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Review of Transdermal Patches Including Menthol Crystal and Eucalyptus Oil: Design, Manufacturing, Development, and Physicochemical Assessment

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Abstract

Transdermal drug delivery systems (TDDS) provide a regulated & continuous release of medicinal substances through the skin, making them a viable substitute for

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traditional methods. Herbal transdermal patches for anti-inflammatory purposes utilize bioactive compounds derived from medicinal plants such as aloe vera, eucalyptus oil, and menthol. These patches bypass first-pass metabolism, improve patient compliance, and provide localized as well as systemic effects with minimal side effects compared to synthetic drugs. Usually, polymers, plasticizers, and penetration enhancers are mixed with herbal extracts in the formulation, which is prepared using techniques like solvent casting, mercury substrate, and aluminum-backed adhesive film. Physical attributes like as thickness, tensile strength, folding durability, moisture content, uptake, and % break elongation test are among the evaluation criteria. Herbal transdermal patches show promising potential in managing inflammatory conditions like arthritis, muscle pain, and swelling, offering a safer, natural, and patient-friendly approach for long-term therapy.

Keywords: Aloe Vera, Eucalyptus oil, Glycerin, HPC, Menthol crystal, Skin, Transdermal patches (TDP).

1. INTRODUCTION

Transdermal drug delivery systems were introduced around three decades ago as an innovative method for administering medications. (Pulipati et al., 2025.) The development in the 1970s began in 1979 with the approval of the first FDA-approved patch, a three-day contraption that prevents sea sickness by administering scopolamine. The introduction of nitroglycerin patches in 1981 paved the way for a wide range of transdermal products. Clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, estradiol, oxybutynin, scopolamine, and testosterone are a few of the medications for which patches are now marketed. Additionally, combined patches for hormone replacement treatment and contraception have been created; Depending on the drug, their durations typically range from one to seven days. (Mali, 2015)

The concept attracted significant attention from the pharmaceutical industry throughout the 1980s and 1990s, eventually leading to the consolidation of many transdermal technology companies by the mid-to-late 1990s. Unlike conventional topical formulations such as creams and ointments, which are mostly used for localized skin conditions, transdermal patches deliver medications systemically at a controlled and sustained rate. This contemporary method improves patient adherence in addition to therapy efficacy and safety. Furthermore, transdermal administration offers a clear benefit over oral or injectable drug delivery methods by avoiding the first-pass metabolism. (Purushotham & Vijetha, 2023)

1.1. *Transdermal Drug Delivery System*

The words "trans," which means across or through, and "derma," which means skin, are the basis of the term "transdermal." (Rana et al., 2016) Transdermal drug delivery (TDD is not painful, non-invasive method of systemically putting the formulation to intact, healthy skin in order to distribute medication. The medication passes through the SC in skin after application, and then continues on to the dermis and epidermis, where it is mostly or entirely maintained. Once the drug reaches the dermal region and enters the microcirculation, it can be absorbed systemically (Alkilani et al., 2015).

Benefits of this approach include increased patient compliance due to lower dosage frequency and appropriateness for patients who are unconscious, vomiting, or self-medicating. (Alkilani et al., 2015) Often called patches, Transdermal Drug Delivery Systems (TDDS) are customized dose forms intended to deliver a therapeutically regulated amount of medicine applied topically. Transdermal delivery offers clear benefits over oral and injectable techniques by improving patient compliance and avoiding first-pass metabolism. (Alkilani et al., 2015)

1.1.1. *Definition*

Medicated adhesive devices called transdermal patches, occasionally called skin patches, are placed to the skin and release a controlled quantity of medication into the bloodstream through the skin. (Mali, 2015)

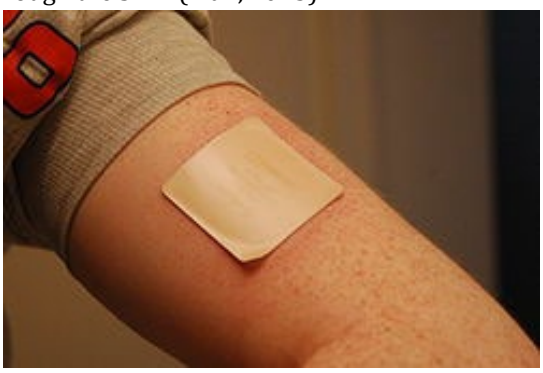

Fig. 1. Transdermal Patch.

