



# EVALUATING THE SAFETY AND EFFICACY OF ESTROGEN PATCHES IN HORMONE REPLACEMENT THERAPY

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## Abstract:-

Menopause is a normal biological occurrence in women, occurring at a median age of 51 years. Hormone replacement therapy (HRT) contains estrogen for relieving menopausal symptoms; for women who still have their uterus it is combined with a progestogen for endometrial protection. The estrogen can be oral, intravaginal, or transdermal. The progestogen can be oral, transdermal, or delivered via an intrauterine device. In HRT regimens the estrogen is taken daily, with progestogen added either sequentially (cyclic regimen) or daily (continuous combined regimen) if it is needed. Tibolone is an oral synthetic steroid preparation with estrogenic, androgenic, and progestogenic actions that can also be used as HRT. Testosterone can be added to HRT, but the role of supplemental testosterone will not be covered in this case (1).

## Introduction :-

## LITERATURE REVIEW

1) Lawton S et al., (2019) ; About 54% of people in the UK will get a skin problem in a given year, and 20–33% of people are affected by skin disorders at any

given time. Every day, nurses examine their patients' skin, and it's critical that they comprehend it so they are able to identify issues when they appear. The construction and function of the skin are examined in this article, which is the first of two parts on the subject.

2) **Ankarberg-Lindgren C et al., (2001)**<sup>2</sup> ; In a clinical observation trial, we used low dosages of transdermal estradiol patches applied only at night to induce puberty in 15 females with hyper- or hypogonadotropic hypogonadism. and contrasted the measured levels of estradiol with those in females in good health. The period of pubertal induction began between 12.3 and 18.1 years of age.

3) **Kováčik A et al ., (2020 )**<sup>3</sup> ; Permeation enhancers, also known as penetration enhancers, percutaneous absorption promoters, or accelerants, are substances that improve drug flux over the epidermal barrier and are the subject of this article. Initially, drug properties, drug penetration mechanisms, and skin components are presented. Next, we talk about characteristics of enhancers, their several classes, modes of action, reversibility and toxicity, structure-activity connections, biodegradable enhancers, and synergistic enhancer combinations.

4) **Zaid Alkilani A et al .,(2015 )** ; Rapid advances in fundamental understanding that support industrial development are driving the TDD sector's continued growth and development. It is anticipated that eventually, improvements in TDD technology would result in better disease prevention, diagnosis, and control, with corresponding improvements in quality of life for patients worldwide in relation to their health.

## **ESTROGEN PATCH**

Transdermal patches containing natural estrogen ( $17\beta$ -estradiol) have become available for treatment of postmenopausal women and have also been used for pubertal induction. The major advantage of transdermal estrogens compared with

oral estrogens is that liver passage is avoided and, therefore, the influence on liver metabolism is minimized. The new generation of transdermal patches with a matrix composition also makes it possible to cut the patches into pieces and thereby to start induction at very low doses(2).

Skin is the largest organ in the human body and its easy accessibility makes it an attractive part of entry for drug administration that dates back to the first medical records of man. The formulations that are applied to the skin can be divided into transdermal (for systemic effects) and topical (for local effects in the skin). Clinical benefits of transdermal drug delivery over conventional routes of drug administration include the following (3).

1. Avoids first-pass metabolism and enzymatic disruption by GIT
2. In a transdermal medication, there is the possibility of self-administration.
3. Topical patches have a constant drug release in the bloodstream.
4. Less painful method of drug delivery.
5. In comparison to oral methods, transdermal patches offer fewer negative effects.
6. Avoids GIT incompatibility of drugs.
7. Dose and therapeutic effects are advanced.
8. TDDS is a durable treatment.
9. Better patient's compliance.
10. Avoiding frequent dose administration(4).

## **TYPES OF ESTROGEN PATCHES**

### **A) TRANSDERMAL PATCHES:**

A transdermal patch is a medicated sticker that you place on your skin to deliver a specific amount of medicine directly into your bloodstream. This method is often used to help heal an injured area of the body. One of the main benefits of using a transdermal patch instead of other forms of medicine (like pills, injections, or creams) is that it provides a steady release of the medicine over time. The patch works by either having a special membrane that lets the medicine pass through, or it

uses your body heat to melt the medicine that is embedded in the adhesive(5).

