# Transdermal Hormonal Patches-Advances, Clinical Applications, and Future Directions

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***Abstract :*** Transdermal patches are a useful system made to deliver medicines through the skin straight into the blood. This way, the drug does not pass from the stomach or liver first, which often destroys a part of it. Because of this, the drug works better and side effects can be less. Patches give the medicine slowly for many hours or even days, so patients find them easy, painless, and more comfortable to use. The main parts of a patch include the drug, a polymer base or matrix, adhesive to stick to the skin, permeation enhancers, a backing layer, and a release liner.When it comes to hormones, patches are becoming very common. They are helpful for both men and women because they can keep hormone levels steady without daily tablets or painful injections. For women, estrogen and progesterone patches are used to control periods, reduce menopause problems, and for birth control. For men, testosterone patches help in hormone deficiency, weakness, and low energy. Other hormones like estradiol and levonorgestrel are also used for hormone replacement and family planning.In making such patches, many challenges are faced like how well the drug passes through the skin, how stable the hormone stays, and how patients may react differently. These problems can be managed with chemical enhancers,stronger adhesives, or better patch materials. In this way, transdermal hormonal patches give a safe, simple, and effective option for hormone therapy, which also improves patient compliance and results in better treatment

***keywords*** **-** Transdermal Patches, Hormonal Therapy, Estrogen, Progesterone, Testosterone, Menstrual Cycle, Menopause, Drug Delivery System.

## Introduction:

Transdermal hormonal patches work in a clever way to deliver hormones through the skin. The skin itself has three main layers: the epidermis on top, the dermis underneath, and the softer hypodermis below. The very outer surface—the stratum corneum—acts like a strong protective shield because it is made up of dead, flat skin cells embedded in a lipid matrix. This tough layer prevents most substances, including medicines or hormones, from passing through easily (1).

Despite this, some hormones are able to cross the skin barrier under the right conditions. When a patch is applied, the hormone first comes in contact with the surface of the skin and partially dissolves there. It then slowly permeates through the stratum corneum, passes the living cell layers of the epidermis, and finally reaches the dermis. In the dermis, blood vessels take up the drug and carry it into systemic circulation. The efficiency of this process depends on several factors such as skin hydration, thickness, temperature, and the physicochemical properties of the hormone itself (3).

The design of transdermal patches ensures precise and sustained drug release. These systems are built with multiple layers, including an adhesive layer that secures the patch to the skin and a drug-containing layer that controls the release rate. This allows for steady hormone levels in the bloodstream, avoiding the fluctuations often seen with oral tablets or injections.
Importantly, since the hormones bypass the gastrointestinal tract and liver metabolism, their bioavailability is significantly improved (6).
Clinically, different types of hormone patches are used. Estrogen patches are commonly prescribed for menopausal symptoms, while combination patches of estrogen and progestogen are used to protect the uterus in women receiving hormone replacement therapy. Testosterone patches are employed in men with hypogonadism or other hormone deficiencies. Additionally, contraceptive patches combine estrogen and progestogen to provide a convenient, weekly method of birth control. These needle-free systems improve patient comfort and compliance compared to injections or daily pills (8).

### 3.1 SKIN:

The skin is known as the largest organ of our body and it works like the first shield that keeps us safe from the outside world. It protects us from dust, germs, chemicals and also saves the body from losing too much water (22). Along with this, the skin also helps in feeling touch, pain, temperature and plays a role in body heat control (23). In recent times, skin is not only seen as a protective cover but also studied as a good way for giving medicines (24).

The skin is not just one flat sheet, but it has three main parts which are called epidermis, dermis and subcutaneous tissue (25). The epidermis is the top layer which directly touches the outside. It has mainly keratin cells and also melanin that gives skin its color and protects from sunlight (26). Below this is the dermis, which is a thick layer. It contains blood vessels, nerves, hair roots, oil glands and sweat glands. This part makes the skin strong and flexible and also helps in temperature balance (27).

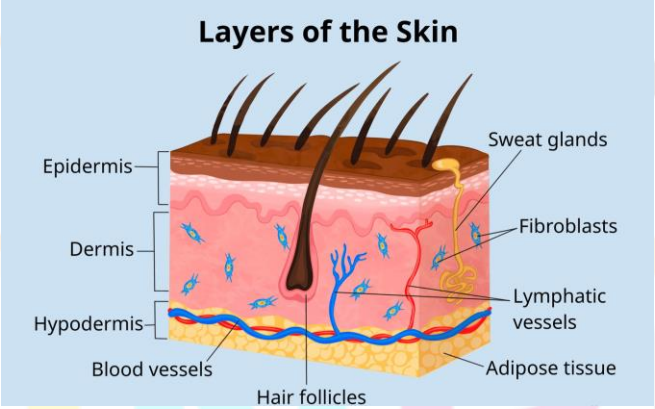


**Fig no. [1] Layers of skin**

The last part is the subcutaneous tissue, which has more fat and connective fibers. It works like a soft padding, stores energy and links the skin with muscles and bones underneath (28).
Because of this structure, skin is both a barrier and also an opportunity for medicine delivery (29). The top epidermis layer makes drug entry difficult, but if the drug is designed properly, it can go slowly and steadily inside the body (30). This is the reason why skin is now widely used for transdermal hormonal patches, which can give hormones like estrogen, progesterone or testosterone in a simple and painless way (31). These patches maintain steady hormone levels and are more comfortable for patients in therapy and contraception (32).

Transdermal drug delivery system is a method in which medicine is given through the skin for producing systemic effect (33). It is different from oral tablets or injections because here the drug passes slowly through skin layers and finally reaches into the blood (34). This system is useful as it can provide

continuous and controlled release of the medicine for a long time (35). Because of this reason the patient does not need to take the dose again and again (36).The main advantage of TDDS is that it keeps the drug level more steady in the body. In oral forms the level goes up and down, but in the patch system the level remains more uniform (12). Another important point is that this route avoids first pass metabolism in the liver which happens with oral tablets. So the availability of drugs becomes better and the dose required is also less in some cases (7).