1.1.2. *Components of TDDS*

The following are the main parts of a Transdermal Patch:

- **Release liner**: The patch is shielded by this layer while being stored. And is eliminated right before application.
- **Drug reservoir**: Considered the most critical part of the TDDS, the reservoir contains the active drug either dissolved or dispersed within a suitable matrix. Different solvents and co-solvents are incorporated to enhance solubility, and their influence must be carefully evaluated during formulation.
- **Adhesive**: The adhesive keeps the interior parts of the patch together and guarantees that it stays affixed to the skin. It must exhibit strong adhesion so that the patch stays in place for the required duration. Typically, pressure-sensitive adhesives are employed, such as silicone-based, polyisobutylene-based, and polyacrylate-based adhesives.
- **Membrane**: This layer regulates the discharge of medication from the reservoir in single- or multilayered patches. The presence or absence of a rate-controlling membrane, but flexibility is essential to prevent cracking or

splitting when the patch is stretched or bent. Commonly used membranes include cellulose acetate, polyethylene films, and ethylene-vinyl acetate copolymer.

- **Backing laye**r: By providing external protection, the backing shields the patch from the weather. In addition to supporting the entire system and protecting the drug reservoir, it must be impermeable to the drug and penetration enhancers. Materials typically used for this purpose are polyesters, aluminized polyethylene terephthalate, and siliconized polyethylene terephthalate. Purushotham & Vijetha, 2023)

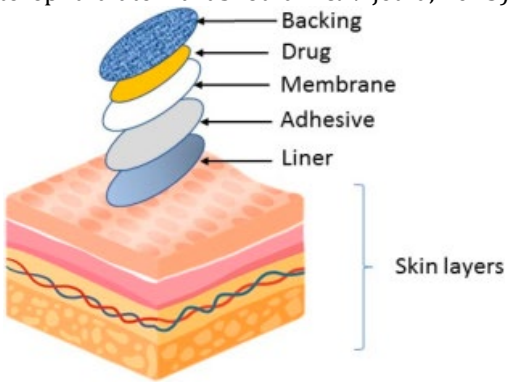

Fig. 2. Basic components of a transdermal medical patch.

1.2. *Transdermal Patch Types (Mali, 2015)*

1.2.1. *Adhesive single-layer drug*

With this method, the medication is included into the sticky layer. As a result, the adhesive not only holds the patch's constituent parts together and secures the device to the skin, but it also directly facilitates the release of medication. The backing layer and a protective release liner, which is taken off before usage, encapsulate the adhesive layer.

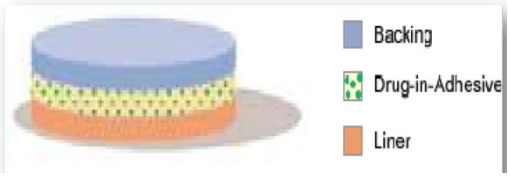

Fig. 3. Adhesive single-layer drug.

1.2.2. *Adhesive multi-layer drug*

Due to their shared reliance on adhesive layers for drug release, this method and the single-layer variant are fairly comparable. In contrast, the multi-layer variant features an additional drug-in-adhesive layer that is often (but not always) separated by a

membrane. Similar to the single-layer patch, it completes the system with a backing and a release liner.

