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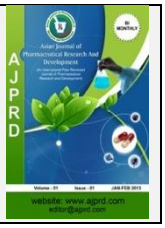

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Review Article

Transdermal Patches: Design and Evaluation

Bhandare Tejaswini S., Dr. Khaire Rahul D., Kathale Ankita A., Korade Payal B., Sankhe Lochani D., Ghuge Samiksha K.

Pravara Rural Education Society's College of Pharmacy (For Women's), Chinchol Nashik,Maharashtra,India.

A B S T R A C T

Transdermal drug delivery systems (TDDS) represent one of the most innovative and patient-friendly approaches to modern pharmacotherapy. Transdermal patches are medicated adhesive systems designed to deliver a specific dose of drug through the skin and directly into the systemic circulation, bypassing the gastrointestinal tract and hepatic first-pass metabolism. This review explores the design, mechanism, and evaluation of transdermal patches, highlighting the key components such as polymer matrices, permeation enhancers, and adhesives that influence drug release and absorption. Factors affecting drug permeation—including skin physiology, physicochemical properties of drugs, and formulation variables—are discussed in detail. Various types of patches such as single-layer, multi-layer, and microneedle-based systems are compared along with their applications in pain management, hormone therapy, and neurological disorders. The article further emphasizes recent advancements, including smart patches, dissolving microneedles, and 3D-printed delivery systems, which enhance therapeutic efficiency and patient compliance. Despite challenges like limited drug permeability and potential skin irritation, continuous innovations in nanotechnology, biomaterials, and active delivery mechanisms are expanding the scope of TDDS in personalized medicine.

Keywords: Transdermal drug delivery, Controlled release, Skin permeability, Drug diffusion, Patient compliance.

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*Address for Correspondence:

Bhandare Tejaswini S, Pravara Rural Education Society's College Of Pharmacy (For Women's),Chincholi Nashik,422102,(Maharashtra),India.

INTRODUCTION

A transdermal patch is a medicated adhesive system designed to deliver a precise dose of drug through the skin and directly into the bloodstream. The first FDA-approved patch appeared in 1981, and since then, a wide range of products have become available. Some common examples include scopolamine for motion sickness, clonidine and nitroglycerin for cardiovascular disorders, fentanyl for long-term pain relief, and nicotine to support smoking cessation.

What makes transdermal drug delivery special is its ability to provide steady, controlled release of medication. This is especially useful for drugs with short half-lives, as the patch maintains a constant level in the body while avoiding the sharp peaks and troughs seen with pills or injections. Compared to oral or injectable routes, TDDS reduces stress on the digestive system and liver, improves patient compliance, lowers the risk of accidental overdosing, and is far more convenient some patches need to be applied only once a week, making it easier for patients to stick to treatment.

Although the oral route remains the most common way to take medicine, it does have drawbacks. Drugs can be broken down by stomach acid, enzymes, or the liver's first-pass metabolism before they even reach circulation. To solve these problems, researchers such as Banker (1990), Chien (1992), and Guy (1996) advanced the concept of transdermal patches. These patches, available in different sizes and

sometimes containing multiple active ingredients, release therapeutic amounts of medication across the skin barrier and into systemic circulation by diffusion.

The skin itself is remarkable—it's the largest organ in the human body, covering 1.5 to 2 square meters in adults. Historically, people have long turned to the skin for healing. Ancient Egyptians and Babylonians (around 3000 BC) used salves, ointments, and plant-based poultices for medicinal and cosmetic purposes. While the ideaof using the skin as a drug delivery route is ancient, the modern transdermal system only gained traction in the late 20th century, when technology

finally allowed precise and reproducible systemic delivery.Today, transdermal patches are seen as an important step forward in drug delivery. Their effectiveness is often judged by looking at blood concentration–time profiles, comparing them to oral or injectable administration. Beyond systemic therapy, they're also used for local effects, such as providing localized anaesthesia or reducing inflammation. While topical delivery focuses only on skin-related conditions, transdermal systems bridge the gap by delivering drugs deep into the body for systemic action.

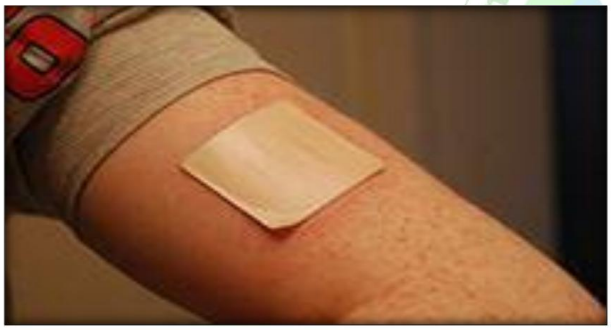

Figure :1 Transdermal patches

What is transdermal patches?

A transdermal patch is a medicated adhesive applied to the skin that delivers a specific dose of drug directly into the bloodstream. Unlike oral, intravenous, or intramuscular routes, these patches provide a steady, controlled release of medication. This is usually achieved either by using a porous membrane over a drug reservoir or by body heat slowly melting thin layers of medication embedded in the adhesive. The main challenge with this system is the skin itself—it's an excellent protective barrier, which means only drugs with molecules small enough to pass through can be effectively delivered.

The very first prescription patch was approved by the U.S. FDA in December 1979, designed to release scopolamine for the treatment of motion sickness. Since then, patch technology has evolved significantly. One major innovation has been the development of microneedle transdermal patches (MNPs). These patches contain tiny needle-like structures that painlessly pierce the skin's outer layer, allowing a wider variety of drugs—including larger molecules that normally couldn't penetrate—to be delivered without the need for complex micronization.MNPs not only maintain the benefits of controlled release but are also easy to apply without needing medical assistance. Advances in this technology have even allowed targeted applications—for instance, cosmetic microneedle patches used as skin whiteners for facial use. Beyond the skin, researchers are exploring microneedle patches that can deliver drugs through other tissues, like the lining of the mouth or digestive tract, offering faster and more precise delivery to specific areas of the body. The schematic diagram of transdermal patches are shown in figure 1.1 and 1.2.