**So in short the process is:**

1. Entry through stratum corneum (main barrier) (4).
2. Diffusion in epidermis and dermis (no storage) (22).
3. Absorption in dermal microcirculation (systemic effect) (5).

There are also some other benefits of this system. It is simple and painless, unlike injections (11). If any problem or overdose occurs, the patch can be removed at once and drug delivery stops, which makes it safer (20). It is also easy for long term use because patients find it more convenient (13).

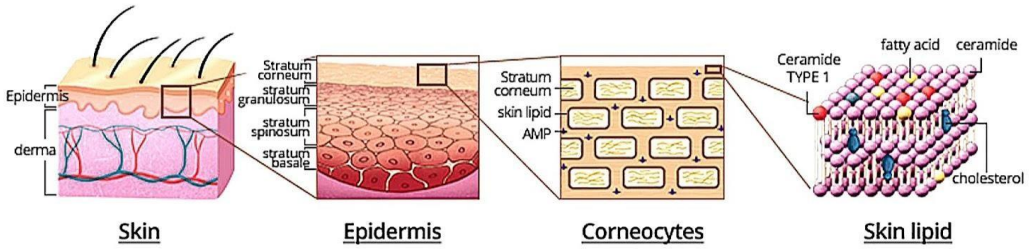


**Fig no. [2]Skin barrier composition**

Nowadays TDDS is used in different conditions like hypertension, angina, hormone therapy, smoking withdrawal by nicotine patch, and in pain management (6). Research is going on for new techniques like microneedle patches and nanotechnology to make penetration easier for drugs which normally cannot pass through skin (25).

### 3.2 Permeation:

Permeation basically means slow movement of a drug or chemical substance across a barrier, most commonly through the skin (8). In pharmacy, we focus on skin permeation because it decides whether a medicine given by transdermal route will actually enter the body (21).

The skin is not flat but has three layers (2). The epidermis is on top, with the stratum corneum being the toughest part (4). This layer is mainly responsible for blocking most drugs (15). Below it, the dermis has nerves, sweat glands, hair roots and blood vessels, which give strength and flexibility (13). The last part, the subcutaneous tissue, has fat and connective fibers that act like cushioning and also link skin with deeper tissues (20).

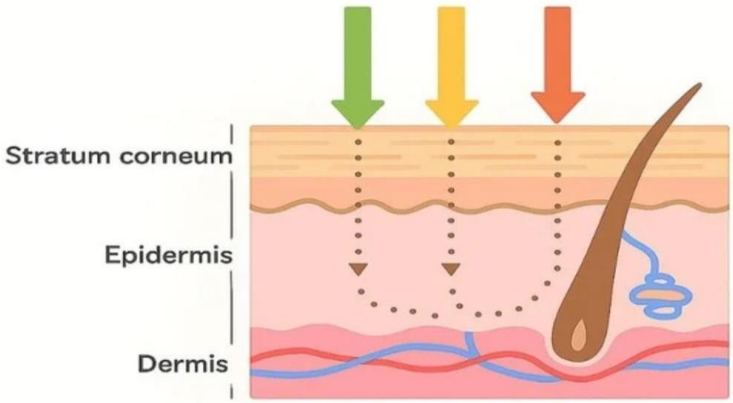

**Fig no.[3] Basic Permeation**

**Drugs can pass through the skin by three main routes-These permeation routes are:**

**1. Intercellular route 2. Transcellular route 3. Follicular route**

1. **The intercellular lipid route:**In the stratum corneum, the interlaminar regions contain less ordered lipids and more flexible hydrophobic chains. Because of this, a nonpolar space is present between the crystalline lipid lamellae and the outer membrane of the nearby cells. This space filled with fluid lipids is very important for trans-epidermal diffusion of lipid-soluble and amphiphilic molecules. These molecules move by occupying this free space and migrate through the intercellular lipid layers. On the other hand, hydrophilic molecules can pass mainly along the water-filled gaps that are present in small amounts in the interlaminar regions. Polar molecules may also use the free space between a lamella and the keratinocyte outer membrane for their movement (32).

2. **The transcellular route:**Inside the skin, the intracellular matrix contains materials like carotene. This does not directly help in drug diffusion but gives strength and stability to the stratum corneum. In normal conditions, diffusion through this route is very limited and not considered as the main path for drug transport. However, studies with confocal microscopy have shown that narrow aqueous pathways do exist. These are seen in regions where the lipid packing is loose, often near wrinkles on the skin surface, and these areas allow easier movement of water-soluble molecules. The contribution of this route can increase if the pathways are widened. This may happen by using electrical methods like iontophoresis, mechanical methods like sonophoresis, or thermal methods. These external techniques can reduce the skin barrier and improve drug penetration (45).

3. **Follicular penetration:**Recently, drug delivery through hair follicles has become an important area of research. Although hair follicles cover only about 0.1% of the total skin surface, they can still act as potential sites for drug entry. Earlier, this pathway was thought to be unimportant, but new studies show that follicles can serve as reservoirs for drugs and help in treating local skin diseases. Therefore, the follicular route is now also considered as a useful option for topical and transdermal drug administration (54).

The rate of permeation depends on many things. For example, the drug properties like size, solubility and polarity matter a lot. Then, the formulation type (gel, patch, ointment) also changes the entry. The skin condition is another factor – healthy, dry, hydrated or damaged skin all behave differently. External techniques like iontophoresis, microneedles or sonophoresis can also be used to improve drug entry by disturbing the skin barrier for some time (27).