## B) COMBINATIONPATCH:

A combination patch is a type of patch that sticks to your skin and has more than one type of medicine in it. It works by slowly releasing the medicines into your body through your skin. These patches are helpful when you need more than one medicine to treat a condition, like hormone replacement therapy (HRT) for menopause.

For example, a patch that has both estrogen and progesterone is used by women who still have their uterus. It helps with menopause symptoms and also protects the uterus from the effects of estrogen. The patch releases both medicines over time, so it's easier for women to manage their treatment without taking multiple medicines.





## FORMULATION OF ESTROGEN PATCH:

\*The main components of a transdermal patch are:

### 1) Polymer Matrix in Transdermal Drug Delivery Systems (TDDS)

The polymer matrix is a key part of transdermal drug delivery systems (TDDS) that controls how the drug is released. Here are some important points about the ideal polymer for this purpose:

#### Examples of Suitable Polymers:

- **Cellulose Derivatives:** Safe and biodegradable, commonly used for their ability to form films.

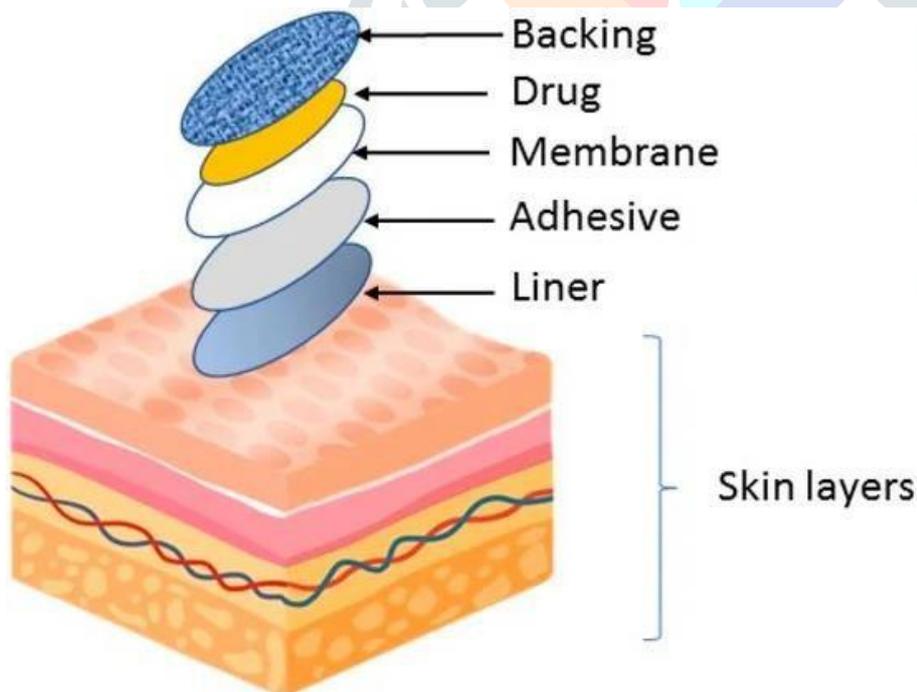
- **Zein:** A protein from corn that helps control drug release.
- **Gelatin:** A natural polymer that's compatible with drugs and used in gels.
- **Shellac:** A natural resin that provides a protective layer.
- **Waxes:** Such as beeswax, which create a moisture barrier.
- **Gums:** Natural substances like guar gum that can form gels for sustained release.

## 2) Drug

The transdermal route, which involves delivering drugs through the skin, is a great choice for certain types of medications. Transdermal patches are particularly useful for:

### Examples:

- **Fentanyl:** A powerful pain reliever.
- **Nitroglycerin:** Used for chest pain



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### 3) Permeation Enhancers

Permeation enhancers are substances that help increase the skin's permeability, allowing more of the drug to enter the body and achieve better therapeutic effects. There are three main types of permeation enhancers:

#### Example:

- **DMSO (Dimethyl Sulfoxide):** A common permeation enhancer that is effective in improving the absorption of various drugs.