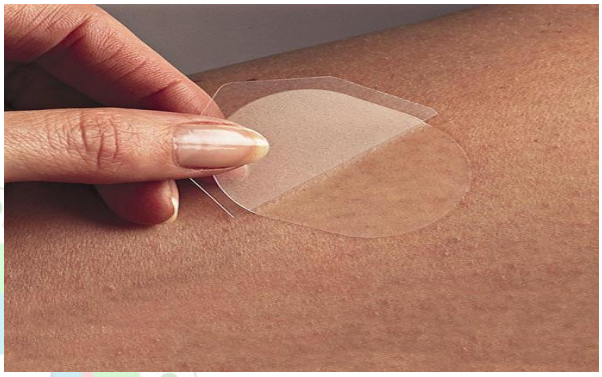

Figure: 2 Medical Transdermal Patches

Transdermal Patch Design

Transportation of drug across the skin is affected by various factors, such as skin permeability, area, and duration of application, as well as metabolic activity of the skin (i.e., first pass metabolism) Every drug has its own unique characteristics that influence how well it can be delivered through the skin. For effective absorption, the drug should ideally be non-ionic and moderately lipophilic, which helps it pass through the skin barrier more easily. Larger molecules—typically those over 500 Daltons—struggle to penetrate the outer layer of skin (the stratum corneum). In addition, the drug works best for transdermal delivery when the required daily dose is fairly small, usually under 10 mgss. of the drug should also be less than 10 mg per day.

The main components to a transdermal patch are:

1. Polymer matrix

The polymer acts as the backbone of the patch, controlling how the drug is released. It must be chemically stable, non-reactive, safe, and affordable.

Natural Polymers: cellulose derivatives, zein, gelatin, shellac, waxes, proteins, gums, natural rubber, starch.

Synthetic elastomers

Synthetic elastomers include materials likepolybutadiene, hydrin rubber, polysiloxane, silicone rubber, nitrile, acrylonitrile, butyl rubber, styrene-butadiene rubber, and neoprene**,** which are commonly used in transdermal patches for their flexibility, durability, and ability to control drug release.

Synthetic Polymers: polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, epoxy resins.

2. **Drug**
The transdermal route is especially useful for drugs that undergo extensive first-pass metabolism, have a short half-life, or possess a narrow therapeutic window. Examples include fentanyl and nitroglycerin.

3. **Permeation Enhancers**
These substances temporarily increase the skin's permeability to allow more drug to pass through the stratum corneum. They are mainly of three types:

1. Lipophilic solvents
2. Surface-active agents
3. Two-component systems (e.g., dimethyl sulfoxide, DMSO)

4. **Adhesive**
Ensures the patch sticks securely to the skin while sometimes also aiding drug permeation.

5. **Backing Laminate**

A protective outer layer that provides flexibility and prevents drug loss. Examples: vinyl, polyethylene.

6. **Release Laminate**

A protective sheet that covers the patch during storage and is removed just before application.

7. **Other Excipients**
Such as plasticizers and solvents, used to enhance flexibility, stability, or drug release. The schematic diagram of Basic Components of medical transdermal patches are shown in figure 1.3

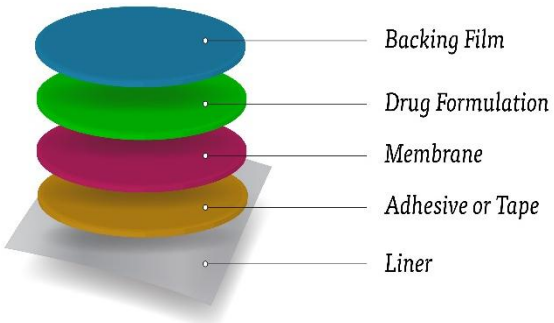

Figure: 3 Basic Components of medical transdermal patches

Routes of Drug Penetration through Skin

Drugs can enter the body through:

- Sweat ducts
- Hair follicles
- Sebaceous glands
- Or directly across the stratum corneum (the most significant route).

The Stratum Corneum (Skin Barrier)

The stratum corneum is the outermost layer of the epidermis, made up of flat, keratin-filled dead cells called corneocytes, which are constantly shed and replaced. It contains about 10–15 layers of corneocytes and is roughly 10–15 µm thick when dry, swelling to 40 µm when hydrated.

This layer is often described as a "brick and mortar" structure:

- **Bricks** → keratin-rich corneocytes
- **Mortar** → an intercellular lipid matrix made of ceramides, fatty acids, triglycerides, cholesterol, and wax esters.

The lipid bilayers formed in this matrix are crucial for barrier function, making drug penetration challenging. Water in the stratum corneum also helps keep it flexible and prevents cracking, while contributing to the natural moisturizing factor (NMF) that maintains skin suppleness.

Drug Permeation Pathways

Within the stratum corneum, drugs can follow two main routes:

- **Transcellular Route:** The drug moves directly through keratinocytes, but must repeatedly pass across alternating hydrophilic and lipophilic domains. This is energy-demanding and not efficient for most drugs.
- **Intercellular Route:** The drug travels through the lipid layers that surround the cells. This is now recognized as the major pathway for most drugs crossing the skin.

Table 1: Ideal Properties of Drugs

S No.	Parameter	Desired Property
1	Dose	Should be low, ideally under 20 mg per day.
2	Half-life	Around 10 hours or less.
3	Molecular Weight	Should be below 400 Daltons.
4	Skin Permeability	Should have good permeability, above 0.5×10^{-3} cm/h.
5	Skin Reaction	Must be non-irritating and should not cause sensitization.
6	Oral Bioavailability	Should be low.

Factors affecting drug permeation through the Skin

pH

The skin's pH is usually acidic, between pH 4 and pH 6, while the internal environment is nearly neutral, ranging from pH 7 to pH 9. It was once believed that an acidic pH offered a defense against microbes. Recent studies show it also helps enzymes function effectively in synthesizing and maintaining skin. The skin's pH comes from water-soluble substances in the stratum corneum, sweat, sebum, and eliminated carbon dioxide. The skin's pH regulates the permeability barrier and maintains the integrity and cohesion of the stratum corneum. It affects how much unionized drug is available for absorption. According to the pH-partition hypothesis, only the unionized form of a drug can cross the lipid barrier in enough quantity. A very low or very high pH in formulations can harm the skin.

Temperature

In theory, warmer skin should allow for better drug penetration. Heat increases the kinetic energy of proteins, lipids, carbohydrates in the cell membrane, and the drug molecules. This enhances the movement of the drug into the dermis, but may reduce local delivery. Studies show that a temperature change of about 5°C is needed to alter cell membrane permeability.