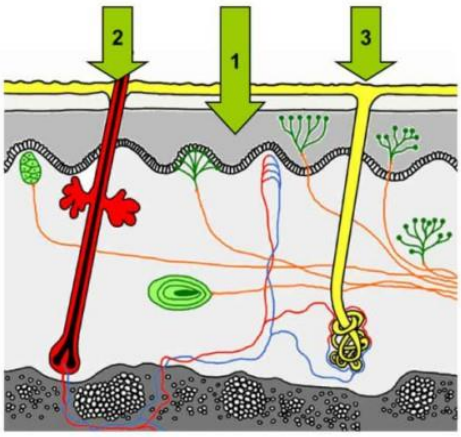

**Fig no.[4] Permeation routes**

In short, permeation is simply the way by which a drug crosses the skin barrier into the body. It is controlled by drug properties, formulation, and skin condition. A good understanding of permeation helps pharmacists and researchers to design better patches and delivery systems (53).

### 3.3 Design of a transdermal hormonal patch:

The design of a transdermal hormonal patch typically contains **four main layers**:

1. **Backing layer** – This is the outer protective layer that shields the medicine from moisture, oxygen, and external damage. It is made from strong yet flexible materials like polyester or polyethylene, ensuring durability and comfort during wear (23).

2. **Drug reservoir or matrix layer** – This layer holds the actual hormone in either a liquid, gel, or solid matrix form. In reservoir systems, the hormone is stored in a compartment, whereas in matrix systems, it is mixed directly with the adhesive (38).

3. **Adhesive layer** – This is responsible for sticking the patch to the skin. It must be gentle enough to prevent irritation but strong enough to hold the patch securely during daily activities. In many designs, the adhesive also helps in controlling the rate of drug release (49).

4. **Release liner** – A protective sheet that is peeled off before applying the patch. It keeps the adhesive and drug protected until use (30).

Transdermal hormonal patches are engineered for steady, controlled delivery of hormones through the skin. As followed below, their structure consists of multiple layers—backing film, hormonal formulation, membrane, adhesive tape, and liner—each designed to protect, regulate release, maintain adhesion, and ensure comfort while achieving effective therapeutic outcomes (57).

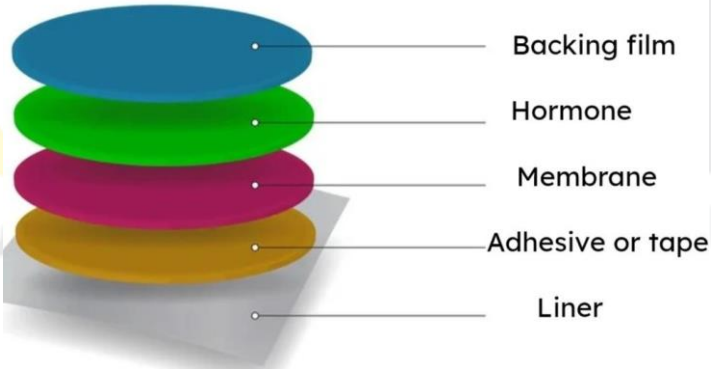


**Fig no[5] Design of TDHP**

Transdermal hormonal patches are an advanced, patient-friendly system designed to deliver hormones directly into the bloodstream through the skin. Instead of taking tabletsOptimisingions, a small medicated patch is placed on the skin, where it

slowly releases a controlled dose of hormones over a fixed period. This delivery method bypasses the digestive system and avoids first-pass metabolism in the liver, which means the medicine reaches the blood in a more active form, resulting in better effectiveness and fewer side effects compared to oral dosage forms (23).

### 3.4 Classification

Transdermal patches can be classified in different ways. Depending on how they are made, they are generally divided into **four types** (28).

**1. Hormone-in-Adhesive (HIA) Type**

In this type, the hormone is directly mixed in the sticky layer (adhesive). The same layer sticks the patch to the skin and also slowly releases the hormone.

Once applied, the hormone passes from the adhesive into the skin over time. These patches are usually very thin and soft, so they are more comfortable.

Example: Nicotine replacement patches can be explained in the same way, but here the idea is used for hormones (29).

**2. Reservoir Type**

In this type, the hormone is kept in a separate storage compartment, mostly in liquid or gel form. A membrane layer is present between the hormone and the skin.The hormone comes out slowly through this membrane and enters the body. This type allows better control of release, but the design is a little more complex (30).

**3. Matrix Type**

Here, the hormone is spread inside a polymer base (matrix) that holds it.

The hormone comes out slowly as it passes through the polymer and reaches the skin.The sticky part of the patch is placed around and partly over the matrix, so it can stay fixed to the skin.Matrix patches are easier to prepare compared to reservoir patches (31).

**4. Micro-Reservoir Type**

This is a mix of reservoir and matrix systems. First, the hormone is dissolved in a liquid, then that solution is spread inside a polymer.This creates tiny pockets (micro-reservoirs) of hormone within the patch. These small storages release the hormone in a slow and steady way.This method gives both controlled release and longer stability of the hormone (32).

Basically, the proper selection of a transdermal hormonal patch is hinged on the hormone to be delivered, the time of the therapy, and the comfort of the patient (10). Every design, either a straightforward adhesive system or a complicated micro-reservoir structure, is intended to offer a steady, controlled hormone release, safety, and easy usage (25). Due to ongoing advances in materials and formulation science, these patches are getting more efficient, reliable, and patient-friendly, thus transdermal delivery is becoming a first-choice method in contemporary hormone therapy (41).

