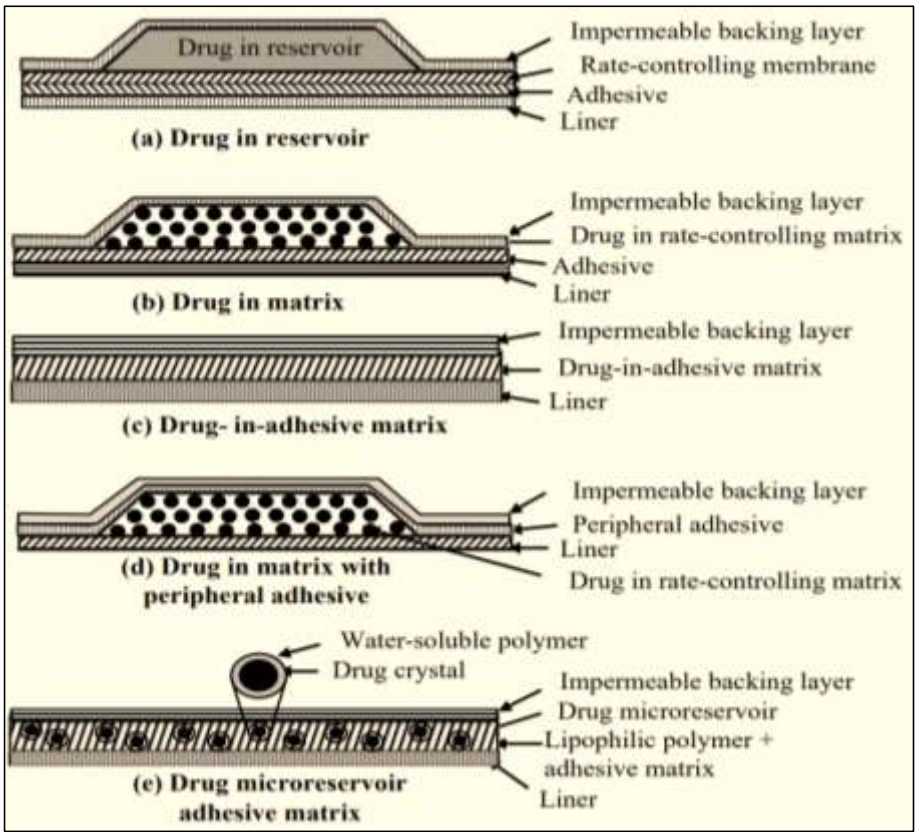

Fig 3: Types of Rate-Programmed Transdermal DDS

Drug in Reservoir (Membrane Patch)

A delivery rate-controlling membrane sits between the skin and the drug reservoir in membrane patches. Dense polymeric membranes, through which the drug permeates by dissolution and diffusion, or microporous membranes, which regulate drug flux by the size and tortuosity of pores in the membrane, can also be employed [12]. Materials that can be used as rate-controlling membranes include polyester elastomers, silicones, high-density polyethylene, ethylene-vinyl acetate copolymers, and polyacrylonitrile. The optimal membrane should retain other formulation excipients while remaining permeable to the medication and enhancer, if any are present. A drug reservoir can be made of many different substances, from straightforward formulations like mineral oil to intricate formulations like polymeric materials and aqueous-alcoholic solutions and gels with or without co-solvents. If the drug is formulated as a suspension, the reservoir material will become saturated with the drug during the product application period, allowing zero-order drug release throughout the delivery period [13].

Drug in Matrix

The medication permeates a polymeric matrix to reach the skin's surface after being evenly distributed throughout. The matrix, which can be thought of as the drug reservoir, is made up of silicone elastomers, polyurethanes, polyvinyl alcohol, and polyvinyl pyrrolidones. The drug molecules from this system dissociate from the crystal lattice, they solubilize and partition in the polymer matrix, and finally they diffuse through the matrix to the skin's surface [14]. These are the steps in the drug delivery process. If a drug is kept at saturation level in the fluid phase of a polymeric matrix and its diffusion rate within the matrix is significantly higher than its diffusion rate outside of it, the drug can be released from the matrix under zero-order kinetics.