Molecular weight

Percutaneous absorption decreases as the molecular weight of a drug increases. This can affect the drug's diffusion coefficient. For passive diffusion in transdermal drug delivery, a molecular weight under 500 Daltons is preferred; however, using penetration enhancers can increase the rate of permeation**.**

Partition coefficient

Log P or partition coefficient is essential for understanding how drugs distribute within the body to achieve their effects. Hydrophilic drugs are poorly absorbed when applied to the skin because of their low ability to pass through the lipid matrix of the stratum corneum. Cutaneous blood flow quickly removes the absorbed drug, leading to low tissue levels. Both water and lipid-soluble drugs are absorbed well through the skin. The intercellular route works for drugs with intermediate partition coefficients (log K 1 to 3) and high lipophilicity. The transcellular route is more common for hydrophilic molecules (log K < 1).

Biotransformation of drugs in the skin

There is strong evidence of enzymes in the skin, including those from the CYP family, which can transform drugs that enter the skin. This transformation can be beneficial, turning a prodrug into an active form, or it may lower the drug's bioavailability. However, it is important to note that this cutaneous first-pass effect is less significant than that seen in the liver.

Cutaneous microcirculation

Better drug absorption through increased tissue perfusion depends on various factors, including the structure of the vessel networks in the skin. The organization of cutaneous microcirculation includes two plexuses of arterioles: an upper horizontal plexus in the papillary dermis just beneath the epidermis, and a lower horizontal plexus in the deep dermis at the border with the subcutaneous tissue. Each plexus branches into networks of capillaries.

Hydration

Hydrating the stratum corneum usually speeds up the penetration of most drugs. It does this by opening the compact structure of the outer layer of skin, making drugs more available. Impermeable films can prevent the loss of water from the skin, thereby enhancing hydration and reducing the distance that drugs must diffuse. The rate of drug transport through the skin depends on skin hydration, partitioning, transport across the stratum corneum, and concentration gradients. Skin hydration can be achieved simply by covering it with plastic sheeting, which leads to sweat accumulation and opens up densely packed skin cells, increasing skin porosity.

Age

Studies show that there is a slight increase in the number of cell layers in the stratum corneum, mainly in males, while there is a decrease in the thickness and number of cells in the cellular epidermis. Skin surface pH changes with age. The amount of unbound water in the skin increases with age, potentially delaying the penetration of hydrophilic drugs. Additionally, the levels of important lipids, especially ceramides, decrease as people age.

Gender

Research indicates that there is no significant difference between males and females in terms of thickness or the number of cell layers in the stratum corneum. However, males tend to have a thicker cellular epidermis compared to females.

Body site

Studies show that the genital areas have the fewest cells in the stratum corneum, while the heels have the most.

Sun exposure

The stratum corneum is thicker in sun-exposed areas and thinner in sun-protected areas.

Blood flow

Drug absorption can be limited by blood flow in the dermis. For example, if a drug with vasoconstrictive properties is administered via another route, it can significantly impact blood flow through the skin, affecting drug clearance in transdermal delivery.

Skin condition

In atopic dermatitis, the stratum corneum has a reduced ability to hold water, making the skin dry and less elastic. Changes in intercellular lipid composition, with increased cholesterol and lower ceramide levels, lead to a decrease in barrier function. The pH of the skin is also higher compared to healthy skin.

Advantages

1. Transdermal patches are very convenient since they usually need to be applied only once a week. This simple dosing schedule makes it easier for patients to stick to their treatment.
2. They are especially suitable for drugs that need to maintain a steady level in the blood.
3. This method is a good alternative for patients who have difficulty swallowing pills or cannot tolerate oral medicines.
4. It is highly useful for patients who are nauseated or unconscious, as no swallowing is required.
5. Medicines that tend to upset the stomach are good candidates because the drug bypasses the digestive system.
6. Drugs that are normally broken down by stomach acids or digestive enzymes can be better absorbed through the skin.
7. Transdermal delivery also avoids first-pass metabolism in the liver, which can otherwise reduce the effectiveness of oral medicines.

Disadvantages

1. The patch can sometimes cause irritation on the skin where it is applied.
2. Side effects like redness, itching, or slight swelling may occur, which can be due to the drug itself, the adhesive, or other ingredients in the patch.
3. In some cases, allergic reactions may develop.
4. Only drugs with a small molecular size (less than 500 Da) can effectively pass through the skin.
5. For a drug to be absorbed properly, it must dissolve well in both water and fats, with a balance reflected by a log P value between 1 and 3. This ensures it can move through the skin layers smoothly.

Types of Transdermal Patches

1. Single-Layer Drug-in-Adhesive Patches

In this system, the drug is mixed directly into a single adhesive polymer layer. This adhesive serves two purposes: it sticks the patch to the skin and also controls drug release. Beneath this adhesive is a non-permeable backing laminate for support. The patch is further protected by a temporary liner that is removed before use.

Example: methylphenidate.

2. Multi-Layer Drug-in-Adhesive Patches

These patches are similar to the single-layer type but contain more than one adhesive layer. Typically, one layer provides immediate drug release, while another offers controlled release over a longer period. Sometimes, the two adhesive layers are separated by a membrane. The patch also includes a backing laminate and a protective liner. **Applications**: Used for pain management, hormone therapy, and smoking cessation. Drug delivery can last up to 7 days.

3. Vapor Transdermal Patches

Vapor patches release essential oils or other vapors from a single adhesive layer designed for vapor delivery. The adhesive sticks the patch to the skin and also allows vapor to escape.

Examples:

- **Nicoderm CQ®** (nicotine vapor patch with essential oils to help quit smoking).

- **Tacura® vapor patches** (used for decongestion). Other vapor patches may help improve sleep, reduce cigarette consumption, or act as antidepressant/sedative aids. These typically release vapor for up to 6 hours.

4. Membrane-Moderated Reservoir Patches

This type of patch contains a drug reservoir enclosed between a backing layer and a rate-controlling polymer membrane. The backing is usually an impermeable metallic laminate, while the polymeric membrane regulates how much drug diffuses over time.
Examples:

- **Transdermal Nitroglycerin** (nitroglycerin, 1-day application).
- **Transdermal Scopolamine** (scopolamine, 3-day application).
- **Catapres®** (clonidine, 7-day application).

