FORMULATION AND EVALUATION OF TRANSDERMAL MEDICINAL PATCH ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT:
The term "pain" describes the breaking down or damage to bodies, cells, and bodily processes. The study consists of the goal that Solution finding out how effective the herbs in marigolds and spinach are at reducing pain when combined into a transdermal patch. Numerous phytochemicals from marigold and spinach in this study enhanced the healing of wounds. The current idea uses transdermal patches to promote wound healing and cure, improve, and prevent a variety of skin allergies. This study's primary goal is to create an herbal transdermal patch that contains marigold extract and spinach extract to treat skin conditions like redness and wound healing. In many nations, herbal remedies continue to be the mainstay of treatment for over 80% of the global population because of their few adverse effects. Moreover, they work better together than synthetic medications. The herbal remedy is made up of medicinal plants, as well as the roots and heeds of those plants, which are rich in different phytochemicals that aid in the treatment of a range of illnesses, injuries, and problems. The moisture content of the patch was found to be 66.67%. the flatness of the patch was determined by using the % flatness formula which was found to be 50%. This study has demonstrated the efficaciousness of marigold and spinach associated with the thickness of the patch was found to be 0.032mm and the standard range for thickness is between 0.16 ± 0.03mm. Randomly 10 patches were selected and the weight variation of patches was calculated, it was found to be 2.35mg. drug content of herbal transdermal patches is done by using UV visible spectroscopy. Although ointments and creams for the treatment of skin conditions have been the subject of numerous research, this one demonstrates the numerous cosmetic benefits of transdermal administration. TDDS has a wide range of potential applications in the future; these include photomechanical waves, bulk penetration techniques, and more. It possesses numerous novel techniques.

Keywords: - Herbal medicine, transdermal patches, marigold, and spinach; healing of wounds.

INTRODUCTION:
Transdermal drug delivery systems are novel drug delivery methods that concentrate on controlling the release and targets of various medications. Version of the system: extended release, target release, delayed release, system update, etc. Because of their multiple benefits and medication-use methods, transdermal drug delivery systems are employed in many applications to provide therapies including local anesthetics and anti-inflammatory agents.medications because of their numerous benefits and usage techniques. Innovation in TDDS has as much room for growth as advancements in healthcare. TDDS often avoids first-pass metabolism and increases the drug's bioavailability. To extend the medication's effects, TDDS aids in delivering the medication inside a therapeutic window. Drugs are delivered to the body through the skin in a controlled and continuous manner using transdermal therapy devices. It also gets rid of a lot of negative effects from traditional medication delivery methods, like discomfort during administration and first-pass drug metabolism. Usually, a transdermal patch that sticks to the skin is used to apply the drug. [1]
TRANSDERMAL PATCH:
An adhesive patch applied to the skin that delivers a precise drug release rate first is known as a transdermal patch. It enters the bloodstream and travels throughout the body. The majority of transdermal systems now available are built around patches, which are semi-permeable membranes. Transdermal drug delivery systems (TDDS), sometimes referred to as transdermal patches or skin patches, are bulk materials intended to administer drugs to the body that are useful in treating inflammation of the skin and nerves. [2, 3, 4, 5]

Too often, the body heals its wounds through stimulated veins. Scopolamine was the first commercially available medication for this illness to be licensed by the US Food and Drug Administration in December 1979. The nicotine patch is the most popular transdermal patch in the US; it distributes nicotine to aid in quitting smoking. In 2007, Europe approved the first vapor patch to be sold commercially to help people quit smoking. Numerous different patches are available on the market, such as those containing lidocaine, nitro-glycerine (used to treat angina), and fentanyl (a medicine used to treat severe pain). Lidoderm is the brand name of a patch that may lessen pain. Buprenorphine, sold under the brand name Bu Trans, is used to treat moderate to severe peripheral pain in cases of herpes zoster (shingles). Today, it is primarily used off-label to treat both acute and persistent pain. A topical NSAID called Flector (Diclofenac epolamine) Patch is used to alleviate severe pain brought on by small sprains, contusions, and strains. It is also used to alleviate pain in long-term illnesses including arthritis and fibromyalgia that respond well to non-steroidal anti-inflammatory medications. Its application in the production of anti-hormonal, anti-anxiety, and even antibiotics and stimulants for the treatment of deficiencies and hyperactivity disorder (ADHD) has increased due to recent advancements. In 2005, the FDA announced that it was investigating reports of drug overdose-related deaths and other adverse events in patients using Duragesic, a fentanyl transdermal patch used to control pain. Duragesic product information was updated to include safety information after June 2005. In 2009, the FDA issued a public health warning regarding the risk of burns during MRI examinations using metal-backed anti-inflammatory drugs. Patients should be instructed to remove anti-inflammatory medications before the MRI scan and replace them with new ones after the scan is completed. [6, 7]

![Transdermal Patch](image)

fig: -1 transdermal patch.