Drug-in-Adhesive Matrix

These are the most basic systems, where an adhesive mixture containing the drug and enhancer is applied to a backing membrane (like a polyester film) to create an adhesive tape. These systems do have certain drawbacks, though:

1. They could interact chemically, which could disrupt the functioning of the adhesive, lead to the disintegration of active species, or create new chemical entities.
2. Different release rates for hydrophilic and hydrophobic drugs may be provided by the physicochemical properties of the drug and adhesive system; for example, silicone adhesives' lipophilicity restricts the solubility of hydrophilic drugs in the adhesive matrix.
3. The adhesive properties and drug release rates of a drug-in-adhesive system may change when additional excipients (Such as skin permeation enhancers) are added.

Drug in Micro reservoir: This TDDS combines matrix-dispersion and reservoir systems. The drug is suspended in

an aqueous solution of a water-soluble polymer to prepare the drug reservoir in this system. The drug-soluble solution is then uniformly dispersed in a lipophilic polymer to form multiple imperceptible, microscopic spheres of drug reservoirs [14-15]. By instantly cross-linking the polymer, the thermodynamically unstable dispersion is stabilized.

Composition of TDDS

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

Polymer matrix / Drug reservoir

The drug's release from the device is regulated by a polymer matrix, which is created by dispersing the drug in an appropriate polymer. The polymers used in TDDS should effectively release the medication throughout the device and be stable, compatible, and non-reactive with the drug and other parts of the system [16].

The following factors need to be taken into account when choosing the polymer for TDDS:

1. The polymer's chemical functionality, glass transition temperature, and molecular weight should all favor the drug's diffusion and release through it.
2. The polymer should possess the following qualities: stability, non-reactivity with the drug, ease of fabrication into the desired product, affordability, and non-toxicity or antagonistic effects on the host for both the polymer and its degradation products.

The following categories apply to the polymers used in TDDS:

Natural Polymers

Gelatin, chitosan, sodium carboxymethyl guar, polymerized rosin, cellulose acetate, methyl cellulose, ethyl cellulose, sodium carboxypropyl methyl cellulose (HPMC), sodium carboxymethyl guar (Sodium CMC), etc.

Artificial Polymers

Silicon rubber, ethylene vinyl acetate copolymer, polyethylene, polyethylene glycol, polyvinylpyrrolidone, eudragits, and polyvinyl alcohol, among others.

Drug

The medication that is incorporated into a TDDS must be carefully chosen. The following categories of drug parameters make up the perfect drug candidate for TDDS:

Physical-Chemical Characteristics

- The drug's molecular weight should be less than 1000 Daltons.
- The medication needs to be affinities for both hydrophilic and lipophilic phases. Severe partitioning characteristics make it difficult to successfully administer medication via the skin.
- The medication ought to have a low melting point.
- Since skin has a pH between 4.2 and 5.6, it is best to use solutions in this range to prevent skin damage. On the other hand, some medications absorb transdermally at pH levels where the unionised form of the medication predominates [17].

Biological Properties

- The medication should have a high potency, requiring a daily dosage of a few milligrams or less.
- The medication's half-life ought to be brief.
- The medication ought to be nonallergic and nonirritating.
- The drug shouldn't become permanently bonded in the subcutaneous tissue; instead, it should be incorporated into TDDS if it breaks down in the GIT or is rendered inactive by hepatic first-pass metabolism [17-18].

Permeation Enhancers

Chemical permeation enhancers

By introducing amphiphilic molecules or extracting lipids, they disturb the stratum corneum's highly ordered intercellular lipid bilayers, reversibly lowering the barrier resistance and permitting better drug penetration when administered in conjunction. The perfect enhancer would be inert, non-toxic, non-allergic, non-irritating, function unidirectionally, and get along with the medications and excipients. Their effectiveness seems to depend on the drug, the skin, and the concentration [18].