## 4. Hormones:

### 4.1 Estrogens:

**Estrogens** are one of the most important hormones in the body, mainly in females but they also have some role in males. These hormones are central for reproduction, maintaining the menstrual cycle, protecting bone health, and also giving benefits to skin, hair, and mood (33). After menopause the level of estrogens falls very much, and because of this many women face different problems. The common problems are hot flushes, sweating at night, changes in sleep, irritation, dryness in vagina, pain during intercourse, weak bones, and higher risk of fractures (34). Earlier, estrogens were mostly given in oral form as tablets. But the oral route has one big issue called first pass metabolism. This means that when the tablet is swallowed, it goes to the stomach, then intestine, and then directly to the liver before reaching blood. In the liver, a large part of the hormone is broken down. Also the liver starts making more clotting factors and lipoproteins, which increases the risk of blood clot, heart attack, and stroke (35).

To avoid these problems, transdermal patches were developed. In this method, the hormone is placed on a patch that sticks to the skin. From the skin it slowly enters the blood. This avoids the liver and gives a more

stable level in blood (36). The patient does not need to take it every day as patches can stay for several days. Side effects like clotting are reduced, and blood levels do not go up and down as much as tablets (37). Because of this, the transdermal method is becoming more popular. In this area, three estrogens are mainly studied and used. They are Estradiol (E2), Estriol (E3), and Ethinylestradiol (EE2). Each of them has special features, uses, advantages, and risks (38).

**[A] Estradiol (E2)**

Estradiol, also called 17β-estradiol, is the strongest natural estrogen in humans. It is produced in the ovaries during the reproductive years (39). It controls the menstrual cycle, supports the growth of the uterine lining, helps in ovulation, maintains bone density, and also has effects on brain and mood (40). In addition, estradiol helps in controlling cholesterol and gives some protection to the cardiovascular system (41). After menopause, the natural level of estradiol falls to a very low amount, which is why symptoms start (42).

When estradiol is given by mouth, a big part of it is destroyed in the liver. This reduces the effect and also increases production of clotting proteins (34). Because of this, oral estradiol has been linked to blood clot problems and higher risk of stroke (12). But when estradiol is given as a patch, the hormone enters through skin directly into blood (49). This avoids the liver and gives a more natural level, close to the premenopausal woman's body (7).

**[B] Estriol (E3)**

Estriol is a weaker natural estrogen compared to estradiol and is mainly formed during pregnancy by the placenta (43). In non-pregnant women, its levels are usually very low (44). Estriol binds to estrogen receptors but has less potency, which means its effects are milder (45). Because of this, estriol is often considered safer with fewer risks of blood clots or cancer compared to stronger estrogens (46). It has been studied for use in hormone replacement therapy (HRT), especially for relieving vaginal dryness, urinary symptoms, and mild menopausal complaints (47). However, its weaker action also means it may not be as effective as estradiol for protecting bones or treating severe menopausal symptoms (48).

**[C] Ethinylestradiol (EE2)**

Ethinylestradiol is a synthetic estrogen, chemically modified to be stronger and longer-lasting in the body (49). It is one of the most commonly used estrogens in contraceptive pills because it has high oral nobility and a strong effect on controlling ovulation
(50). In transdermal systems, EE2 has been explored for use in contraceptive patches and hormone replacement (51). However, compared to natural estrogens, EE2 carries a higher risk of liver effects, clotting disorders, and cardiovascular problems (52). For this reason, its use in long-term hormone therapy is limited, and natural estrogens like estradiol are generally preferred (53). **Advantages**

1. Avoids first-pass liver metabolism (18).
2. Lower risk of blood clots (venous thromboembolism) (52).
3. Provides stable and steady hormone levels (7).
4. Safer for women with migraine, hypertension, or cardiovascular risk (41).
5. Convenient and non-invasive (easy to apply/remove) (25).
6. Flexible dosing (patch strength and frequency can be changed) (33).
7. Better protection for bones (prevents osteoporosis) (59).
8. Cardiovascular benefits without raising triglycerides (12).
9. Fewer gastrointestinal side effects (no nausea, vomiting, indigestion) (28).
10. Suitable for long-term hormone replacement therapy (HRT) (46).

## 4.2 Progesterone:

Progesterone is a natural steroid hormone which has a very important role in the female body. It takes part in the regulation of the menstrual cycle, prepares the uterus for pregnancy, and also helps in balancing the effects of estrogen (11). In the past, progesterone was mainly given by oral tablets, injections, or vaginal formulations. But all these routes have their own disadvantages (34). When given orally, a large portion is broken down in the liver before it becomes active (8). Injections, on the other hand, are painful and not very comfortable for patients (27). Vaginal preparations are also inconvenient and sometimes cause discomfort (49). Because of these limitations, transdermal drug delivery systems (TDDS) have been developed (2). In this method, progesterone is absorbed slowly through the skin which helps to maintain steady hormone levels and also improves convenience for patients (18).

One of the biggest advantages of the transdermal route is that it bypasses the first-pass metabolism (53). In oral administration, a part of the drug is lost in the liver before reaching systemic circulation (19). But when delivered through patches, progesterone directly enters the bloodstream (37). This results in more stable hormone concentrations over time (5). The steady release improves the effectiveness of treatment and reduces side effects like nausea, sleepiness, and liver strain (45). Along with this, patches, gels, and creams are painless and very easy to apply, which makes patients more regular in following their treatment (22).

There are many clinical uses of transdermal progesterone. In postmenopausal women, it is given along with estrogen as part of hormone replacement therapy (HRT) to protect the uterus from abnormal tissue growth (60). In contraceptive patches, progesterone is used in combination with estrogen to prevent pregnancy (12). In infertility management like in-vitro fertilization (IVF), it supports the luteal phase and makes the endometrium ready for implantation of the embryo (28). Apart from these, transdermal progesterone is also useful in problems such as irregular periods, amenorrhea, premenstrual syndrome (PMS), and premenstrual dysphoric disorder (PMDD) (44).

Different types of formulations are available in TDDS such as patches, gels, creams, and sprays (21). In recent years, research has also focused on newer techniques like microneedle-based systems to improve skin absorption (39). However, this route has some drawbacks. The absorption of progesterone can change based on factors like thickness of skin, hydration level, and the site where the patch is applied (6). Some patients may also experience mild skin irritation (31). In special cases such as luteal support during IVF, vaginal preparations may still give better results than the transdermal route (17).