5. Micro-Reservoir Transdermal Patches

These combine features of both matrix and reservoir systems. The drug is first suspended in an aqueous polymer solution and then dispersed within a lipophilic polymer using strong mechanical force. This creates thousands of microscopic spheres that trap the drug, ensuring stable dispersion. To further maintain stability, cross-linking agents are often added.
Drug release usually follows zero-order kinetics, meaning a constant and steady drug level is maintained in the blood. Shown in fig.1.4

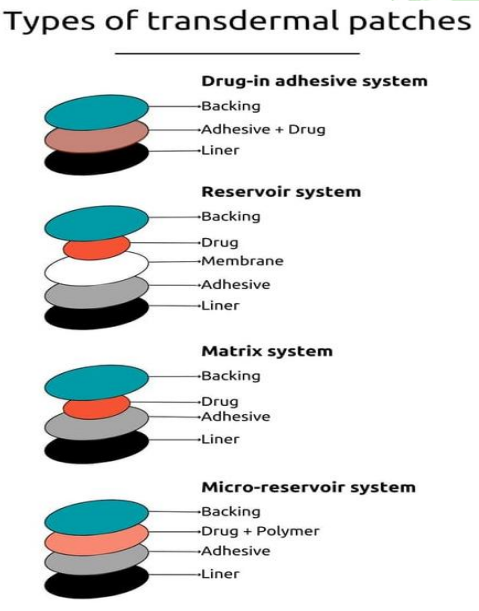

Figure: 4 Types of patches

Drug Properties Ideal for Transdermal Patches

To ensure a patch is reliable and effective, certain physical characteristics are analyzed:

1. **Organoleptic Evaluation**

   The patch is first examined visually and by simple sensory checks for its color, odor, flexibility, and surface texture**.**

2. **Thickness Measurement**

   Using a caliper, the thickness of the patch is checked at five different points. The readings are then averaged to get the final thickness value.

3. **Weight Uniformity**

   Each patch is weighed individually on a digital balance. The average weight is calculated to confirm that all patches are consistent in their formulation. The schematic diagram of layers of transdermal patches are shown in figure 1.5

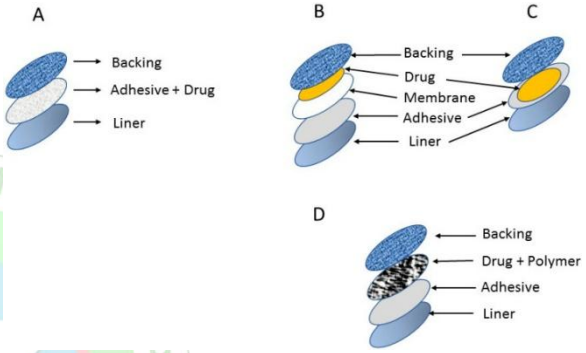

Figure: 5 Layers of patches

Mechanism of Action of Transdermal Patches

The main challenge in transdermal drug delivery is getting the drug to pass through the skin's natural barrier. The outermost layer, called the stratum corneum, is the thickest layer of the skin and is made up of multiple layers of keratin-rich cells called corneocytes. It has two distinct regions that the drug must pass through:

1. **Aqueous region**: Surrounds the keratin filaments.
2. **Lipid matrix**: Found between the keratin filaments.

To make drugs effective via the transdermal route, they must diffuse through both these regions.

Recent advancements have introduced several enhancement methods to improve drug delivery through the skin:

- **Microneedles**: Tiny needles, either hollow or solid, loaded with the drug. They penetrate the stratum corneum painlessly and can deliver drugs with higher molecular weights.
- **Iontophoresis**: Uses a low-voltage electrical current to push charged drug particles through the skin. The drug release can be controlled either by a microprocessor or the patient.
- **Thermal Method**: Applying gentle heat opens tiny pores in the skin, making it easier for drugs to diffuse.

- **Electroporation:** A brief high-voltage pulse creates temporary pores in the skin to allow drug passage.
- **Conventional Chemical Enhancers**: Special chemicals applied to the skin increase permeability or alter the drug's properties to improve absorption.
- **Ultrasound**: Sound waves temporarily disrupt the stratum corneum, enhancing drug penetration.

Applications of Transdermal Patches

Transdermal patches are used for a wide variety of medical purposes, providing controlled and convenient drug delivery:

- **Nicotine Patches:** The most popular transdermal patch in the U.S., it delivers controlled doses of nicotine to help people quit smoking. The first vapor-based patch for smoking cessation was introduced in Europe in 2007.
- **Pain Management:** Strong opioids like fentanyl (Duragesic®) and buprenorphine (BuTrans®) are available as patches to provide continuous pain relief.
- **Hormone Therapy:**
  1. Estrogen patches are used to treat menopausal symptoms, post-menopausal osteoporosis, and for hormone therapy in transgender women.
  2. Contraceptive patches (Ortho Evra® / Evra®) provide an alternative to oral birth control.
  3. Testosterone patches are available for men (Androderm®) and women (Intrinsa®).
- **Cardiovascular Therapy:**
  1. Nitroglycerin patches are used to manage angina as an alternative to sublingual tablets.
  2. Clonidine patches provide antihypertensive therapy.
- **Motion Sickness & Neurological Drugs:**
  1. Transdermal scopolamine helps prevent motion sickness.
  2. Rivastigmine patches (Exelon®) are used to treat Alzheimer's disease.
  3. Daytrana®, a methylphenidate patch, is used for ADHD management.
  4. Secuado®, a patch for the atypical antipsychotic asenapine, treats psychiatric conditions.
- **Antidepressants:**

Emsam®, a patch containing the MAOI selegiline, was the first transdermal antidepressant approved in the U.S. in 2006.

- **Nutritional & Stimulant Patches:**
  1. 5-Hydroxytryptophan (5-HTP) patches were introduced in the U.K. in 2014.
  2. Caffeine patches deliver caffeine through the skin for stimulation.
- **Innovative Medical Applications:**

In 2019, Robert S. Langer and his team developed a technique where patches could deliver a "quantum dot dye" with vaccines to invisibly label individuals and store medical information subcutaneously. This innovation could help track health records in areas with limited medical infrastructure.

Adverse Effects of Transdermal Patches

While transdermal patches are a popular and convenient way to deliver medications, they can sometimes cause skin-related side effects. Common reactions include:

1. Irritation at the application site, such as redness, itching, or mild burns.
2. Allergic reactions, which may occur due to the drug itself or components of the patch like adhesives and other ingredients.
3. Contact dermatitis or allergic contact dermatitis, often triggered by the patch materials or the active drug.
4. Improper use of patches can also lead to more serious issues: applying multiple patches when only one is prescribed or leaving a patch on longer than recommended can increase drug absorption, raising the risk of overdose or toxicity.