### 4) Adhesives

Adhesives help improve the skin's ability to absorb medications, allowing for higher levels of the drug to enter the body. By enhancing the permeability of the outer skin layer (the stratum corneum), these adhesives ensure that more of the drug reaches its target, leading to better therapeutic effects.

### 5) Backing Laminates

Backing laminates are the outer layers of transdermal patches. They should be flexible, which means they can bend easily without breaking. This flexibility helps the patch stay comfortable on the skin.

#### Examples:

- **Vinyl**
- **Polyethylene**

These materials are commonly used because they are both flexible and durable.

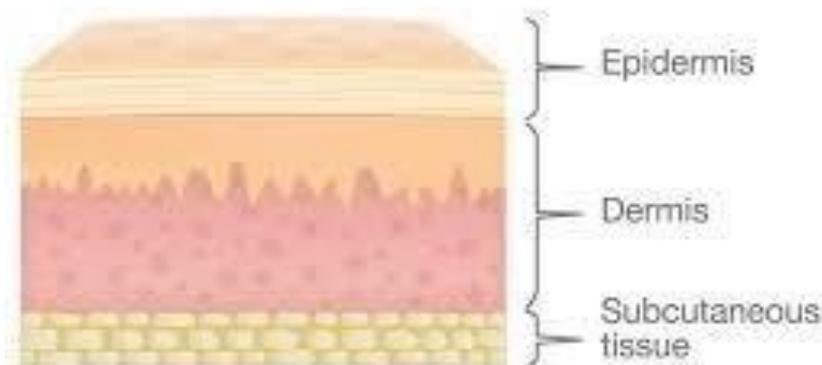
### 6) Release Liner

The release liner is a protective cover for the patch that keeps it safe while it's being stored. You need to remove this liner before you use the patch.

## 7) Other excipients like plasticizers and solvents (6).

### STRUCTURE OF SKIN:

#### The Layers of Skin



The skin is divided into several layers, as shown in figure 1) **EPIDERMIS :**

The epidermis is the outer layer of skin made up of many flat cells. It mainly consists of two types of cells:

1. **Keratinocytes:** These are the most common cells that make up the skin.
2. **Dendritic Cells:** These cells help protect the skin by recognizing foreign substances.

The epidermis is usually divided into four layers based on how the keratinocytes look and where they are as they change into tougher cells:

1. **Basal Cell Layer (Stratum Germinativum):** The bottom layer where new skin cells are created.
2. **Squamous Cell Layer (Stratum Spinosum):** The layer above the basal layer where cells begin to flatten.
3. **Granular Cell Layer (Stratum Granulosum):** This layer has cells that start

to develop granules as they move towards the surface.

4. **Cornified or Horny Cell Layer (Stratum Corneum):** The top layer made of dead, flattened cells that help protect the skin.

Together, these layers work to keep the skin healthy and protected (7).

## 2) DERMIS:

The dermis is the inner layer of skin and is much thicker than the outer layer (epidermis), measuring between 1 and 5 mm. It sits between the basement membrane (which connects it to the epidermis) and the subcutaneous layer (which is the layer of fat below the skin).

### Main Functions of the Dermis:

1. **Protection:** It helps cushion and protect the deeper parts of the body from injuries.
2. **Nourishment:** It provides essential nutrients to the epidermis to keep it healthy.
3. **Wound Healing:** It plays a crucial role in helping the skin heal when it's damaged (7).

### SUBCUTANEOUS TISSUE:

•: The subcutaneous tissue is mostly made up of fat cells called lipocytes. Even if your body weight changes, the number of these cells stays the same; instead, the amount of fat inside them changes.

• **Inflammation:** When the fat in this layer gets inflamed, it's called panniculitis.