The most popular permeation enhancer is ethanol; other examples include essential oils or terpenes (Cineole, carveol, menthone, citral, menthol, d-limonene); dimethyl sulfoxide; propylene glycol; N-methyl-2-pyrrolidine; ethyl pyrrolidine; polyethylene glycol 400; isopropyl myristate; myristic acid; succinic acid; laurocapram (Azone); methyl laureate; lauric acid; sodium lauryl sulphate; non-ionic surfactant (spans, tweens); pluronic; oleic acid; diethylene glycol monomethyl ether; urea, etc.

Enhancers of Physical Permeation

Iontophoresis uses a low-density electric current to improve and regulate medication penetration through the skin. By applying high voltage pulses to the skin for a brief period of time, a process known as electroporation, new aqueous pathways for drug diffusion are created in the stratum corneum. A single low-energy pulse is applied by an Erbium: Yttrium-Aluminum-Garnet (Er: YAG) laser to ablate the stratum corneum layers. The stratum corneum is broken down by ultrasound or the use of microneedles, which opens up tiny passageways for medication penetration [19].

Other permeation enhancer

It has been reported that protransferosome gel, niosomes, ethanolic liposomes, and prodrug approach increase permeability by increasing drug solubilization and partitioning into the skin.

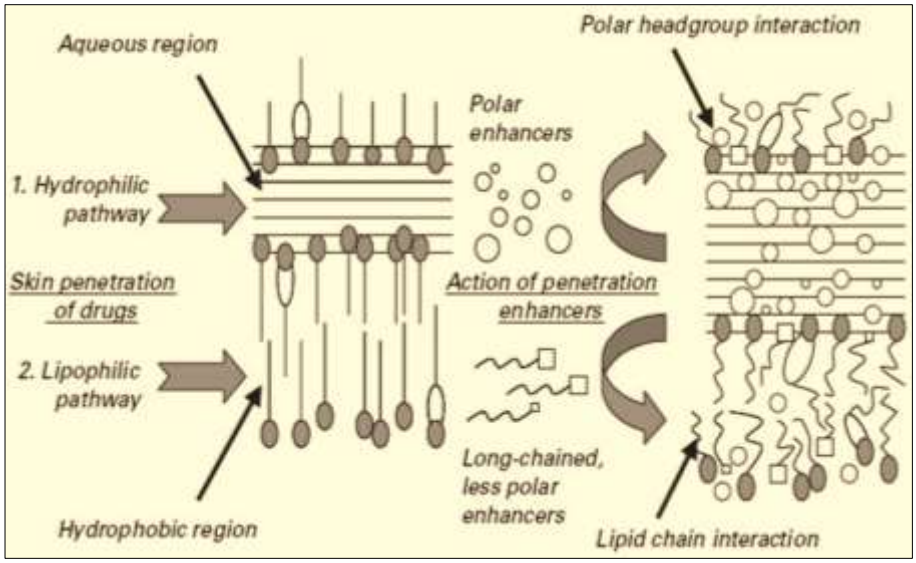

Fig 4: Hydrophilic and lipophilic pathways of drug penetration and action mode of penetration enhancers.

4) Pressure-Sensitive Adhesives (PSAs)

These are substances that, when removed with little force, leave no trace of their attachment to a substrate (Skin in TDDS). Only when these materials are in close proximity to one another do interatomic and intermolecular attractive forces form at the interface. If the material is pressure-sensitive, meaning it deforms under light pressure, then this degree of contact can be achieved. Because adhesives involve a liquid-like flow, they cause the skin's surface to become wet when pressure is applied, and they solidify in that state when pressure is released. PSAs in the commercial domain comprise silicones, polyacrylate, and polyisobutylene [20]. The backing membrane is responsible for giving TDDS its appearance, flexibility, and occlusion properties. For this reason, when designing a backing layer, the material's chemical resistance should be taken into serious consideration. It is important to take into account the compatibility of the excipients with the backing layer because extended contact between the two can lead to leaching of the excipients from the layer or diffusion of the excipients, drug, or penetration enhancer through the layer.