Anatomy of Skin

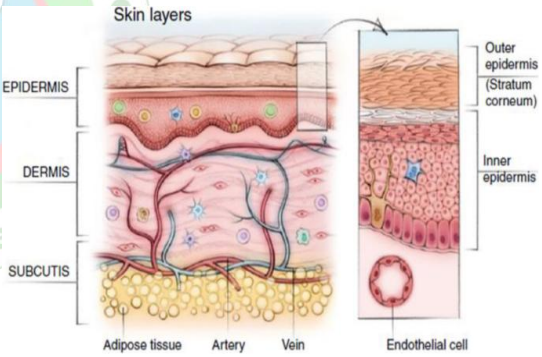

Figure: 6 Schematic illustration of the skin anatomical structure

Indeed, the skin is the body's largest organ, acting as a crucial protective barrier safeguarding the body from a range of external factors and potential threats. Its large surface area, approximately 1.7 square meters in an average person, allows it to effectively shield the body from microorganisms, ultraviolet (UV) radiation, chemicals, allergens, and water loss. This protective function is vital for maintaining overall health and well-being.8,12,13 Additionally, the skin also plays a role in regulating body temperature, sensation, and the synthesis of vitamin D through exposure to sunlight. Taking care of the skin is essential to support its functions and maintain good health.

The skin is commonly categorized into three primary layers: The outermost layer, known as the epidermis; (b) The middle

layer, referred to as the dermis; and (c) The innermost layer, called the hypodermis.

Here's a brief overview of each layer

The structure of human skin can be categorized into four main layer

1. The epidermis
2. The viable epidermis
3. Anon-viable epidermis (Stratum corneum)
4. The over lying dermis
5. The inner most subcutaneous fat layer (Hypodermis)

The epidermis

The epidermis is a renewing, stratified squamous epithelium covering the whole outer surface of the body and constituted primarily of two elements: the living or viable cells of the malpighian layer (collectively referred to as viable epidermis) and dead cells of the stratum corneum, commonly known as the horny layer. The epidermis constitutes the skin's outermost layer. It provides a waterproof barrier and contains no blood vessels. The cells in the epidermis include keratinocytes, which produce the protein keratin and help make the skin tough and protective. The epidermis includes melanocytes, responsible for skin color, and Langerhans cells, integral components of the immune system. The epidermis has several sub- layers, including:

1. Stratum corneum
2. Stratum granulosum
3. Stratum spinosum
4. Stratum basale

It's different thickness in different parts of our body, about 0.8 mm thick on our palms and the soles of our feet.13 The epidermis is made up of layers of skin cells. Most of these cells are called keratinocytes. They make up about 95% of the cells in the epidermis. The epidermis houses various cell types, including melanocytes, Langerhans cells, and Merkel cells.

On top of the epidermis, there's a super thin layer called the stratum corneum. It's the very surface of our skin and touches everything around us. This layer is special because it keeps our body safe. Its thickness and how much water it has are important. The stratum corneum is made mainly of tough proteins (70% keratin) and some fats (20% lipid).15 Water in this layer is connected to these proteins

Stratum corneum

The stratum corneum is the outermost layer of the skin, and it is the first line of defense of our body's largest organ. This particular layer is part of the epidermis, which is the outermost layer that does a number of important things. The structure of this layer consists mainly of dead skin cells, which are no longer alive but are still very important to the health of the skin. These cells have a flat and hard structure, mainly because they are packed with a fibrous protein called keratin, which is a major component of their strength and protective properties (Zhang & Fan, 2021). The main function of the stratum corneum is to protect our body from harmful germs, possibly damaging chemicals, and excessive water loss, thereby keeping us hydrated. It functions very much like a strong shield that protects the skin from the outside world. With time, the old cells that live in this protective layer slowly shed away, giving way to new fresh cells that move from the deeper layers of the skin below. This ongoing process is necessary, as this layer is very important in keeping our skin safe, intact, and healthy.

Viable epidermis

The viable epidermis is a living and essential component of the epidermis, situated directly beneath the outermost layer, consisting of dead cells referred to as the stratum corneum. This essential layer consists of a number of living strata of cells that are accountable for the processes of skin growth and self-repair. Other than the role they play in growth and repair, these living cells are also crucially involved in the formation of new skin, the protection from infection, and the control of moisture, keeping the skin strong and resistant. In contrast to the stratum corneum, consisting solely of non-living cells, the viable epidermis does consist of actively functioning cells; however, the fact must be pointed out that this layer does not have any blood vessels. The viable epidermis, therefore, plays a crucial and essential role in our overall skin health and protective processes.

Dermis

Dermis is the middle layer of the skin that is just underneath the epidermis. The dermis is the active part of our skin. The layer is alive and contains very essential things such as blood vessels, nerves, sweat glands, and hair roots. The dermis makes us sense touch, pain, and heat. It makes our skin firm and elastic as it contains collagen and elastin fibers. The dermis is what heals cuts and wounds if we get one. It is very essential in maintaining our skin healthy, well-nourished, and well-connected to the rest of the body.

The dermis is located beneath the epidermis which is 3 to 5 mm and is thicker than the epidermis. The dermis is responsible for providing nutrients to the epidermis and housing the skin's appendages and sensory receptors.

It comprises diverse structures, such as:

1. Blood vessels
2. Hair follicles
3. Sweat glands
4. Sebaceous glands
5. Nerve endings
6. Collagen and elastin fibers.

Tiny blood vessels called capillaries are really close to the skin surface, about 0.2 mm away. These capillaries act like drains, pulling away most of the stuff that tries to get through the skin. This is essential because it keeps the concentration of substances that enter the skin very low. This difference in concentration between the inside and outside of the skin helps push things through it.

When it comes to delivering medicines through the skin, this layer is like a gel made mostly of water. For most medicines that dissolve in water, this layer doesn't offer much resistance, making it easier for the medicines to pass through. However, if a medicine is oily (like some lotions or creams), this layer can create more of a challenge for it to get through.

Hypodermis

The hypodermis is the lower skin layer, or the subcutaneous layer. It lies beneath the dermis and consists of fat and connective tissue. The layer acts as a cushion, which keeps our bones and muscles safe from bumps and injuries. The hypodermis fat heats the body and stores energy. It holds the skin in place against the muscles beneath and gives the skin a soft and flexible texture. Thus, the hypodermis is extremely important in protection, warmth, and support.