Skin structure:
Four distinct tissue layers make up the skin: the intact epidermis, the active substance, the useable skin, and the subcutaneous tissue. The skin's thin, protective outer layer is called the epidermis. The outer layer of the epidermis, known as the stratum corneum, is waterproof and keeps the majority of germs, viruses, and other foreign materials out of the body if it isn't damaged. In addition, the epidermis shields blood vessels, muscles, nerves, and internal organs from harm. The epidermis's keratin layer is somewhat thicker. The skin's active epidermal layer is between 50 and 100 µm thick. The living epidermis shares a physico-chemical structure with other living tissues. Numerous fibrils hold cells together. The humidity is about 90%. The dermis, the skin's next layer, is a thick layer of elastic and fibrous tissue that gives the skin its strength and flexibility. Blood vessels, sweat glands, sebaceous glands, and hair follicles are all found in the dermis. It is made up of blood and lymphatic vessels contained in loose, whitish, fibrous connective tissue. [8]
Types of Transdermal Drug Delivery Systems:

- **Single-Layer Drug Adhesive System:** In this kind of patch, the medication is contained in the body's sticky layer. The sticky layer is in charge of the drug's release in addition to certain skin functions that affect the skin as a whole. A backing and liner are used as temporary coverings for the adhesive layer.

- **Reservoir System:** The membrane that separates the rate control layer from the rear layer in this setup houses the chemical reservoir. Membrane release is regulated by the amount of medication that enters the micropores. The medication can be spread throughout a solid polymer matrix in the reservoir compartment, or it can be in the form of a gel, suspension, solution, or both.

- **Matrix Systems:**
  a) **Drug Binding Systems:** To reveal the polymer adhesive, a frost-free layer must be formed by melting from the solvent or adhesive (if using hot glue).
  b) **Matrix dispersion system:** The medication is combined with either a lipophilic or hydrophilic polymer matrix in this approach. The drug and polymer are immobilised on an occlusive substrate inside a drug-impermeable back sheet chamber. During this procedure, a sticky edge is produced by spreading the adhesive around the circular as opposed to coating the drug chamber's surface \(^9\).
Micro reservoir system: Reservoir and matrix-dispersion systems are combined in this system, wherein the drug is suspended in an aqueous solution of a water-soluble polymer before being uniformly dispersed in a lipophilic polymer to create thousands of tiny, impenetrable drug reservoir spheres.\(^{[10]}\)

**ADVANTAGES:**
- First-pass metabolisms of the drug get avoided.
- Gastrointestinal incompatibilities are avoided.
- Self-medication is possible.
- Duration of action gets extended & predictable.
- Unwanted side effects get minimized.
- Drug plasma concentration is maintained.
- The number of doses is reduced which improves patient compliance.
- The therapeutic value of many drugs is increased by avoiding problems associated with drugs like lower absorption, GI irritation, and decomposition due to hepatic first-pass metabolism.\(^{[11,12]}\)

**DISADVANTAGE:**
- Probability of allergic reactions, such as rashes, local edema, itching, etc., at the application site.
- Drugs with greater molecular sizes (over 1000) have more difficulty being absorbed.
- On the same or different people, the skin's barrier function differs depending on the location.
- Because of their lower permeability, drugs with hydrophilic character are less suited than those with lipophilic character.

**LIMITATIONS FOR SELECTION OF TDDS:**
- This method of administration cannot be used for any kind of medication; the medication needs to have certain desirable physicochemical characteristics.
- Unsuitable for medications requiring elevated plasma concentrations.
- Not appropriate for medications that cause contact dermatitis and skin irritation.
- Not appropriate for medications with large molecular weights.
- Unsuitable for medications that are metabolised while being transported through the skin.
- The transdermal method is not suitable for a big.
- Many medications, as the skin functions as an extremely effective barrier to prevent drug entry.
- It is only possible to provide a small dose.
- The skin's barrier properties vary from site to site within an individual, between individuals, and with ageing.\(^{[13]}\)

**MATERIAL AND METHOD:**

- **Material:**
  The Marigold Extract, Spinach Extract, Quercetin, and Terpenes extract [Citrus Fruit] were prepared in the lab. The Starch powder was obtained from Potatoes on a laboratory scale in Vidya Niketan College of Pharmacy, Lakhewadi. Chloroform and methanol were purchased from Swaroop Enterprises, Aurangabad, Maharashtra.