Some marketed products of progesterone TDDS are Estalis® (estrogen + progesterone patch) and Progestogel® (topical gel) (25). Overall, transdermal progesterone gives a modern and patient-friendly approach for hormone delivery (50)

**Advantages**

1. Bypasses first-pass metabolism (higher bioavailability) [1].
2. Improved patient compliance (non-invasive, easy to use) [2].
3. Controlled and sustained hormone release [9].
4. Reduced side effects compared to oral forms [6].
5. Better skin and tissue absorption with enhancers [31].
6. Compatible with combination therapy (with estrogen) [4].
7. Convenient for special populations (e.g., liver issues) [16].

### 4.3 Testosterone:

Testosterone is the main male hormone. It helps in building muscles, keeping bones healthy, and also plays a part in the growth of male organs (7). When the amount of this hormone becomes low because of age or diseases like hypogonadism, a person may feel weak, lose interest in sex, or lose body strength (32). Usually, testosterone is given by tablets, injections, or implants (14). These methods have problems. Tablets are broken down in the liver and give less effect (46). Injections can be painful and cause sudden changes in hormone levels (10). Implants need a small surgery, which many people do not like (38).

Now patches and gels are used as another way to give testosterone (9). In this method, the drug passes through the skin and mixes directly in the blood, so it does not go to the liver first (43). Some ingredients are added to help the hormone move through the skin (35). This system releases the drug slowly, which keeps the hormone level steady in the body (4).

This route has many good points. It gives better absorption, is easy to use, and does not need needles (48). It avoids high and low changes in hormone levels, so mood and heart problems are less (20). The dose can also be changed easily by using a smaller or bigger patch or by applying more gel (52).

There are also some problems. The skin can become red or itchy where the patch or gel is used (26). The amount of drug that enters the body can change depending on the person's skin and temperature (56). Sometimes the hormone can rub off on another person if they touch that area (15). People with skin problems may not be able to use it (41).

Doctors mostly use testosterone patches or gels for men who have low hormone levels to make them feel normal again (57). It is also used sometimes in boys with late puberty or people with muscle-loss problems (13). Common examples are Androderm® patch, Testoderm® patch, and gels like Testim® and Fortesta® (24). This method is safe and simple compared to tablets or injections (30).

**Advantages:**

1. Avoids first-pass metabolism by the liver (12).
2. Gives better absorption than oral tablets (33).
3. Non-invasive and easy to use (45).
4. Provides steady and controlled hormone release (19).
5. Reduces side effects like mood swings and heart strain (28).
6. Improves patient comfort and regular use (50).
7. Dose can be adjusted easily (42).
8. Safe and convenient for home use (58).

**5. Role in regulating (HRT):**

Hormone replacement therapy is given when body stops making enough hormones, mostly when women reach menopause or when men have low hormone levels with age. This therapy helps to bring back the normal balance in body. The main hormones used are estrogen, progesterone and testosterone. These hormones control many body functions like growth, mood, bones, and sexual health. When they reduce, a person feels weak, tired or faces different changes. HRT helps to correct this and make a person feel better again. It can be given in many forms like tablets, skin patches, gels or injections depending on what doctor decides (11).

**[A] Estrogen** is the main female hormone which is made in ovaries. It keeps the menstrual cycle regular, bones strong and skin healthy. When a woman reaches menopause, estrogen level goes down and many symptoms start like hot flashes, dryness, irritability and weak bones. Giving estrogen through therapy helps to reduce these symptoms and maintain body function. It also helps to stop bone loss and keep cholesterol normal. Estrogen can be given as a tablet, cream, gel or patch. Patches are preferred because they release slowly and avoid passing through the liver. But when estrogen is given alone for a long time, it can cause thickening of the uterus lining, which is not safe. So it is always better to give estrogen with progesterone for protection. Estrogen mainly helps to control menopause problems and improves comfort and daily life of women.(6).

**[B] Progesterone** is another important hormone in HRT. It is made by ovaries after ovulation. It helps in preparing uterus for pregnancy and keeping the menstrual cycle proper. During menopause, progesterone level becomes low and causes mood change, disturbed sleep and irregular cycle. In therapy, progesterone is used to balance estrogen and stop it from causing uterus problems
(6). It also helps in relaxing mood and improving sleep. Progesterone is available in tablets, gels and skin patches (11). Natural or body-like progesterone is mostly used because it is safer and works smoothly. It mainly acts as a balancing hormone in therapy. Without progesterone, estrogen alone may cause side effects. So both are needed together for safe and natural treatment (21).

**[C] Testosterone** is known as male hormone but it is also present in small amounts in females. It is made in testes in men and in small quantities in ovaries and adrenal glands in women. Testosterone helps in building muscles, bones, strength and sexual drive. When men become older, testosterone level goes down and they feel tired, low energy, weak muscles and low interest in sex. This condition is called andropause. Testosterone therapy helps to bring the level back to normal. It gives energy, improves confidence, and helps in muscle growth (20). Testosterone is given as injections, gels, patches or implants (40).

When estrogen, progesterone and testosterone are used together in right way, they give better and safer results. Estrogen controls menopause, progesterone keeps balance and protects uterus, and testosterone adds energy and strength. Together they help in keeping the body stable and healthy. HRT helps to maintain hormones which get low due to age or health issues. It prevents problems like mood change, bone weakness and tiredness (11). Nowadays patches and gels are more used because they are easy and give slow release (14). Dose must be checked by a doctor to keep it safe. HRT is helpful for both men and women when used properly. It makes life more active and comfortable by keeping hormones in balance. In

short, hormone replacement therapy plays a big role in maintaining health when the body cannot make enough hormones on its own (40).