When medicines are applied to the skin, like creams or patches, they have to go through these three layers to get into our bloodstream. For some medicines, they need to go even deeper, reaching our body's circulation. But for most skin treatments, they just need to get through the outermost layer, the stratum corneum, and stay in the skin layers to work effectively. The schematic diagram of anatomy of skin is shown in fig 1.6

Recent Advancement of Transdermal Patch:

Traditional transdermal patches serve only two purposes: storage and release of drugs. While this method has some advantages, traditional patching has many challenges and drawbacks, for example limited dosage or low release. To date, there have been several advances in the field of transdermal drug delivery. These include the design of novel patches, which include the ability to sense and release drugs accurately, higher loading, and enhanced penetration and release of drugs. Overall, the field of transdermal drug delivery is an active area of research and development, with many exciting new developments on the horizon, as discussed below.

Smart Patches:

Sensors and other technology included into smart patches allow them to track patient status and modify medication distribution as necessary. A smart insulin-releasing patch made of 121 microneedles with nanoparticles was the product of research and development. The patch enters the interstitial fluid between subcutaneous skin cells without causing any discomfort. Insulin and the glucose-sensing enzyme glucose oxidase, which changes glucose into gluconate, are found in the nanoparticles in each needle. Hypoxia-responsive polymers envelop these molecules. Figure 4 illustrates this. Medicina 2023, 59, x for peer reviews the hypoxia-responsive polymer detects the oxygen 7 of 22 deprived environment created by increased glucose oxidase activity in response to elevated glucose, which causes the nanoparticles to degrade and release insulin.

Dissolving/Degradable Patches:

These patches don't need to be taken off and thrown away because they are made to disintegrate on the skin. These patches are often composed of biodegradable substances that the body absorbs after usage. In a 2019 proof-of-concept study, scientists used a dissolving patch to successfully give the antibiotic gentamicin to a mouse model of bacterial illness.

Three-Dimensional (3D)-Printed Patches:

Transdermal patches that are personalized to each patient's needs can be made using 3D printing technology.[25] The use of a 3D-printed patch for wound healing is a nice example. Gelatin methacrylate was examined as a potential solution with adjustable physical characteristics in a research by Jang. Because hydrogel inks shear thin, which contains a peptide that mimics vascular endothelial growth factor (VEGF), was effectively printed using a 3D bio-printer. The hydrogel patch's three-dimensional structure exhibited significant porosity and water-absorption capabilities. The 3D Gel-MA-VEGF hydrogel patch may be utilized as a wound dressing because the VEGF peptide, which is gradually released from hydrogel patches, can encourage cell survival, proliferation, and tubular structure creation.

High Loading/Release Patches:

A new pressure-sensitive adhesive (PSA) modified with hydroxyphenyl (HP) was created to enhance drug-polymer miscibility and regulate drug release in transdermal patches. Because of the reversible and somewhat strong dual-ionic H-bonds that exist between HP-PSA and pharmaceuticals of the R (3)N and R (2) NH types, patches can greatly enhance drug loading and regulate drug release rates without altering the overall release profile. The HP-PSA-based high-load patch enhanced the area under the concentration-time curve (AUC), prevented abrupt release, and raised the average dwell duration by more than six times while achieving sustained drug concentrations in plasma. The creation of long-acting transdermal drug delivery systems is aided by HP-PSA's excellent drug loading efficiency and regulated drug release capabilities. In order to deliver non-steroidal anti-inflammatory drugs (NSAIDs), researchers also created a high-capacity, high-release transdermal patch using COOH polyacrylate polymer (PA-1). This showed that ion-ion

repulsion by decreasing hydrogen bonding can be a practical method of creating large-capacity, high-emission patches

Principles of transdermal permeation

Earlier, skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration (Aggarwal 2009; Kasting et al., 1992). Skin is the most intensive and readily accessible organ of the body as only a fraction of milimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and permeation through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ

Routes of Drug Penetration Through Skin

Drug penetration across the skin can occur through two routes: the trans epidermal pathway, which involves penetration through the epidermis, and the trans appendegeal pathway, which involves penetration through appendages such as hair follicles and sweat glands.

Trans epidermal Pathway: In this pathway, drugs permeate through the skin's outermost layer, known as the stratum corneum. This layer is a structurally complex, multi-layered, and multi-cellular barrier.

Intra-cellular Route: Some drugs can go through specific skin cells called corneocytes, which are specialized skin cells. This route is for substances that dissolve in water (hydrophilic or polar solutes).

Inter-cellular Route: Other drugs can move through the spaces between these skin cells. This route is for substances that dissolve in fats (lipophilic or non-polar solutes). They travel through the continuous fatty layer of the skin.

Trans appendegeal Pathway: This pathway involves drugs passing through sweat glands and hair follicles in the skin.

Sweat Glands and Hair Follicles: These are like tiny tunnels or openings in the skin that some substances can travel through.

So, when drugs need to get into our body through the skin, they can either go through the outer layer of skin cells or use these tiny tunnels created by sweat glands and hair follicles. Each pathway has specific characteristics, allowing different types of substances to enter the body.

MATERIALS AND METHODS

Materials

The pharmaceutical used in the research was Ketorolac, which was obtained from Cipla Pharmaceuticals Pvt. Ltd., Baddi, Himachal Pradesh (India) and different polymers, excipients and solvents from authentic suppliers.

Methods

Pre-formulation Studies

Solubility Study

Solubility of Ketorolac Tromethamine was studied in different solvents such as hydrochloric acid (HCl), ethanol, methanol, water, and phosphate buffer (pH 6.8). The investigation has been carried out to identify the most appropriate solvent for formulation development and to provide better dissolution and permeability of the drug in the transdermal system .

Determination of Melting Point

Melting point of Ketorolac Tromethamine was determined to determine its purity and thermal stability. A minute quantity of the drug was filled in a capillary tube closed at one end and strapped onto a thermometer with the help of a string. The capillary tube was submerged in Thiel's tube, and the temperature at which the drug melted from solid to liquid was noted. The determination was made under ever-mounting pressure to achieve precision since the melting point is an important physicochemical parameter in drug characterization.

Preparation of Standard Calibration Curve

a. Determination of λmax

The maximum absorption wavelength (λmax) determination of Ketorolac Tromethamine was done with a UV-visible spectrophotometer. An appropriate solvent-based standard solution of Ketorolac Tromethamine was prepared at a concentration of 20 µg/mL, according to Beer-Lambert's law. The solution was scanned from the wavelength range of 200–400 nm to detect the absorption maximum. The UV spectrum recorded showed the maximum absorbance peak at 322 nm, which was chosen as the analytical wavelength (λmax) spectrophotometric analysis.

b. Preparation of Calibration Curve

Ketorolac Tromethamine calibration curve was developed by making a stock solution of 1000 µg/mL in phosphate buffer (pH 6.8). Working stock solution of 10 µg/mL was prepared and then diluted to get standard concentrations of 2, 5, 10, 12, and 15 µg/mL. The absorbance of the solutions was determined at 322 nm with a UV-visible spectrophotometer,

and calibration curve was constructed in order to determine the linearity of the method for quantitative analysis.