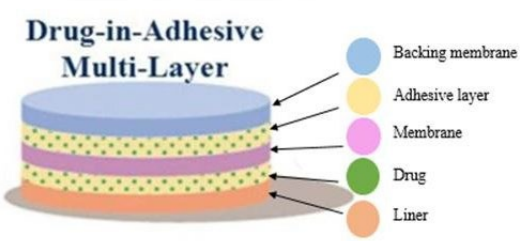

Fig. 4. Adhesive multi-layer drug.

1.3. *Reservoir System*

Unlike methods that rely on adhesives, the reservoir patch features a separate medication compartment. Here, an adhesive coating keeps the medication away from the skin while it is kept in liquid form as a suspension or solution. The patch is supported by the supporting layer, and this kind of technology often releases the medicine at a zero-order rate, which is a steady release throughout time.

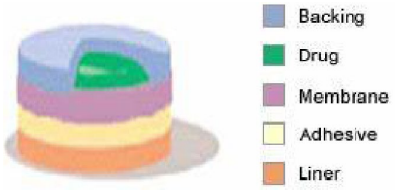

Fig. 5. Reservoir.

1.4. *Matrix System*

This kind has the medication suspended or in solution within a semisolid matrix. In order to help the system adhere to the skin and allow for regulated medication release, the adhesive layer partially overlaps rather than completely covers the drug layer.

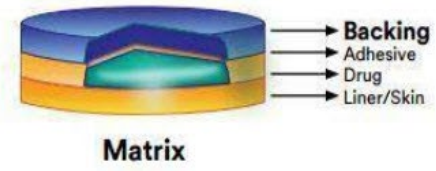

Fig. 6. Matrix system.

1.5. *Advantages of Transdermal Patches*

- Avoid intestinal metabolism, hepatic first pass metabolism, and salivary metabolism.

- In an emergency, the patch can be removed from the skin's surface at any moment.
- Simple medication delivery removal in the event of toxicity. (Patel & Shah, 2018)
- By avoiding certain issues related to the drug, transdermal distribution can enhance the therapeutic effectiveness of numerous medications. For instance, gastrointestinal distress, decreased absorption,
- Decomposition as a result of the "hepatic first pass" impact.
- They are noninvasive, they avoid the inconvenience of parenteral therapy.
- By withdrawing Drug therapy can be promptly discontinued by applying the medication from the skin's surface.
- With these systems, self-administration is possible.
- It provides an extended period of activity. (Purushotham & Vijetha, 2023)

1.6. *Transdermal patches' drawbacks*

- Only highly potent drugs can be effectively administered through transdermal systems. (Purushotham & Vijetha, 2023) (Mali, 2015)
- Some patients may irritate the skin where it is applied. (Purushotham & Vijetha, 2023) (Patel & Shah, 2018)
- The method can be costly compared to other drug delivery systems. (Purushotham & Vijetha, 2023)
- Transdermal treatment is typically not appropriate for ionic medications (Purushotham & Vijetha, 2023) (Patel & Shah, 2018). This method works best for medications that have a low molecular weight (less than 500 Daltons). (Purushotham & Vijetha, 2023)
- Maintaining adhesion of the patch for a long period can be challenging. (Purushotham & Vijetha, 2023)

2. SKIN

The largest organ in the human body is the skin, with 1.2 to 2.2 m^2 of surface area. With a weight of roughly 4–5 kg (9–11 pounds), it accounts for almost 7% of an adult's body weight. Its thickness ranges between 1.5 and 4.0 mm. The skin serves multiple roles, including sensory perception, metabolic activities such as synthesis, excretion, and absorption. One of its primary functions is to shield the body against water loss and protect it from mechanical, chemical, microbial, and physical harm. The outermost layer, the epidermis, provides the skin with its protective characteristics. (Sheth & Mistry, 2011)

Three functioning layers make up the skin:

1. The epidermis
2. The dermis
3. The Hypo dermis (subcutaneous tissue)

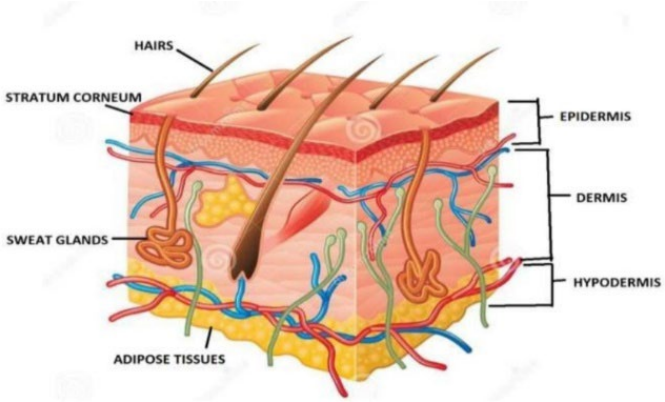

Fig. 7. Skin.

2.1. *Epidermis*

The outermost layer of the skin, the epidermis, is essential for protecting the body from outside factors. As old cells are shed and replaced, it is composed of numerous cell layers that are continually replenished. (Yilmaz et al., 2023) This layer acts as a waterproof barrier and lacks blood vessels. Keratinocytes are one of its primary cell kinds; they generate keratin, which fortifies and shields the skin. Langerhans cells, which are critical for immunological defense, and melanocytes, which control skin color, are also found in the epidermis. (Saharan et al., 2024)

There are multiple sublayers of the epidermis, including:

1. Stratum corneum
2. The stratum lucideum
3. Granulosum stratum
4. The stratum spinosum
5. The Basal Stratum

2.1.1. *Stratum Corneum*

Dead skin cells that make up the stratum corneum, the outermost layer of the epidermis provides the body with a protective barrier.

2.1.2. *Stratum Lucidum*

This thin, transparent layer offers further protection against environmental stress and friction and is primarily found in areas of thick skin, such as the palms and soles.

2.1.3. *Stratum Granulosum*

Protecting the underlying layers, this layer acts as a transitional zone and enhances the skin's defenses.

2.1.4. *Stratum Spinosum Layer*

The slightly larger which contains actively dividing cells, supports the skin's structure.

2.1.5. *Stratum Basale*

It is the that produces new skin cells, which is located at the base of the epidermis. (Yilmaz et al., 2023)

2.2. *Dermis*

The Dermis, the deeper a layer of the skin, lies between the epidermis and the subcutaneous tissue. With a thickness of 1 to 5 mm, in comparison to the epidermis, it is somewhat thicker.

It is composed of various structures, such as:

1. Blood vessels
2. Follicles of hair
3. The glands that produce sweat
4. The sebaceous glands
5. Nerve terminations
6. Fibers of collagen and elastin.

The main function dermis is:

- The dermis' primary roles are to protect
- Nourish the epidermis.
- Contributing significantly to the healing of wounds. (Sharma et al., 2013)

2.3. *Hypodermis*

The hypodermis is the skin's deepest layer. or subcutaneous tissue. It serves as a location to store fat and supports the dermis and epidermis. In addition to providing a nutritional reserve and protecting the body from mechanical stress, this layer is essential for controlling body temperature. (Tiwari et al., 2022) When topical medications such as creams or patches are applied before entering the bloodstream, they have to go through all three layers of the skin. (Saharan et al., 2024)

3. WORKING OF TRANSDERMAL PATCHES

In transdermal administration methods, drugs enter the body through the skin in two main ways: the Trans epidermal route, which travels through the epidermis directly, and the trans appendageal pathway, It utilizes skin features such as sweat glands and hair follicles.

3.1. *Transepidermal channel*

Medication enters the body through the transepidermal channel through the stratum corneum, which is the skin's outermost layer. This layer has a complex structure and is a multicellular, multilayered barrier.

