A REVIEW: FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF AQUEOUS EXTRACT OF AZADIRACHTA INDICA

Mr. Vishal S. Madankar*1, Mr. Pranav D. Gawari*2, Ms. Pratiksha B. Bansude*3, Mr. Prakash R. Shitole*4, Ms. Prasanna V. Kharade*5

*1Department Of Pharmaceutical chemistry, Delight College Of Pharmacy Koregoan Bhima, Pune, Maharashtra, India.
*2,3,4,5Department Of Pharmacy, Delight College Of Pharmacy Koregoan Bhima, Pune, Maharashtra, India.

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ABSTRACT

A transdermal patch is an adhesive patch that has been medicated and is applied to the skin to allow the skin to absorb the prescribed quantity of medication. In most cases, this helps an injured body part heal. One advantage of transdermal drug delivery over other forms of medication delivery, such as oral, topical, intravenous, intramuscular, and so on, is that the patch allows for a controlled release of medication into the patient. This usually occurs through a porous membrane covering a reservoir of medication or by thermoregulation melting thin layers of drug incorporated in the adhesive. Transdermal patches are currently available in a wide range of therapeutics. Neem’s bitter flavor is responsible for the tree’s therapeutic efficiency. Man must have known the therapeutic potential of neem since ancient times due to persistent experimentation with nature. Neem is beneficial to the skin when used both externally and internally. It cleanses the blood and treats acne, pimples, boils, and other skin problems. This review will attempt to concentrate on the transdermal administration of certain herbal drugs.

Keywords: Extraction, Neem, Transdermal Patch, NDDS.

I. INTRODUCTION

One of the novel methods for systemic medication delivery through intact skin is the Transdermal medication Delivery System (TDDS). The ultimate objective of this dosage design is to reduce drug metabolism and retention in the skin while simultaneously optimizing drug flow through the skin. Additionally, it guarantees that chemicals reach the systemic circulation—ideally at a predetermined rate. Certain drugs can be administered to the systemic circulation via TDDS more efficiently and conveniently than through traditional dose forms.

The acceptability of marketed treatment systems is ample evidence of the potential of the skin as a route of drug administration. Transdermal drug delivery systems are skin-applied patches that disperse medications at a predetermined, regulated rate for systemic effects. An apparatus called a transdermal drug delivery system, which can be active or passive, enables you to apply medication via your skin. With these technology, medications can be administered via the epidermal barrier. The usage of transdermal patches is, theoretically, very easy.

A reasonably high quantity of medication is applied to the inside of a patch that is worn on the skin for a prolonged amount of time. The drug diffuses into the skin and enters the bloodstream right away procedure. The medication will continue to diffuse into the blood for a long period, maintaining a constant drug concentration in the blood flow, because the blood has a low concentration and the patch has a high concentration.

TRANSDERMAL DRUG DELIVERY SYSTEM:

The (TDDS) are described as discrete, self-contained dosage forms that, when applied to intact skin, allow the drug(s) to be delivered to the systemic circulation at a controlled pace through the skin. When administering strong, low-molecular-weight medicinal medicines that are either too sensitive to the harsh conditions of the gastrointestinal tract or undergo significant first-pass metabolism by the liver, transdermal drug delivery is a feasible method of administration.
Transdermal drug delivery systems are topically applied medications in the form of patches that distribute medications at a predefined, regulated rate for systemic effects. A transdermal drug delivery device is a gadget that can have an active or passive design. It offers a different method of delivering drugs. Pharmaceuticals can now be administered across the skin barrier thanks to these devices.

Transdermal patches are really easy to apply. A comparatively large amount of medication is put to the inside of a patch, which is worn on the skin for a long time. The medication enters the body through a diffusion process. bloodstream via the skin immediately. The medication will continue to diffuse into the blood for a considerable amount of time, keeping the consistent concentration of drug in the blood flow, because there is a high concentration on the patch and a low concentration in the blood.