Compatibility Study (FTIR)

Fourier Transform Infrared (FTIR) spectroscopy was conducted to characterize Ketorolac Tromethamine and examine potential interactions between drug and excipients. FTIR spectra of the pure drug and formulated transdermal patch were measured by the FTIR-1700 Shimadzu analyzer. The spectra were measured by the KBr pellet technique, and peaks corresponding to characteristic peaks were examined to verify the presence of functional groups and confirm drug-excipient compatibility

Differential Scanning Calorimetry (DSC)

Analysis of Differential Scanning Calorimetry (DSC) was conducted to analyze possible chemical and physical interactions between excipients and Ketorolac Tromethamine. The thermal behavior of the pure drug and its composite mixtures were examined via a DSC-60 Shimadzu instrument.

Preparation Method of Transdermal PatchesSolvent Casting Method

Matrix-type transdermal patches of Ketorolac Tromethamine were prepared using the solvent. The schematic presentation of Methods of preparation transdermal patches are shown in fig 1.7

Evaluation of Patches

Physicochemical Characterization

Physicochemical characterization of the formulated patches was carried out to evaluate their mechanical and surface properties. The thickness of each patch was measured using a digital micrometer (Mitutoyo, Model MDC-25PX, Japan). Folding endurance was assessed by repeatedly folding a patch at the same point until it broke, providing an indication of flexibility. Tensile strength was determined using a tensile tester (Instron Universal Testing Machine, Model 3345, USA) to evaluate the mechanical strength of the patches. The surface pH of the patches was measured by placing them on agar gel and recording the value using a digital pH meter.

Moisture Studies

Moisture studies were conducted to evaluate the water content and stability of the patches. Moisture loss was determined by weighing the patches and storing them in a desiccator containing anhydrous calcium chloride for 72 hours, after which the percentage weight loss was calculated. Moisture uptake was assessed by placing the patches in a desiccator maintained at 75% relative humidity using a saturated KCl solution for 72 hours, and the percentage increase in weight was calculated to determine the moisture absorption capacity of the patches [18].

Drug Content Uniformity

An accurately cut patch (1 cm^2) was dissolved in 10 mL phosphate buffer (pH 7.4), sonicated (PCI Analytics Ultrasonic Bath, Model UCB40), filtered, and analyzed at 290 nm using UV–Vis spectrophotometer (Shimadzu UV-1900, Japan) [19].

In-Vitro Drug Release

In-vitro release was carried out using Franz diffusion cells (Orchid Scientifics, India, Model FDC-07) with receptor chamber (20 mL) filled with phosphate buffer pH 7.4 maintained at 37 ± 0.5 °C on a thermostatic magnetic stirrer. At regular intervals (0–24 h), 2 mL samples were withdrawn and replaced with fresh medium. Etifoxine concentration was determined using UV–Vis spectrophotometer (Shimadzu UV-1900, Japan).

Ex-Vivo Permeation Studies

Excised goat ear skin (obtained from a local slaughterhouse, Nashik, India) was carefully cleaned, dermal fat removed, and mounted on Franz diffusion cells. The donor compartment contained the patch, and the receptor compartment was filled with phosphate buffer (pH 7.4) at 37 ± 0.5 °C. Samples were collected up to 24 h. Flux (J), permeability coefficient (Kp), and drug deposition were calculated. Release data were fitted into zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine release kinetics and mechanism [21].

In-Silico Docking Studies

Docking simulations were performed using AutoDock Vina v1.2.0. The 3D crystal structure of the GABA-A receptor benzodiazepine binding site (PDB ID: 6HUP) was retrieved from the Protein Data Bank. Ligands (Etifoxine, Diazepam) were optimized using SwissParam. Binding energy, hydrogen bonding, and hydrophobic interactions were visualized with Discovery Studio Visualizer.

Pharmacological Screening

Optimized transdermal patch batch was subjected to non-animal pharmacological screening using the SH-SY5Y human neuroblastoma cell line. Cells were treated with Etifoxine-loaded optimized patch extract (equivalent to 5–50 µM Etifoxine), and GABAergic activity was quantified using a GABA ELISA Kit. Antioxidant activity was evaluated by FRAP assay and DPPH radical scavenging assay to confirm the formulation's potential in modulating neurotransmission and protecting against oxidative stress.

Evaluation of Prepared Transdermal Patches

Organoleptic Test

The transdermal patches were evaluated for organoleptic properties to ensure their physical integrity and aesthetic appeal. The patches were visually inspected for color, clarity,

flexibility, and smoothness to confirm uniformity and acceptable formulation characteristics. These parameters are essential for patient compliance and overall quality assessment of the patches.

Weight Uniformity

The weight uniformity of the transdermal patches was assessed by weighing four patches from each batch using a digital balance. The average weight and standard deviation were calculated to ensure consistency in patch formulation. This test ensures uniform drug distribution and reproducibility of the transdermal patches.

Thickness of the Films

The thickness of drug-loaded polymeric films was measured using a digital vernier caliper to ensure uniformity. Measurements were taken at five different points four at the corners and one at the center of the patch. The average thickness and standard deviation were calculated for each formulation to confirm consistency and reproducibility.

Folding Endurance

Folding endurance was determined to assess the mechanical strength and flexibility of the transdermal patches. A 2 × 2 cm^2 strip of the patch was repeatedly folded at the same point until it broke. Alternatively, the film was manually folded at a 180° angle until it developed cracks or broke, and the number of folds was recorded. The average folding endurance and standard deviation were calculated from three readings for each formulation, ensuring durability and handling stability of the patches.A strip of specific area (2 cm*2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance.