- **Intracellular Route**: Specialized skin cells called corneocytes allow the passage of some drugs. For polar or hydrophilic solutes—compounds that dissolve in water—this technique is appropriate.
- **Intercellular Route**: The gaps between these skin cells allow other medications to pass through. This method is for compounds (lipophilic or non-polar solutes) that dissolve in fats. They pass through the skin's constant adipose layer. (Saharan et al., 2024)

3.2. *The Transappendigeal System*

Drugs in this system pass via the sweat glands and hair follicles on the skin. Large, challenging-to-transport macromolecules across epidermal cells because of their size and distinct partition characteristics can be moved via this channel. It is also necessary for moving polar or ionisable compounds. (Purushotham & Vijetha, 2023) (Alkilani et al., 2015)

3.2.1. *Hair Follicles and Sweat Glands*

Certain substances can enter via these small holes or passages in the skin. (Saharan et al., 2024)

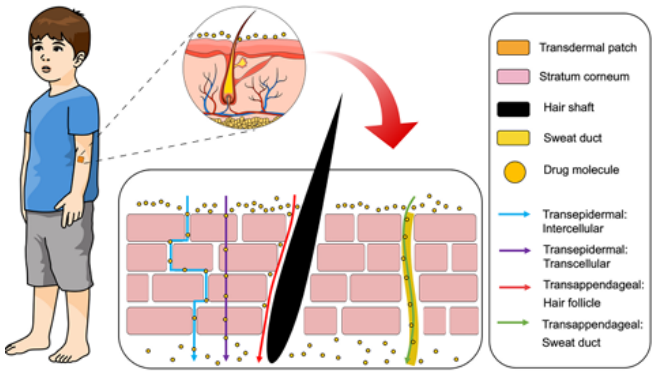

Fig. 8. Drug permeation routes across the skin.

4. MATERIALS AND METHODS

4.1. *Materials*

4.1.1. *Eucalyptus Oil*

- **Botanical name**: Eucalyptus globulus
- **Family**: Myrtaceae
- **Genus**: Eucalyptus
- **Order**: myrtales
- **Molecular formula**: $C_{10}h_{18}O$
- **Chemical constituents**: 8-cineole [eucalyptol], α-pinene, limonene, comphene, p-cynene, γterpinene, globulol, aromadendrene, and α-terineol are the chemical components.

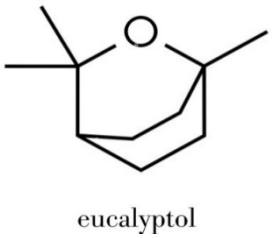

Fig. 9. Chemical Structure of Eucalyptol.

Eucalyptus citriodora and Eucalyptus globulus are the two most common eucalyptus species in India. It is known by various regional names throughout the nation, including Karpuramaram (Tamil), Safeda (Hindi), Harit Parn (Gujarati), Blue-gum (English), and Taliparna (Sanskrit). (Soral et al., 2021)

The leaves of Eucalyptus globulus, a member of the Myrtaceae familyproduce eucalyptus essential oil, which is valued for its many biological benefits. Its chief constituent is eucalyptol (1, 8-cineole), a monocyclic monoterpene ether that constitutes nearly 70–90% of the oil. In addition, smaller amounts of compounds such as limonene, cuminaldehyde, α-pinene, α-phellandrene, p-cymene, terpinen-4-ol, and trans-pinocarveol. Clinical investigations have examined its effectiveness in conditions such as muscle pain, high blood pressure, migraines, COVID-19, tick infestations, gingivitis, and dental plaque.