#### • Types of Panniculitis:

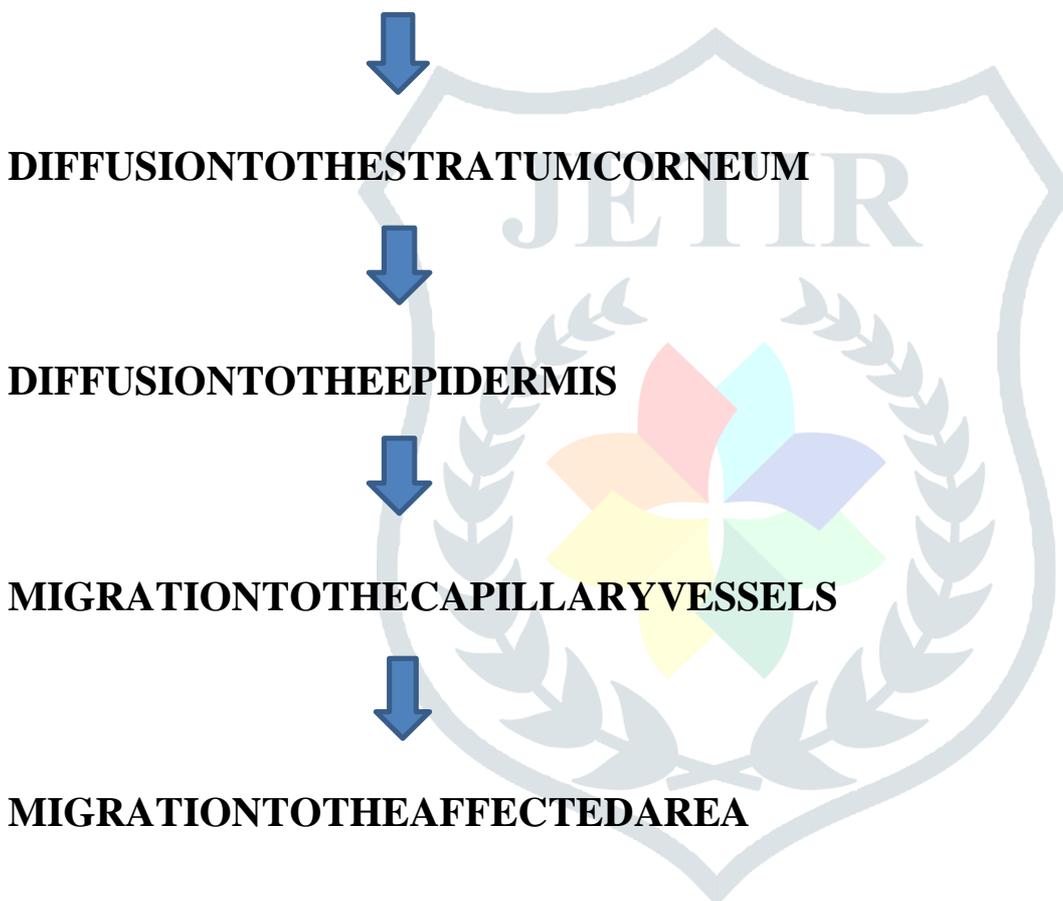
◦ **Lobular Panniculitis:** This type affects the lobules (small sections) of the fat.

◦ **Septa Panniculitis:** This type affects the connective tissue that separates fat lobules.

• **Connection to Cellulite:** The septa (the connective tissue) can cause cellulite. It can trap water and lymph fluid, leading to a bumpy or irregular appearance under the skin (8).

**MECHANISMOFACTION:**

The drug first gets through the outer layer of skin and then moves into the deeper layers, including the dermis, without building up in that area. Once the drug reaches the dermis, it can enter the bloodstream through the tiny blood vessels there(9).

**RELEASEFROMTHEBASEMATERIALOFTHEPATCH****BENEFITS AND RISK OF ESTROGEN PATCHES:**

Estrogen is the best treatment for menopausal symptoms like hot flashes. Women who still have a uterus need to take estrogen with a progestogen to protect their uterus. If a woman doesn't have a uterus, she can take estrogen alone. The decision to use hormone therapy (HT) should consider a woman's age, how long it's been since she went through menopause, and her overall health. It's important to talk with a healthcare provider to decide the best type of hormone therapy, how to take it, and when it might be

best to stop using it(10).

## **HOW TO USE ESTROGEN PATCHES:**

When to start it If you are not already using HRT, you can start Estradiol Transdermal Patches at a convenient time for you. If you are already using a different type of HRT, your doctor can advise you when to switch to Estradiol Transdermal Patches.