## 6. Advances:

Transdermal hormonal therapy (THT), often called THT, has become one of the better ways to give hormones through the skin instead of by mouth (1). This method helps the body avoid the liver's first-pass effect and keeps hormone levels in the blood more steady over time (11). Since the medicine goes straight into the bloodstream through the skin, it tends to work better and causes fewer stomach-related issues (6). People also find it easier to use compared to pills or injections (12). In contrast to oral hormone replacement, the transdermal form reduces irritation in the digestive system and avoids the ups and downs that usually happen with traditional dosing (5).

Over the last several years, many researchers have tried to find ways to make the outer layer of the skin, known as the stratum corneum, easier for drugs to pass through, because that layer mostly blocks the medicine from entering the body (41). A number of techniques are being explored, including the use of certain chemicals to open up the skin barrier a bit, applying gentle pressure, and using carrier materials that can hold and slowly release the hormone (31). At the same time, better polymers and improved formula designs have made these patches and gels more stable and comfortable for longer use in hormone treatments such as menopause therapy, testosterone replacement, and even in contraceptive systems (2). All these gradual changes show a clear move toward safer, steadier, and more convenient ways to deliver hormones through the skin (13).

### 6.1. Nanotechnology-Based Delivery Systems

Nanotechnology has completely changed how drugs can be sent through the skin. It gives new ways to deal with the limits of old patches and gels that often fail to give steady results (43). Systems that use nanocarriers, like liposomes, nanoemulsions, lipid nanoparticles, and polymeric nanocapsules, have shown good results, especially for fat-loving hormones such as 17β-estradiol (E2) (38). These small systems keep the hormone locked inside a layer of lipids or polymers, which helps protect it from air, light, or other things that can make it break down easily (43). They also help form a kind of pressure or difference in concentration that makes the hormone move better through the outer skin layer (38).

A study in 2024 by de Assis Ramos and co-workers in the Journal of Pharmaceutical and Pharmaceutical Sciences pointed out that both lipid nanoparticles and polymer-based carriers can keep releasing estradiol slowly for several hours. This helps keep the right amount of the hormone in the blood and means patients don't have to apply the medicine as often (38). The steady release helps avoid sudden highs and lows in hormone levels that could cause unwanted side effects (13). Besides this, the nanoformulations also stay stable for longer periods and are less likely to cause any irritation when used on the skin (43).

Still, even with all these good points, bringing these systems into large-scale commercial use has not been easy. The main issues are the high production cost, problems in getting the same results each time they are made, and the fact that large clinical studies are still missing to confirm how well and safely they work (57).

### 6.2. Microneedle (MN) Technology

Microneedle use is a new idea in transdermal hormonal therapy (54). It gives a simple and almost painless way for hormones to go into the body through the skin (45). Microneedles are very small needle-like points that are often made from materials which can dissolve or break down after use (49). They make tiny holes in the top layer of the skin, called the stratum corneum, without causing pain or bleeding (46). These holes let the hormones move into the deeper skin layers where blood vessels help carry the drug into the body (48).

Many studies have shown that microneedle patches filled with estradiol or testosterone work faster and give more correct doses than normal patches (44). Because they are small and easy to use, people can apply them quietly and take care of their treatment by themselves (45). When the microneedles dissolve, there is no sharp waste left, which makes them safe for the environment

(47). But there are still problems like keeping the same drug amount in every patch and making sure the needles stay strong enough (56). New research is looking at how to make better needle shapes, stronger materials, and slow-release systems so microneedle therapy can become safe and useful for real medical use (46).

### 6.3. Hybrid Enhancement Techniques

When the combination of nanocarriers with microneedles is used, enhanced results are achieved (43). Layer-by-layer drug delivery through skin application can be done by iontophoresis and electroporation (31). With the application of small electric currents through these methods, drugs penetrate deeper into skin tissue (14). In iontophoresis, the weak electrical current is used for the purpose of driving charged drug molecules to penetrate through the skin surface (41). Electroporation uses brief electrical pulses to create small openings in skin layers which allows hormones and other large molecules to enter the body more efficiently (42).

The combination of these methods with microneedle patches and tiny drug carriers makes it possible to achieve precise control of medication release rates and amounts (45). The method is very effective for the problem of hormone stability in estrogen therapy treatment (38). The systems allow the users and medical staff to change treatment doses which they believe will result in safer and more individualized care (57).

Researchers have developed the first test patches that combine basic electronic components with drug formulations to achieve controlled hormone release from small wearable devices powered by simple batteries (56). The evolution of this technology stands for the very first step toward a new flexible transdermal route of hormone delivery (54).

### 6.4. Nanoparticle-Loaded Patches and Hybrid Systems

Nanoparticle-loaded transdermal patches are one of the major moves that link new drug formulations to patient-friendly application (38). These systems have minute lipid or polymer-based nanoparticles mixed in the patch layer or hydrogel base, thus creating an in-built drug depot which gives drug release that is slow and steady and at the same time, helps the patch adhere to the skin better (43).

The combination of nanocarrier technology with the conventional patch design stabilizes the hormone, impedes the crystallization process, and extends the shelf life of the medicine (55). As an illustration, lipid-polymer hybrid nanoparticles combine the advantageous features of both materials (38). The lipid component provides softness and safety to the skin, whereas the polymer component adds strength and also facilitates the slow release of the drug for a longer time (55).

The combination enhances hormone permeation through the skin, reduces the possibility of irritation, and increases the shelf life of the patch (43). Comparative studies on biological models have demonstrated that these kinds of hybrid patches are capable of maintaining the hormone dose at a constant level for nearly 72 hours, thus, they are more efficient than most patches which are already present on the market (55).