The backing with the highest moisture vapour transmission rate, the best oxygen transmission, and the lowest modulus or highest flexibility is the most appropriate. For systems that contain medication in a liquid or gel, the backing material needs to be heat-sealable in order to enable form-fill-seal, or fluid-tight, packaging of the drug reservoir. The backing with the lowest modulus or highest flexibility, good oxygen transmission, and high moisture vapour transmission rate will be the most comfortable. Examples of backing materials are films made of vinyl, polyethylene, polyester, aluminium, and polyolef. Some types of backing materials include vinyl, polyester films, polyester-polypropylene films, Co Tran 9722 film, polypropylene resin, polyethylene resin, polyurethylene, and ethylene-vinyl acetate.

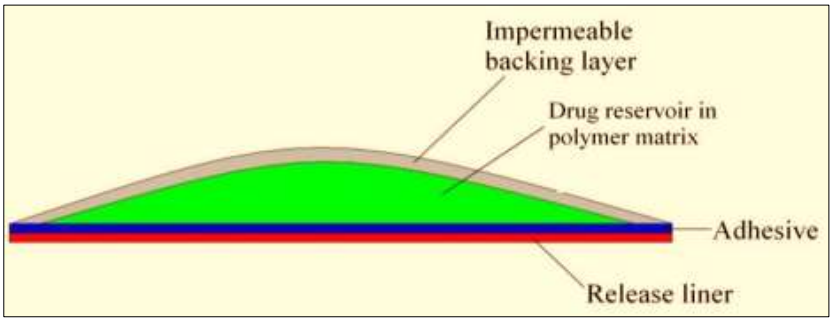

Fig 5: Matrix diffusion controlled film

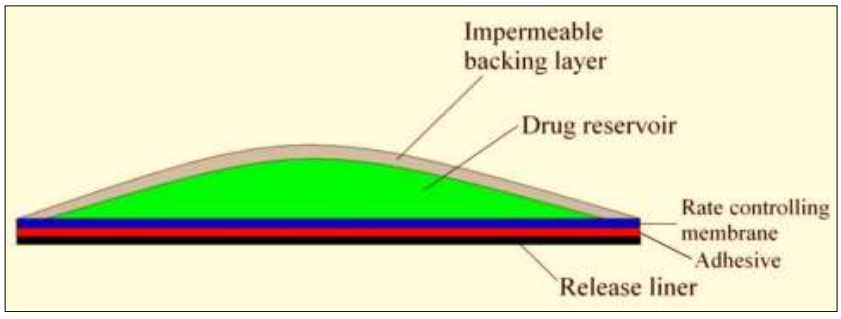

Fig 6: Membrane permeation controlled film

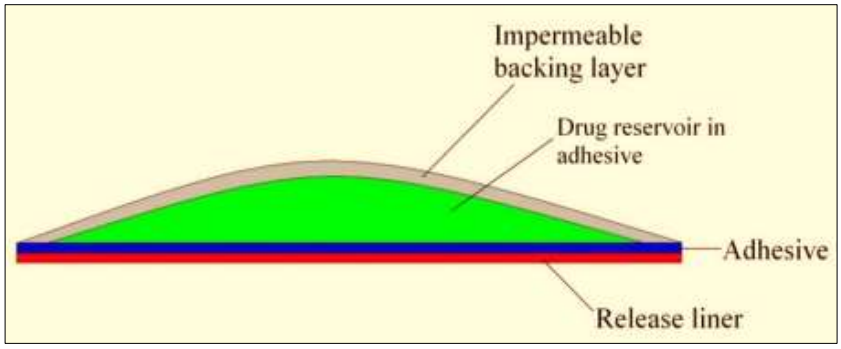

Fig 7: Adhesive diffusion controlled film

6) Release Liner

For the duration of its storage, the transdermal patch is shielded by a protective liner. The liner is taken off and thrown away before the patch is applied to the skin. Since the liner and transdermal patch are in close contact, it should be chemically inert. A release liner is composed of an occlusive base layer (Such as polyethylene or polyvinyl chloride) or a non-occlusive base layer (Such as paper fabric) and a silicon or Teflon release coating layer. For TDDS release liners, metalized laminates and polyester foil are also utilised [21].