### **How much to use**

Estradiol Transdermal Patches patches come in four strengths. You will usually start with the Estradiol 0.025mg/day Transdermal Patches patch. Your doctor will check your progress and may change you to a different strength, depending on your response to treatment(11).

## **EFFICACY OF ESTROGEN PATCH:**

### **1) Improvement in vaginal dryness:**

Estrogen patches are worn on the skin and release a steady amount of estrogen into the bloodstream. This helps raise estrogen levels in the body, which can improve vaginal health by increasing moisture, reducing irritation, and improving the flexibility of vaginal tissues.

Research shows that estrogen patches are very effective in reducing vaginal dryness. For example:

- A 2018 study published in *Menopause* found that women who used estrogen patches for 12 weeks saw a big improvement in vaginal dryness and overall vaginal health.
- A 2020 study in the *Journal of Women's Health* showed that estrogen patches helped relieve vaginal dryness and other menopause-related symptoms better than a placebo.

**More Vaginal Moisture:** Estrogen patches directly help the vaginal area by restoring moisture and easing dryness.

**Less Irritation and Pain:** Estrogen therapy can reduce discomfort, burning, and pain during sex.

□ **Convenience:** Patches are easy to use and non-invasive. You typically apply them once or twice a week.

## 2) Relief of menopause symptoms

Estrogen patches work by releasing a steady amount of estrogen through the skin into the bloodstream. This helps replace the estrogen that drops during menopause. Estrogen is important for regulating body temperature, and when levels fall, it can cause hot flashes and night sweats. By restoring estrogen, these patches can help reduce these symptoms

1. **Hot Flashes:** Research shows that estrogen patches are very effective in reducing hot flashes. For example:

- A 2013 study in *Menopause* found that estrogen patches helped lower both the frequency and severity of hot flashes in women after menopause.
- A large study in *JAMA* (2018) also showed that these patches reduced hot flashes and made them less intense.

2. **Night Sweats:** Estrogen patches are also helpful for night sweats, which often happen along with hot flashes. Studies show:

- Estrogen therapy, including patches, is one of the best treatments for night sweats, reducing both how often and how strongly they occur.
- A 2020 study in *The Journal of Clinical Endocrinology & Metabolism* showed that estrogen patches worked better than a placebo in reducing night sweats

**Quick Relief:** Many women start feeling better within a few weeks of using estrogen patches, with reduced hot flashes and night sweats.

**Steady Hormone Delivery:** Estrogen patches give a steady amount of estrogen, helping to keep hormone levels stable and provide consistent relief.

**Fewer Side Effects:** Estrogen patches are less likely to cause side effects like

nausea or stomach issues, which can happen with oral estrogen, because the estrogen is absorbed through the skin instead of the stomach.

### 3) **Prevention of osteoporosis:**

Estrogen plays a crucial role in regulating bone remodeling, which is the process where old bone is replaced by new bone tissue. During menopause, estrogen levels drop significantly, which makes bone remodeling less efficient. This leads to bone loss and an increased risk of fractures. Estrogen therapy, such as estrogen patches, can help slow down bone loss and maintain bone density by restoring estrogen levels in the body.

1. **Bone Density Improvement:** Studies show that estrogen patches are effective in preventing bone loss in postmenopausal women. For instance:

- A study published in *The Journal of Clinical Endocrinology & Metabolism* (2003) found that estrogen therapy, including transdermal estrogen patches, was successful in maintaining bone density and reducing the risk of fractures in postmenopausal women.

- A meta-analysis in *JAMA* (2002) demonstrated that estrogen therapy significantly increased bone mineral density (BMD)

in areas like the spine and hips, which are commonly affected by osteoporosis.

2. **Reduction in Fracture Risk:** Estrogen patches not only help prevent bone loss but also lower the risk of fractures. For example:

- A study published in *Osteoporosis International* (2009) showed that estrogen therapy reduced the risk of spine fractures by about 30–50% in postmenopausal women.

- Research also suggests that estrogen patches help reduce the risk of hip fractures, a major concern for women with osteoporosis

3. **Improved Bone Density:** Estrogen patches help maintain or increase bone mineral density (BMD), which lowers the risk of fractures, particularly in the spine and hip.