- **Preparation method of the transdermal patch:**
  - Asymmetric TPX membrane method.
  - Circular Teflon Mold method.
  - Mercury substrate method.
  - Use the "IPM film" method.
  - Use the "EVAC membrane" technique.
f) Preparation of TDDS using preformed liposomes.

g) Use the free film method.

h) Solvent casting method.

**Solvent casting method**: A drug-loaded matrix-type marigold transdermal patch is prepared by solvent casting method. Use a Petri dish with a total area of 44.15 cm². Carefully measure the polymer (starch), dissolve it in 10 mL of water and methanol (1:1) solution, and let it sit until a clear solution forms. Dissolve the medicine (spinach extract) in the above solution and stir until a clear solution is obtained. Quercetin (30% w/w of the total polymer) was used as the plasticizer and terpenes (15% w/w of the total polymer) as the penetrant. The resulting mixture is thrown into a Petri dish, lubricated with glycerol, and dried at room temperature for 24 hours. Place an inverted funnel over the Petri dish to prevent rapid evaporation of the solvent. After 24 hours, dried patches were removed and stored in a desiccator for further studies.¹⁴

**Methodology:**

```
Collection of all ingredients
i.e. marigold flower petals, spinach, orange peel, etc.

drying of marigold flower petals and orange peel in the shade

extraction of spinach from its leaves

after drying of marigold flower, the petals are collected and grinded to make the powder

Marigold extract is collected by sieving fine powder through a mesh/sieve

extraction of terpene and quercetin is done from orange peel by the Soxhlet extraction method

weigh all the ingredients

mix 8ml chloroform and 4ml methanol in a beaker using a magnetic stirrer

Then add 2.5 ml terpene and 2.5 ml quercetin
```
Repeat stirring continuously with a magnetic stirrer

Add each medicinal plant extract with continuous stirring with 10-15min (i.e. 5ml spinach extract and 5ml marigold extract)

Now add 5gm starch with constant stirring using a magnetic stirrer for 5min

But add 1gm starch at a time interval of 1 min

After 10-15min then formulation becomes viscous then it added to the glass petri plate which were coated using aluminum foil.

Then petri plate was placed in a hot air oven at 50°C for a certain time period for evaporation of the solvent

Generally, for 10-15 min

Dry film is separated

EVALUATION OF TRANSDERMAL ROUTES:

1. Physical and chemical measurements:
   - Thickness: The thickness of the transdermal membrane is measured from different points of the membrane using a kinetic meter, comparator, screw meter, or micrometer. [15,16,17]
   - Determination of the content of the drug: It can be determined by filling a small area (1cm²) of the polymer film with a certain volume of appropriate solvent. Choose a freely soluble solvent. Measure the selected area before dissolving in a solvent. All contents were shaken continuously for 24 h in a shaking incubator and then sonicated and filtered. Analyse chemicals in solution using appropriate analytical techniques. [18]
   - Moisture content: The prepared films were weighed one by one and stored in a desiccator containing calcium chloride at room temperature for 24 hours. The video gets heavier after a certain period until it finds a constant weight. Use the formula below to calculate moisture content. [19]
     \[
     \% \text{ moisture content} = \frac{(\text{starting weight} - \text{final weight}) \times 100}{\text{Final weight} \times \text{Moisture}}
     \]
   - Absorption: Keep the film weight on in a dryer at room temperature for 24 hours. It is then removed and exposed to 84% relative humidity in a desiccator using saturated potassium chloride solution until the weight becomes constant. The % moisture absorption is calculated as follows. [20]
% Moisture Absorption Rate = \frac{\text{Final Weight} - \text{Starting Weight}}{\text{Starting Weight}} \times 100

- **Flatness:** Transdermal patches should have a smooth surface and not fade or shrink over time. This can be seen by surveying the plains. Cut one strip down the middle of the patch and two strips on each side of the patch to determine flatness. The length of each strip is measured and the change in length is measured by determining the percent shrinkage. Zero percent shrinkage equals 100% flatness.

\[ \% \text{ Flatness} = \frac{(L_1 - L_2)}{L_1} \times 100 \]

Where,
\[ L_2 = \text{Final length of each strip} \quad \text{L}_1 = \text{Initial length of each strip}. \]

- **Tack properties:** The polymer can adhere to the substrate with little contact pressure. Tack is dependent on the molecular weight and composition of the polymer as well as on the use of tackifying resins in the polymer \([21]\) It includes a thumb tack test, rolling ball test, quick stick (Peel tack) test, and probe tack test. A thumb tack test is performed by touching the surface of a pressure-sensitive adhesive with the thumb and feeling the force required to break the bond. Thus, the force required to remove the thumb from the adhesive is a measure of tack. Measuring ball roll involves measuring the distance a stainless-steel ball travels with the rod pointing up. The less sticky the ball can travel further \([22]\)

- **Weight variation:** A specific area of patch is to be cut in different parts of the patch and weigh in the digital balance. The average weight and standard deviation values are to be calculated from the individual weights. The prepared patches are dried at 600°C for 4 hours before testing \([23,24,25,26]\)

**RESULTS:**

**Thickness:**
The thickness of the transdermal film is determined by the vernier caliper instrument. The thickness of the patch was found to be 0.032mm.