Therapeutic applications: Eucalyptus oil is known for its anti-inflammatory action, which helps reduce pain and swelling in disorders such as rheumatoid arthritis. Moreover, research has also indicated its potential antioxidant activity. (Surbhi et al., 2023)

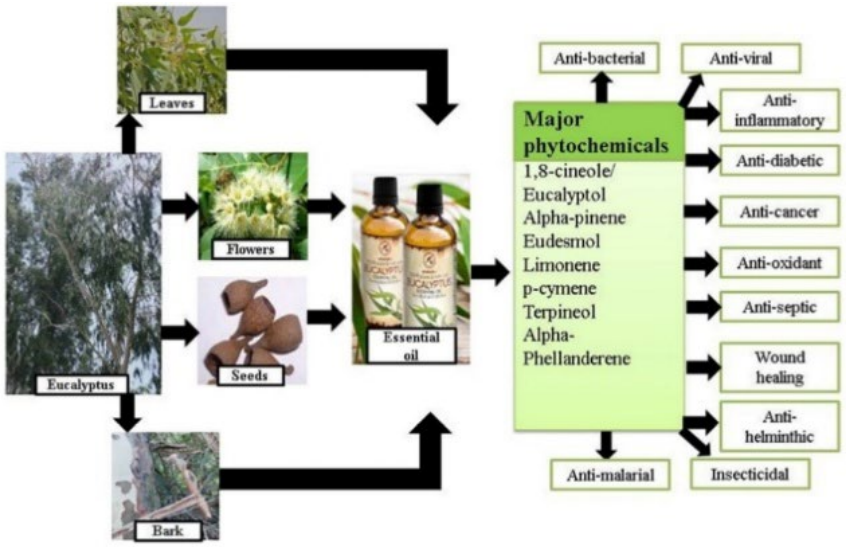

Fig. 10. Illustration of the main components of eucalyptus, together with their phytochemicals and associated health advantages.

4.1.2. *Aloe Vera*

Fig. 11. Aloe Vera gel.

- **Botanical name**: Aloe Vera
- **Family**: Asphodelaceae
- **Genus**: Aloe
- **Order**: Asparagales
- **Species**: Aloe Vera
- **Molecular formula**: $C_{21}H_{22}O_9$

- **Chemical constituents**: Polysaccharides, anthrquinones, vitamins, enzymes, minerals, phenolic compounds, amino acid, fatty acid, saponins. (Askarov et al., 2022)

Because aloe Vera gel's polysaccharides are biocompatible, biodegradable, and safe for skin application without generating negative side effects, they can be used as polymers in transdermal patches. (Puttarak et al., 2015) Aloe Vera is rich in flavonoids and tannins, which exhibit anti-inflammatory, astringent, and soothing properties, helping to alleviate pain [23]. Its moisturizing ability has been extensively demonstrated through various topical formulations. (Yustiza et al., 2023.)

4.1.3. *Hydroxypropyl Cellulose (HPC)*

The selection of an appropriate polymer for the formulation is crucial in the creation of film-forming polymeric solutions as TDDS. In addition to influencing the mechanical characteristics of the resulting film, such as its abrasion resistance or flexibility, its ability to adhere to the skin (in conjunction with the plasticizer), or its appearance (transparency, smoothness, and gloss), the drug's capacity to pass through the film and enter the skin is also influenced by the film former. Drugs and polymers may interact in a variety of ways, such as through hydrogen bonds, ionic forces, or the extent to which the drug is soluble in the polymer, depending on their chemical characteristics.

The polymer's capacity to affect the drug's physical state in the matrix by functioning as a crystallization inhibitor may be a significant factor influencing drug penetration. The medication dissolves entirely when the formulation is put to the skin. The drug concentration in the formulation increases when the solvent evaporates, increasing the drug's thermodynamic activity and, consequently, its flow. (Esuendale & Gabriel, 2016)

HPC functions as a polymer in transdermal patches (TDP). It is a non-ionic, water-soluble derivative of cellulose (Soral et al., 2021), widely applied as a coating agent, emulsifier, stabilizer, suspending agent, thickener, film former, tablet binder, and as a matrix for sustained-release formulations. HPC has also been employed in the preparation of nanofibers. Studies have shown that incorporating HPC into polyurethane (PU) nanofiber mats can improve the drug release rate. Nevertheless, there is still no documented evidence regarding the direct influence of HPC alone on the release rate when combined with PU. (Gencturk et al., 2017)