Moreover, these patches can be engineered to react to external factors such as temperature or pH changes in the body, thus enabling hormone release to vary naturally with body requirements (38). There are still a few issues such as ensuring good adhesion, large-scale production, and meeting the requirements for approval that need to be sorted out before the patch can be used in real patients even though the outcomes so far have been very promising (58).

## 7. Clinical application:

### 7.1. Contraceptive Therapy

One of the most popular ways to offer birth control for women is by the use of a transdermal hormonal patch, a method that is simple and effective when applied just once a week (12). Unlike oral pills that need daily use, the patch maintains steady compliance and hormone levels (23). Most of these patches combine ethinylestradiol and norelgestromin, while some newer designs use estradiol with levonorgestrel (21). By applying it to the skin, they continuously release a small and controlled dose of hormones into the bloodstream (28). This steady delivery helps the body maintain hormonal balance, avoiding the peaks and drops often seen with oral contraceptives (11). These patches prevent pregnancy mainly by stopping ovulation and thickening cervical mucus, making sperm entry more difficult (4). Additionally, they alter the uterine lining, reducing the chances of implantation (27). Because the patch bypasses the liver's first-pass metabolism, digestive side effects are much less common (40). The regimen is easy to apply one patch each week for three weeks, then rest for one week before restarting (26). Several studies have concluded that transdermal contraceptive patches provide efficacy equal to combined oral contraceptives while

improving user adherence and hormone stability (7). Modern patches containing progesterone acetate and ethinylestradiol further reduce skin irritation and improve durability (18). Overall, this technology successfully merges comfort, effectiveness, and convenience, making it a modern and user-friendly method of hormonal contraception (2).

### 7.2. Androgen Replacement Therapy

Currently, male hypogonadism has been effectively managed using transdermal patches as part of androgen replacement therapy
(33). Traditionally, testosterone has been administered through injections or oral tablets, but both routes come with drawbacks
(20). Injections often lead to hormonal ups and downs, which can cause sudden mood and energy changes, while oral testosterone can harm the liver due to the first-pass metabolism process (11). On the other hand, transdermal patches steadily release testosterone into the bloodstream, maintaining more consistent hormone levels and reducing these complications (28). These patches are generally applied to the back, upper arms, or abdomen areas where the skin is thin enough for proper absorption (41). They help sustain stable plasma testosterone levels for up to 24 hours, restoring normal functions like muscle growth, bone strength, mental focus, and sexual health (33). Many patients report improved energy stability and fewer side effects compared to injectable or oral methods (36). Another key advantage is the reduced need for frequent dosing, which makes this therapy easier and more comfortable for long-term use (29). In recent developments, patch formulations have been refined to improve skin adhesion, reduce irritation, and enhance hormonal balance (24). Some advanced versions now use micro-reservoir or nano-enhanced systems to boost the diffusion rate of testosterone across the skin (55).
Overall, transdermal androgen therapy stands out as a safe, effective, and non-invasive alternative, offering better patient compliance and stable hormone control (37).

### 7.3. Treatment of Hypoestrogenism

One of the main treatments for hypoestrogenism involves using transdermal hormonal patches (40). This condition can occur for several reasons, such as ovarian failure, surgical removal of ovaries, premature menopause, or hypothalamic dysfunction (27). Low estrogen levels often lead to symptoms like hot flashes, irregular menstrual cycles, vaginal dryness, mood swings, and if untreated can increase the risk of bone loss and heart disease (16). Transdermal estrogen patches help restore normal hormone levels in a way that closely mimics the body's natural hormone release (12). Unlike oral estrogen tablets that must pass through the liver before entering the bloodstream, transdermal patches deliver estrogen directly through the skin (11). This avoids first-pass metabolism and reduces the risk of liver strain and blood clotting problems (17). Because the patch provides a steady release of estrogen, it maintains more consistent hormone levels compared to oral forms (28). Many patients report better symptom relief and fewer side effects when using patches (29). These patches are especially recommended for women experiencing early menopause or those who have undergone hysterectomy (21). They are also useful for young women with ovarian insufficiency, helping to maintain proper growth, reproductive health, and bone density (33). Modern patch designs now feature improved adhesion and enhanced skin compatibility, which increases comfort and compliance (24). Overall, transdermal estrogen therapy remains a safe, effective, and physiologically balanced option for treating hypoestrogenism and restoring hormonal equilibrium in women (50)

### 7.4. Palliative Care in Prostate Cancer

One of the key parts of palliative care in advanced or metastatic prostate cancer is hormone suppression, and transdermal estrogen patches have become a promising method for this purpose (40). Traditionally, treatments such as GnRH agonists, anti-androgens, or even surgical castration are used to lower testosterone levels (27). However, these treatments often come with unwanted effects like hot flashes, metabolic disturbances, and increased cardiovascular risks (33). Oral estrogen was once used as well, but it caused a high risk of blood clots because of its strong first-pass metabolism in the liver (17). Transdermal patches avoid this issue completely by delivering estrogen directly into the bloodstream, thus significantly lowering the chances of thrombotic complications (12).
In clinical practice, estrogen patches provide a steady and controlled release of estrogen into the body (21). This leads to strong suppression of the hypothalamic-pituitary-gonadal axis, which in turn reduces testosterone to very low levels (33). Such suppression slows tumor growth and helps relieve symptoms

like pain, urinary obstruction, and discomfort from bone metastases
(16). Patients generally prefer patches because they avoid injections and prevent the hormone-level swings seen with some other therapies (36). Another benefit is that transdermal estrogen may support mood stability and help maintain bone health—two major concerns in long-term prostate cancer management (50). Recent research suggests that estrogen patches could be used as long-term maintenance therapy, offering complete testosterone suppression with fewer systemic side effects (57). This makes them a valuable tool in palliative care, especially for patients needing symptom control and improved quality of life in the advanced stages of prostate cancer (60)

### 7.5. Gender-Affirming Hormone Therapy (GAHT)

Transdermal hormonal patches are one of the main tools that have changed gender-affirming hormone therapy for the better (58). This is mainly because hormones can be administered in a safer and more controlled manner to transgender individuals (40).