7) Additional Excipients

To prepare the drug reservoir, a variety of solvents are used either singly or in combination, including water, ethanol, isopropyl myristate, isopropyl alcohol, and dichloromethane. In addition to the permeation enhancer, co-solvents such as ethanol and propylene glycol are employed. The trans-dermal patch gains its plasticity from plasticizers such as diethyl phthalate, dibutyl phthalate, glycerol, triethyl citrate, polyethylene glycol 400, EudraLex, and propylene glycol.

Product	Drug Reservoir	Backing	Membrane	Adhesive	Release Liner
Androderm (testosterone) TheraTech, Inc./Smith-Kline Beecham	Drug, alcohol, glyceryl monooleae, methyl laurate gelled with acrylic acid copolymer	Metallizd polyester/ ethylene methacryic acidcopolyer/ EVA	Polyethylen microporous membrane	Peripheral acrylic adhesive	Siliconecoated polyester
Estraderm (estradiol) Alza/Ciba Geigy	Drug and alcohol gelled with hydroxypropyl cellulose	Polyester, polyethylene composite	EVA copolymer with 5% vinyl acetate	Light mineral oil and PIB	Siliconized polyethylene terephthalate

Fig 8: Composition of some marketed transdermal therapeutic systems.

Evaluation Parameters of Transdermal Patches

The evaluation methods for transdermal dosage form can be classified into following type:

- Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

Physicochemical evaluation

Interaction Studies

The majority of pharmaceutical dosage forms include excipients as a necessary component. The compatibility of the drug excipients determines a formulation's stability. Only when the drug and excipients are compatible can a stable product be produced; consequently, it is important to identify any possible physical or chemical interaction that might have an impact on the drug's stability and bioavailability [22]. Compatibility studies are crucial to the development of new formulations if excipients that haven't been used in formulations with the active ingredient are used. By contrasting their physicochemical characteristics, interaction studies are conducted in chromatographic, thermal analysis, FTIR, and UV spectroscopy techniques.

Patch Thickness

A digital micrometre is used to measure the thickness of prepared drug-loaded patches at various points. In order to make sure that the thickness of the prepared patch is within the standard bounds, this also calculates the average thickness and standard deviation.

Weight Uniformity

The prepared patches are dried at 60 °C for four hours prior to the test. A designated patch area is divided into several sections and weighed using a digital balance. The individual weights are used to compute the average weight and standard deviation values.

Folding Endurance: From the prepared patches, a strip of a specific area is cut and folded over and over until it breaks. The folding endurance value is indicated by the number of times the film has been folded at the same location without breaking [22-23].

Percentage moisture contents

The percentage moisture content of the prepared films should be measured individually and then stored at room temperature for 24 hours in a desiccator filled with fused calcium chloride. The films must be reweighed after a 24-hour period in order to calculate the moisture content percentage using the formula below.

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

Percentage Moisture Uptake

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

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

Water Vapour Permeability (WVP)

An air-forced oven is swapped out for one with natural air circulation. Water Vapour Permeability can be calculated using the foam dressing method. The following can be used to calculate the WVP:

Formula: WVP=W/A

Where, WVP is expressed in gm/m per 24 hrs,
W is the amount of vapour permeated through the patch expressed in gm/24 hrs and **A** is the surface area of the exposure samples expressed in m2.

Drug Content

A predetermined portion of the prepared patch is dissolved in a volume-specific solvent that is appropriate. After passing the resultant solution through a filter medium, the drug content is examined using UV spectroscopy or an HPLC method. The average of three separate samples is represented by each value [23].