4.1.4. *Menthol*

- **Biological name**: Mentha arvensis.
- **Family**: Lamiaceae.
- **Order**: Lamiales.
- **Genus**: Mentha.
- **Synonym**: pudina, brandy mint, peppermint.
- **Molecular formula**: $C_{10}H_{20}O$. (bin Hasnadi & Razak, 2022)

- C**hemical constituents**: menthol, menthol Easters, mentho furan, methane, methyl acetate, methyl isovalerate, jasmone.

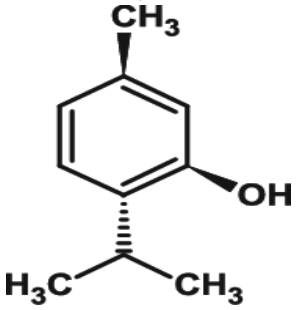

Fig. 12. Structure of Menthol.

Fig. 13. Menthol Crystal.

4.1.4.1 Menthol crystal

Menthol is a cyclic monoterpene alcohol obtained mainly from peppermint, which is rich in menthol. It is considered one of the most significant flavoring agents after vanilla and citrus. Menthol is widely incorporated as a cooling and flavor-enhancing compound in pharmaceuticals, cosmetics, insect repellents, confectionery items, chewing gums, liqueurs, toothpastes, shampoos, and soaps. (Li et al., 2022) In addition, it is commonly employed as a penetration enhancer due to its strong efficiency and favorable safety profile. (Chen et al., 2019)

4.1.5. *Glycerin*

Glycerin is used as a plasticizer. (Lynthong et al., 2022.) (Ramadon et al., 2022) Glycerin improves the solubility of active ingredients and moisturizes the stratum corneum, which improves penetration. Additionally, glycerin raises the value of hygroscopic moisture patches.

Table 1. Ingredients and their role.

Sl. No	Ingredients	Role
1	Eucalyptus oil	Anti-inflammatory
2	Aloe Vera	Anti-inflammatory, permeation enhancer
3	HPC	Polymer
4	Menthol crystal	Cooling effect, permeation enhancer
5	Glycerin	Plasticizer

5. METHODS

5.1. *Different Techniques for TDDS Preparation*

1. The method of solvent casting
2. The technique of mercury substrate
3. The process of aluminum-backed adhesive film

5.1.1. *Method 1: Method of Solvent Casting*

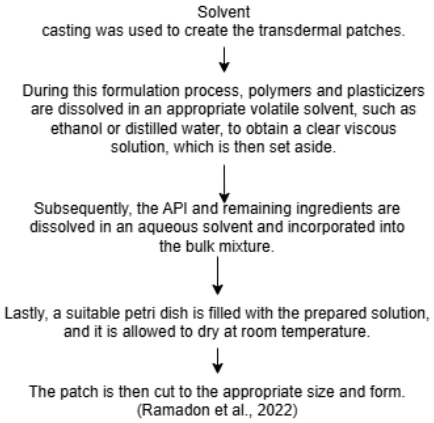

Fig. 14. Method of Solvent Casting.

5.1.2. *Method 2: The Technique of Mercury Substrate*

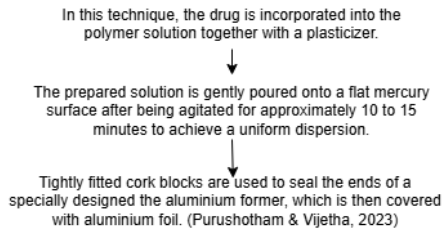

Fig. 15. Method 2: The Technique of Mercury Substrate.