![Fig: 4 Herbal transdermal patch](image)

**Weight variation:**

Randomly 10 patches were selected and individually weighed, the weight of the individually weighed patches is given below:

<table>
<thead>
<tr>
<th>Patch Number</th>
<th>Weight of patch</th>
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<tbody>
<tr>
<td></td>
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<td></td>
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<td>---</td>
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</tr>
<tr>
<td>1.</td>
<td>4.319</td>
</tr>
<tr>
<td>2.</td>
<td>0.331</td>
</tr>
<tr>
<td>3.</td>
<td>4.447</td>
</tr>
<tr>
<td>4.</td>
<td>1.214</td>
</tr>
<tr>
<td>5.</td>
<td>1.260</td>
</tr>
<tr>
<td>6.</td>
<td>5.172</td>
</tr>
<tr>
<td>7.</td>
<td>1.492</td>
</tr>
<tr>
<td>8.</td>
<td>1.410</td>
</tr>
<tr>
<td>9.</td>
<td>3.377</td>
</tr>
<tr>
<td>10.</td>
<td>0.487</td>
</tr>
</tbody>
</table>

Weight variation is calculated by using the following formula:

\[
\text{Weight Variation} = \frac{\text{Average of weight}}{\text{Number of patches}}
\]

\[
= \frac{23.509}{10}
\]

\[
= 2.35\text{mg}
\]

**Determination of the content of the drug:**

Determination of the drug content of herbal transdermal patch is done by using UV visible spectroscopy.

![Graph of UV spectroscopy](image-url)
Moisture content:
The moisture content of the patch is calculated by using the following formula:

\[
\frac{\text{% moisture content}}{\text{Final weight Moisture}} = \frac{(\text{starting weight} - \text{final weight}) \times 100}{0.3}
\]

\[
= \frac{(0.5 - 0.3) \times 100}{0.3}
\]

\[
= 66.67\%
\]

Absorption:
The moisture absorption rate of a patch is calculated by using the following formula:

\[
\frac{\% \text{ Moisture Absorption Rate}}{\text{Starting Weight}} = \frac{\text{Final Weight} - \text{Starting Weight} \times 100}{0.5}
\]

\[
= \frac{0.7 - 0.5 \times 100}{0.5}
\]

\[
= 40\%
\]

Flatness:
The flatness of the patch is calculated by using the following formula:

\[
\frac{\% \text{ Flatness}}{\text{L1}} = \frac{(\text{L1} - \text{L2}) \times 100}{4}
\]

\[
= \frac{(4 - 2) \times 100}{4}
\]

\[
= 50\%
\]

Tack properties:
It is determined by the thumb tack test, the sticking time of patch was found to be 5 min.

CONCLUSION:
This medicinal herbal transdermal patch was prepared using marigold powder, spinach extract, and extracts of terpene and quercetin. Due to marigold high concentration of anti-inflammatory and antioxidant compounds, it is a popular ingredient in skincare products. It can reduce redness, and inflammation and speed up the healing of wounds. And marigold is suitable for all types of skin, herbal plants provide a rich source of healthcare to prevent and treat different pathological states. It contains quercetin which has exhibited a wide range of beneficial biological activities including antioxidant, anti-inflammatory, antiviral effects. it also has been shown to increase bioavailability it also contains spinach extract which helps to reduce appearance of fine lines and wrinkles. Nowadays certain terpenes are widely used in natural medicines., it has antiseptic and anti-inflammatory property. This patch contains all natural and herbal ingredients. Herbal pain relief patches are particularly beneficial for chronic pain conditions as they offer sustained relief without the need of frequent dosing. Herbal patches are way more convenient than synthetic patches as they contain herbal ingredients instead of chemicals, also herbal patches are showing more effectiveness than synthetic patches. It is suitable for all types of skin, which avoid any skin related problems or issues. Also, herbal patches have less chances of having allergic action, redness, inflammation and skin irritation.
ACKNOWLEDGMENT:

I want to say thank you to everyone who helped us finish this report. My parents also deserve recognition for their assistance and support. I would especially like to thank Mr. Vaibhav B. Bhagwat, our instructor, for his support, insightful advice, and encouragement during the entire report-writing process. I also want to express my gratitude for his work in proofreading and fixing my numerous errors.

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