Content uniformity test

Ten patches are chosen, and each patch's content is decided. Transdermal patches pass the content uniformity test if nine out of ten have content that falls between 85% and 115% of the specified value, and one patch has content that falls between 75% and 125% of the specified value [23-24]. However, an additional twenty patches are tested for drug content if three of the patches have content within the range of 75% to 125%. The transdermal patches pass the test if the range of these 20 patches is between 85% and 115%.

Peel Adhesion Test

Peel adhesion is the force needed to remove an adhesive coating from a test substrate. The molecular weight of the adhesive polymer as well as the kind and quantity of additives added can be used to determine the peel adhesion properties. In this test, a backing membrane of choice or a stainless steel plate are covered with a single piece of tape. After that, the tape is pulled away from the substrate at a 180-degree angle, and the force needed to do so is calculated [24].

Thumb Tack Test

This qualitative test establishes the adhesive's tack property. This test finds the relative tack property by pressing the thumb against the adhesive.

Flatness test

Three longitudinal strips-one from the centre, one from the left side, and one from the right side-are cut from each film at different points for this test. Every strip's length is measured, and the percent constriction-0% constriction being equal to 100% flatness-is used to calculate the variation in length caused by non-uniformity in flatness.

Rolling ball tack test

This test determines a polymer's softness in relation to tack. A 7/16-inch-diameter stainless steel ball is released onto an inclined track in this test, causing it to roll down and make contact with the horizontal, upward-facing adhesive. The amount of tack, measured in inches, is the distance the ball travels along the adhesive [24-25].

Probe Tack Test

The adhesive is in contact with the tip of a clean probe that has a predetermined surface roughness in this test. The act of removing the probe after it has formed a bond with the adhesive causes it to break mechanically. The tack value, which is measured in grammes, is the force needed to remove the probe from the adhesive at a predetermined rate.

***In vitro* evaluation**

***In vitro* release studies**

The donor and receptor compartments of a Franz diffusion cell can be used to assess transdermal patches *in vitro*. The receptor compartment has an effective surface area of 1–5 cm2 and a volume of 5–12 ml. A magnetic bar continuously stirs the diffusion buffer at 600 rpm. A water jacket enclosing the receptor compartment allows thermo stated water to circulate, maintaining the temperature in the majority of the solution. A suitable method is used to analyse the drug content, and sink condition must be maintained [25].

***In vitro* Skin Permeation Studies**

To conduct this test, diffusion cells are used. An electric clipper is used to remove hair from the abdominal region of male Wistar rats weighing 200-250 g. After thoroughly cleaning the dermal side of the skin with distilled water to get rid of any blood vessels or adhering tissues, the skin is equilibrated in phosphate buffer (pH 7.4) or dissolution medium for an hour. It is then put on a magnetic stirrer with a tiny magnetic needle to ensure that the diffusing is distributed evenly.

***In vivo* Evaluation**

Transdermal patches can be assessed *in vivo* in relation to the most accurate representation of a drug's performance comes from *in vivo* tests. *In vivo* studies allow for the full exploration of variables that are not possible to account for

in vitro studies. Human volunteers or animal models can be used to evaluate TDDS *in vivo*.