A commonly accepted practice for transgender women includes the use of estradiol patches, which are a good source of typical feminization by providing relatively steady and physiological estrogen blood levels (28). The number one reason why the transdermal path in GAHT is so good is that it shields the liver from first-pass metabolism, lowering the chances of thrombosis and cardiovascular complications associated with high-dose oral estrogen (11).

This is why patches are chosen by people who have health-related risk factors and by those who simply prefer a safer long-term therapy option (12). Transdermal patches slowly release estradiol over time, helping maintain stable hormone levels and reducing mood fluctuations and hormonal peaks seen with oral or injectable estrogen (14). Patients also appreciate that patches are simple to use and reduce the need for frequent clinical visits, supporting better treatment adherence (36).

Testosterone patches may be used in transgender males as an alternative to injections, helping achieve more stable hormone levels that lead to improved mood, increased muscle mass, and a sense of well-being (33). Although fewer individuals currently use testosterone patches and injections remain more common, patches are valuable for those who dislike needles or prefer predictable pharmacokinetics (20).

Recent improvements in patch technology — including better skin adherence, reduced irritation, and enhanced hormone penetration — have made transdermal (GAHT) more convenient and reliable compared to older systems (24). Overall, these patches provide a flexible treatment method that supports the goals of physical transition while prioritizing long-term health (60).

## 8. Future Directions:

### 1. Development of Smart and Responsive Transdermal Patches

The next major evolution of transdermal hormone delivery is anticipated to be "smart" patches (59). Their goal is to not only release drugs passively but also to regulate hormone release depending on the body's current requirements. Scientists are looking for ways to equip patches with tiny biosensors that can register skin temperature and sweat pH (12), and can also detect subtle changes in hormone levels in the blood (33). By sensing these parameters, the patch can modify its release rate—either slowing or increasing hormone diffusion (41). Such technology could greatly reduce hormone fluctuations and provide a more physiologically stable therapy option for menopausal women, transgender individuals, and patients on long-term hormone replacement (26).

### 2. Combining Micro-Needle Arrays With Patch Technology

Transdermal systems have been successful, but one major limitation is their inability to deliver large molecules and peptides (14). Future devices aim to merge micro-needle arrays with a patch surface, creating a hybrid system (46). These micro-needles create micro-channels that allow large or hydrophilic hormones to penetrate the skin more effectively (21). When combined with a controlled-release backing, this hybrid design can maintain hormone levels steadily for extended durations (38). Integrating micro-needles may also support new hormonal analogues that traditionally cannot pass through the skin (57).

### 3. Development of Longer-Acting, Low-Maintenance Patch Formulations

Most hormonal patches today need replacement every 1–3 days (7). Future research is focused on creating polymer matrices and adhesive systems that can release hormones continuously for a week or month (52). This will reduce treatment burden, especially for patients who often forget to replace patches on time (43). Extended-release patches also promote more stable hormone levels by avoiding abrupt stop-start cycles (19). These systems are expected to significantly improve adherence in elderly individuals and those

requiring long-term treatment (28).

**4. Advancements in Nanotechnology for Enhanced Penetration and Stability**

Nanotechnology is expected to dramatically enhance future transdermal patches (60). Nano-delivery carriers like lipid nanoparticles, polymeric nano-capsules, nano-emulsions, and solid lipid particles help protect hormones from degradation caused by heat, oxidation, or light (24). These nano-vehicles can also soften skin lipids or increase drug solubility to improve penetration
(16). Nanotech permits highly controlled and predictable release patterns (40). Advanced patch designs may eventually release multiple hormones at varying rates or respond to specific biological signals for triggered delivery (35).

## 9. Summary:

The study shows, how transdermal hormonal patches release hormones through the skin for a gradual, regulated absorption. In comparison to oral or injectable methods, patches do not go through the liver metabolism, side effects are diminished, and the patient's comfort is increased. The article tells about the skin's part in drug permeation and gives an account of different kinds of patches such as matrix, reservoir, micro-reservoir, and hormone-in-adhesive systems. It refers to the application of patches in therapy with estrogen, progesterone, and testosterone for contraception, HRT, cancer treatment, and GAHT. Additionally, it gives information about the innovations such as nanotechnology, microneedles, and smart patches that can make the delivery efficient in the coming days.

## 10. Conclusion:

Transdermal hormonal patches play a special role in hormone therapy because they provide a safe, more stable, and more comfortable way of delivering hormones to the body. These patches, since they do not go through the digestive system and the liver's first-pass metabolism, allow the hormones that are mixed with the blood to be already the direct ones, thus increasing bioavailability and decreasing the number of side effects in oral tablets or injections comparison. Therefore, they are the most effective for long-term treatments such as hormone replacement therapy, contraceptives, hypoestrogenism management, androgen deficiency, prostate cancer care, and gender-affirming hormone therapy.

The multilayered design of their structure-adhesive-based, reservoir, matrix, or micro-reservoir allows hormones to be released in a controlled and continuous manner, thus ensuring that the body keeps stable hormonal levels. This drastically diminishes the occurrence of hormonal fluctuations that are the main causes of changes in the mood, discomfort, and inconsistency of therapeutic effects. Patients may also find patches advantageous in terms of ease and comfort, i.e., they are pain-free, simple to apply, and require fewer doses. Innovations such as nanotechnology, microneedles, advanced polymers, and sensor-based smart systems are the forefront breakthroughs that are further improving the effectiveness of patches, skin penetration, and dose control. These technologies are considered to be the next generation of transdermal therapy, and they will enable hormone delivery to be more personalized and precise. To sum up, transdermal hormonal patches are a modern, patient-friendly, and highly viable option for safe and effective hormone management.

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