5.1.3. *Method 3: The Process of Aluminium-backed Adhesive Film*

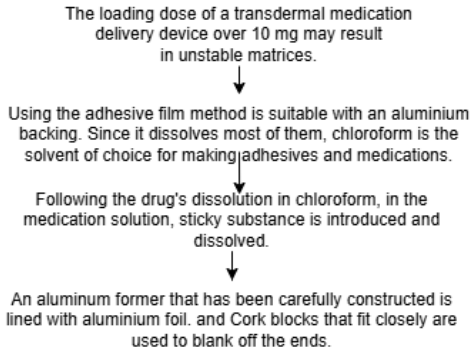

Fig. 16. Method 3: The Process of Aluminium-backed Adhesive Film.

6. ASSESSMENT

6.1. *Physical appearance*

To evaluate the created patches' color, transparency, air bubble presence, flexibility, and surface smoothness, a visual inspection was conducted.

6.1.1. *Thickness*

The thickness of the patch was assessed using a digital thickness gauge, taking measurements at four distinct locations, and the mean value was calculated. (Shivalingam et al., 2021)

6.1.2. *Weight Uniformity*

Three patches were randomly selected for each formulation. The mean weight of the three samples was then calculated after weighing each patch independently to look for weight variation. (Zhang et al., 2022.)

6.1.3. *Folding Endurance*

To evaluate the plasticizer's efficacy, folding endurance was measured. During this test, the prepared patches were repeatedly folded by hand at the same location until they broke. The greatest number of folds a patch could withstand in one place before breaking was known as folding endurance. (Trivedi & Goyal, 2020)

6.1.4. *The Moisture Content Percentage*

After accurately weighing the patches, they were exposed to anhydrous calcium chloride in a desiccator. They were removed and weighed again after three days.

Using the previously established techniques, the moisture content of the transdermal patches was computed as a percentage. (Gowda et al., 2025)

$$\%\ Moisture\ Content = \frac{Beginning\ Weight - Final\ Weight}{Initial\ Weight} X\ 100 \quad (1)$$

6.1.5. *Studies on Moisture Absorption*

After carefully weighing the patches, they were placed within a desiccator with 100 milliliters of an aluminum chloride-saturated solution that kept the relative humidity at 84%. Three days later, the patches were removed and weighed. Using the following procedure, the percentage of moisture absorption was determined. (Borkar et al., 2021.). The percentage Final weight minus beginning weight ÷ final weight × 100 is the moisture uptake.

6.1.6. *The Test for Percentage Elongation Break*

After recording the length right prior to the breaking point, the percentage elongation break was calculated using the formula below.

$$\%\ Elongation = \frac{\text{Final length of strip} - \text{Intial length of strip}}{\text{Intial length of strip}} X\ 100 \quad (2)$$

6.1.7. *Tensile Strength*

A tensiometer (Erection and Instrumentation, Ahmedabad) was used to measure the patch's tensile strength. The apparatus is made up of two grips that are fixed to load cells; the upper grip is moveable. Two-by-two-centimeter film strips were placed between the grips and a steady strain was applied until the strip broke. The dial reading was then converted to kilograms to establish the tensile strength.

7. CONCLUSION

Innovative topical medicine delivery devices called herbal transdermal patches are made to transport anti-inflammatory substances derived from plants straight through the skin and into the bloodstream. Compared to oral dose forms, they offer regulated and reduced gastrointestinal adverse effects, enhanced bioavailability, avoided first-pass metabolism, and extended medication release. Common herbal extracts used include Aloe Vera, Eucalyptus oil, Menthol, which exhibit anti-inflammatory, analgesic, and soothing effects. The patch matrix is usually composed of polymers (HPC, HPMC, PVP, EC), plasticizers (glycerin, PEG), and adhesives, ensuring flexibility, adherence, and effective release of active ingredients.

The evaluation process includes physicochemical tests such moisture absorption, tensile strength, folding endurance, thickness, weight, percentage elongation at

break, and moisture content. To ascertain the effectiveness of drug delivery, it also includes skin penetration and in vitro drug release investigations.

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