Therapeutic Application of Transdermal Patches

- To ensure adequate drug delivery, histidine, a medication used to treat multiple sclerosis, can be formulated in TDDS with oleic acid acting as a permeation enhancer.
- TDDS-formulated non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac sodium and celecoxib, have the potential to mitigate gastric lesions linked to oral dosing.
- TDDS can be formulated for drugs with short biological half-lives and significant first-pass metabolism, such as captopril, verapamil, terbutaline sulphate, pinacidil, and propranolol that are used for long-term dosing in chronic diseases. This will prolong steady state plasma concentration [25-26].
- Drug delivery can be prolonged with hydrophobic polymers like ethyl cellulose, but faster drug release may be achieved with hydrophilic polymers like polyvinylpyrrolidone.
- The lipid disperse system of betahistine in gel formulation holds promise for the creation of an effective transdermal drug with controlled release.
- Co-solvent and enhancer may work in concert to improve the way peptides like thyrotropin-releasing hormones are delivered throughout the human skin.
- By using membrane-controlled total dosage distribution, prazosin hydrochloride can be administered in amounts that maintain the minimum effective concentration while preventing the hypotension that can result from high initial oral dosage.
- When compared to non-ion paired forms, diclofenac sodium, which is anionic at skin pH, can be formulated as ion pairs with enhancers that are oppositely charged to improve transdermal delivery.
- The TDDS formulation of zidovudine, an anti-Human Immunodeficiency Virus (Anti-HIV) medication, may mitigate the harmful effects linked to repeated higher oral dosages [26].

Future Aspects of Transdermal Patches

Future developments in drug delivery systems will involve microemulsion, liposomes, and niosomes. The purpose of this development is to enhance drug delivery, as the majority of classical formulation excipients have low inherent solubility. Numerous medications, including steroids, methotrexate, interferon, antifungals, and antibiotics, are being developed with the intention of being delivered. Transdermal patch sales are expected to rise in the future and have grown at a rate of 25% annually in recent years. As new devices are developed and the number of transdermal drugs that are marketed rises, this number will rise in the future.

As long as design advancements are made, transdermal analgesic delivery is expected to gain more and more traction. Studies are being conducted to improve efficacy and safety. To enhance practical aspects such as the patch wearer's experience and to offer more accurate drug delivery linked to longer duration of action. Other possible advancements include enhanced transdermal technology, which raises the energy of the drug molecules or modifies the skin barrier to increase drug flux through the skin by using mechanical energy. Many "active" transdermal technologies are being researched for a variety of medications following the successful design of patches utilising iontophoresis.

The three methods are as follows: sonophoresis, which uses low frequency ultrasonic energy to break the stratum corneum, electroporation, which uses brief, high-voltage electrical pulses to create temporary aqueous pores in the skin, and thermal energy. Drug flux across the skin has been studied in relation to magnetic energy, or magnetophoresis. The safest, easiest, and substitute method for systemic drug delivery is the transdermal drug delivery system (TDDS). Systemic drug delivery via skin has a number of benefits, including maintaining a steady drug level in blood plasma, fewer adverse effects, enhancing bioavailability by avoiding hepatic first pass metabolism, and boosting patient adherence to treatment regimen. Skin is now thought to be the safest route for administering drugs because it allows for continuous drug release into the bloodstream.

Conclusion

Scientists with high achievement rates are widely utilising their potential for controlled release. Transdermal delivery is an incredibly successful mode of administration for drugs with the proper combination of pharmacology and physical chemistry. Drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers, and solvents are some of the fundamental parts of a transdermal patch that are essential to the drug's skin release. Transdermal patches come in a variety of forms, including matrix, reservoir, membrane matrix hybrid, micro reservoir type, and drug-containing adhesive type. These patches are prepared using various techniques using the fundamental TDDS components. Following their preparation, transdermal patches are assessed for stability, physicochemical, *in vitro* permeation, animal, human, and skin irritation investigation. Future TDDS developments are probably going to concentrate on expanding the range of drugs that are available for use and giving more control over therapy regimens.

To ensure that the requirements of science, regulations, and consumers are satisfied, both subjective and objective analysis of these devices is necessary. Comparing the devices under development to traditional transdermal patch therapies, they are more expensive and intricate. Furthermore, the device's effects on the skin must be reversible because any long-term harm to the SC would cause it to lose its barrier qualities and, consequently, its ability to function as a protective organ. Data supporting the device's safety when worn on the skin for either short- or long-term use will also be needed for regulatory bodies. Therefore, it is necessary to address the novel drug delivery technologies' safety, efficacy, portability, user-friendliness, cost-effectiveness, and potential market if they are to succeed and rival those that are currently available on the market.

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