Percentage Moisture Content

The percentage moisture content of the prepared films was determined to assess their moisture retention and stability. Initially, each film was weighed individually and then placed in a desiccator containing silica gel at room temperature for 24 hours to allow moisture to evaporate. After 24 hours, the films were weighed again and the percentage moisture content was calculated using the following formula: % Moisture Content= [(Initial weight – Final weight)/Final weight] x 100

Drug Content Uniformity

The drug content uniformity of the transdermal patches was assessed to ensure consistent distribution of the active pharmaceutical ingredient (API) in each patch. A standard test procedure was followed as per established pharmacopoeia guidelines. Each 2 × 2 cm^2 film from the batch was cut and mixed with 50 mL of phosphate buffer (pH 6.8), resulting in a concentration of 1000 µg/mL. The solution was then filtered using Whatman filter paper, and a 1 mL aliquot was pipetted into a 100 mL volumetric flask, diluted with phosphate buffer (pH 6.8) to achieve a concentration of 10 µg/mL. The resulting solution was analyzed using a Shimadzu spectrophotometer at 323 nm. The drug concentration was determined by comparing the absorbance of the test solution with the standard drug absorbance for Ketorolac Tromethamine, ensuring that the drug content falls within the acceptable limit of 85–115% for content uniformity.

In-vitro Dissolution Test

In-vitro drug diffusion studies were conducted using a 20 mL Franz diffusion cell to evaluate the release of Ketorolac Tromethamine from the transdermal patch. Before mounting, the membrane was stabilized to remove any soluble components. The membrane was then placed between the donor and receptor compartments. The receptor compartment was filled with 20 mL of isotonic phosphate buffer (pH 7.4), and the system was maintained at 37 ± 0.2°C with hydrodynamics ensured by a magnetic stirrer. A 2 cm × 2 cm patch, moistened with a few drops of pH 7.4 phosphate buffer, was placed in the donor compartment. 1 mL samples were withdrawn from the receptor compartment at predetermined time intervals (1, 2, 3, 4, 6, and 8 hours) and replaced with an equal volume of fresh pH 7.4 phosphate buffer. The percentage of drug permeated was calculated by measuring the absorbance of the samples at λ max 323 nm using a UV-Visible spectrophotometer. This study provides insights into the drug release kinetics and permeation profile of the formulation.

Tensile Strength

The tensile strength of the patch was evaluated by using the tensiometer . It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2*2 cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

In Vitro Permeation Study

An in vitro permeation study was carried out by using Franz diffusion cell. Full thickness abdominal skin of male Wistar rat weighing 200 to 250 g was used. Hair from the abdominal region was removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hour in phosphate buffer pH 7.4 before starting the experiment, and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the

compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of 5 mL was removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was replaced. Samples were filtered through watman filter and were analyzed using Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated ($mg*cm^2$) versus time in hours and permeability coefficient was deduced by dividing the flux by the initial drug load ($mg*cm^2$).

Limitation and Challenges in transdermal drug delivery systems:

While transdermal patch technology offers numerous advantages in drug delivery, it also faces several challenges and limitations that hinder its widespread adoption and efficacy . Addressing these challenges is crucial for advancing the field and unlocking the full potential of transdermal patch technology. This section explores some of the key challenges and limitations encountered in transdermal patch development and deployment.

1. **Skin Barrier:** The main limitation is the natural barrier provided by the skin, especially stratum corneum that restricts the diffusion of majority of drugs. Only small, lipophilic molecules easily permeate the skin layer
2. **Properties of Drugs:** The drugs have to possess certain properties-low molecular weight, adequate lipophilicity, and potency-to be released trans dermally. Hydrophilic or large drugs are least able to penetrate the skin.
3. **Low Drug Dosages:** TDDS is not ideal for drugs that need high doses because only a certain amount of the drug can be absorbed through the skin at any given time.
4. **Variable Skin Permeability:** The permeability of the skin can be variable for all individuals, varying between different parts of the body, or due to a factor of age, race, or existing health conditions. As a result, it leads to inconsistent drug absorption.
5. **Adhesion Issues:** The patches or systems used in the TDDS should have good adhesion to the skin over an extended period. Sweat, friction, and irritation of the skin can impede patch adhesion and consequently drug delivery efficiency.
6. **.**Irritation and Sensitization Local irritation, allergic responses, or sensitization might occur from prolonged skin contact; this is primarily due to the adhesive components or the drug.
7. **Slow Onset of Action:** Though TDDS may deliver a steady release, the onset of action is often slower than the oral or parenteral route, thereby not being ideal for drugs that have an immediate need for therapeutic effect.
8. **Drug Stability:** The drug must remain chemically stable during storage and during the delivery period; however, if the patch is exposed to environmental factors such as heat or moisture, then it becomes difficult.
1. **Complexities of production:** With TDS, specialized technology will be involved to ensure that the drug is released at a constant rate. It could be very technologically demanding and pricey.
2. **Very narrow spectrum of drugs:** TDDS can only be applied to highly potent drugs which can deliver the same effect at a small dosage.

Future of Transdermal Drug Delivery

System Future aspects in Drug delivery system include liposomes, Niosomes and micro emulsion. Aim of this development is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal patches has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will increase in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetic energy, magnetophoresis, has been investigated as a means to increase drug flux across the skin. The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase. In current scenario, transdermal route of drug delivery system in comparison with oral treatment as the most successful innovative research area in new drug delivery system, with around 40% of the drug delivery candidate products under clinical trails related to transdermal or dermal system. The transdermal drug delivery systems (TDDS) have been designed as an alternative, safest and easy route for systemic drug delivery. The systemic drug administration though skin holds several advantages such as

maintenance constant drug level in blood plasma, less by circumvention of hepatic first pass metabolism and increase patient compliance with respect to drug regime used for treatment. In recent times, skin considered as a safest port for drug administration, to provide continuous drug release into systemic circulation.

CONCLUSION

Transdermal patches are one of the most patient-friendly and innovative developments in contemporary drug delivery systems. Through the controlled, sustained, and non-invasive delivery of drugs across the skin, these systems provide notable benefits like increased bioavailability, prevention of hepatic first-pass effect, easier patient compliance, and less frequent dosing. A transdermal system is effective depending on several factors like drug physicochemical characteristics, skin permeability, and the design and composition of the formulation.

Ongoing research has resulted in tremendous technological developments, including microneedle arrays, intelligent patches, and biodegradable polymer-based platforms, which have increased the variety of drugs that can be efficiently administered transdermally. Although current limitations such as poor drug permeability, irritation, and complexity exist, forthcoming improvements in nanotechnology, biomaterials, and 3D printing are likely to overcome these.In total, transdermal drug delivery has grown from basic adhesive patches to highly advanced intelligent systems with the capability of accurate and customized therapy. With continued interdisciplinarity research, transdermal patches are set to become a central player in the next generation of pharmaceutical delivery systems, providing safer, more effective, and patient-tailored healthcare.

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