4.

5. **Convenient and Steady Hormone Delivery:** Estrogen patches provide a consistent dose of estrogen, absorbed through the skin, which avoids the gastrointestinal system. This makes them a convenient option for many women.
6. **Reduced Risk of Fractures:** Estrogen therapy, including patches, is associated with a reduced risk of fractures, especially in the spine and hip, which are common sites for osteoporosis-related fractures.

## **.SAFETYOFESTROGENPATCH RISKOFBLOODCLOTANDSTROKE**

Estrogen patches are generally safe for many women, but they can have some risks, especially for those with certain health problems or higher risk factors. One main concern with estrogen therapy, including patches, is the higher risk of blood clots, which can cause deep vein thrombosis (DVT), pulmonary embolism (PE), or even stroke. Estrogen can make blood clot more easily, and while estrogen patches have a lower risk of blood clots compared to pills, the risk is still there. Women with a history of blood clots, blood clotting problems, obesity, smoking, or those who are inactive or over 60 are at higher risk. Estrogen therapy can also slightly increase the risk of stroke, especially for women with high blood pressure, smoking habits, or heart disease. The risk is lower for healthy women under 60 who don't smoke, but it increases for older women or those with other health problems(12).

### **1) RISKOFBREASTCANCERANDENDOMETRIALCANCER**

Estrogen therapy, including estrogen patches, can slightly increase the risk of certain cancers, such as breast and endometrial cancer. The risk depends on the duration of use, the type of estrogen, and whether it is combined with other hormones like progesterone. Estrogen patches can slightly raise the risk of breast cancer, especially with long-term use, as estrogen alone may promote the growth of some breast cancer cells.

However, estrogen patches might have a lower risk compared to oral estrogen because they deliver the hormone through the skin, bypassing the liver. While the

risk is lower, it is not completely eliminated. When estrogen is combined with progesterone (combined hormone therapy), the risk of breast cancer can be higher, as progesterone can also stimulate breast cell growth. Regarding endometrial cancer, using estrogen alone (without progesterone) can increase the risk, particularly for women who have a uterus, as estrogen can cause the uterine lining to become too thick. However, when estrogen is combined with progesterone, the risk of endometrial cancer is much lower because progesterone helps prevent the overgrowth of the uterine lining(13).

## **FUTURE PROSPECT:**

### **Future Prospects of Estrogen Patches for Hormone Replacement Therapy**

1. **Personalized Medicine:** Advances in genetics and biomarkers could help doctors create customized hormone therapy plans. This means estrogen patches could be tailored to fit each woman's unique health needs and symptoms.
2. **Improved Formulations:** Research may lead to better estrogen patch designs that improve how the hormone is delivered, make it more effective, and reduce side effects. There's even the possibility of developing "smart patches" that release hormones based on the body's needs.
3. **Combination Therapies:** Future research might look at combining estrogen patches with other treatments, like progestogens or non-hormonal options, to provide better symptom relief while minimizing risks.
4. **Long-term Safety Studies:** As more women use estrogen patches for longer periods, it's important to study their long-term safety. This includes understanding any potential risks, like heart issues or breast cancer.
5. **Education and Awareness:** Raising awareness about menopause and treatment options can help women feel empowered to seek help. Better education can lead to more informed choices about hormone therapy.
6. **Global Accessibility:** Efforts to make estrogen patches available in different healthcare settings can provide better options for women around the world, especially in areas where access to hormone treatments is limited.
7. **Integration of Technology:** Using telehealth and digital tools can help

women manage their hormone therapy remotely, allowing for easier adjustments and better support.

## CONCLUSION:

Estrogen patches represent a highly effective and convenient option for hormone replacement therapy in menopausal women, alleviating symptoms such as hot flashes, vaginal dryness, and promoting bone health. By bypassing first-pass metabolism, these patches minimize potential side effects associated with oral estrogen, enhancing patient compliance. The choice to initiate HRT should be personalized, taking into account individual health profiles, risks, and preferences. Overall, estrogen patches provide a promising solution for managing menopausal symptoms, warranting continued research to optimize their use and understand long-term implications.

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