**Figure 1:** Structure of Transdermal Patch

### Advantages of TDDS:
There are numerous benefits to this form of medicine delivery over conventional ones.

- As an alternative to the oral method
- With its associated risks of enzymatic and pH-related deactivation, gastrointestinal absorption can be avoided with transdermal drug delivery.
- This technique also permits lower pharmacological dosage because of the shorter half-life. transdermal route's metabolization pathway in comparison to the gastrointestinal pathway
- Additionally, the patch allows for continuous dosage as opposed to the peaks and valleys in medicine levels that are connected to oral pharmaceutical administration. treatment for several days using just one application. in an emergency, quick notification of drug availability and the ability to stop fast medication effects by patch removal

### Disadvantages of TDDS:

- The medication that requires high levels of blood cannot be provided and may potentially result in skin irritation or hypersensitivity.
- The adhesives might not be comfortable to wear and might not stick to all skin types.
- The product's cost is another significant barrier to its acceptance among consumers.
- The components that affect how the medication diffuses through transdermal administration from the vehicle
- Through the skin barrier, the pharmacological reaction is activated.

### Basic Components of Transdermal Drug Delivery Systems
1. Polymer matrix or matrices
2. The drug
3. Permeation enhancers
4. Other excipients
1. Polymer matrix:
The drug’s diffusion out of the device is regulated by the polymer. The following natural polymers could be helpful for transdermal devices: a. Derivatives of cellulose, such as Zein, Gelatin, Shellac, Proteins, carbohydrates, gums and their derivatives, waxes, natural rubber, etc. b. Synthetic elastomers: nitrile, acrylonitrile, silicon rubber, polybutadiene, hydriin rubber, polysiloxane, butyl rubber, styrenebutadiene rubber, neoprene, etc. c. Synthetic polymers, such as epoxy, polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone, and polymethyl methacrylate, among others.

2. Drugs
The drug must be carefully chosen in order to build a transdermal drug delivery system that works. Some of the desired characteristics of a medication for transdermal distribution are as follows:

Physicochemical characteristics
- The medication’s molecular weight should be less than about 1000 Daltons.
- The medication needs to be able to bind to hydrophilic and lipophilic phases. a severe partitioning features that make it difficult for a drug to be successfully absorbed through the skin.
- The drug should also be strong, have a short half-life, and not cause irritation.
- It should also have a low melting point

3. Permeation Enhancer:
These substances change the skin’s ability to act as a barrier to the flow of a desired penetrant, increasing skin permeability. These easily fit into the following main types:

A. Solvents
These substances may improve penetration by dissolving lipids and/or consuming the polar route. Water alcohols, such as methanol and ethanol, and alkyl methyl Dimethyl sulfoxide, dimethyl acetamide, dimethyl formamide, and alkyl homologs of methyl sulfoxide; pyrrolid one: N-methyl, 2-pyrrrolidone, and 2-pyrrrolidone; laurocapram (Azone); and various solvents: propylene glycol, glycerol, silicone fluids, and isopropyl palmitate.

B. Surfactant
These substances are thought to improve the transport of medicines via polar pathways, particularly hydrophilic ones. The polar head group and the length of the hydrocarbon chain determine a surfactant’s capacity to change penetration.

4. Other Excipients

A. Adhesives:
So until now, all transdermal devices have been attached to the skin using a pressure The device can have a sensitive adhesive placed on its face, in its back, and extending outwards. The following requirements should be met by both adhesive systems:
- It should not leave an unwashable residue on the skin; it should stick to the skin firmly and be quickly removed.
- It shouldn’t irritate or sensitize the skin

B. Backing membrane:
Printing is accepted, the medicine is kept inside the dosage form by the flexible backing membrane, which also forms a strong link with the drug reservoir. The product is shielded from the skin by an impermeable material, such as an adhesive foam pad made of flexible polyurethane with an occlusive base plate made of aluminum foil, metallic plastic laminate, plastic backing with an absorbent pad, etc.

Qualities that make transdermal patches desirable:
- Relatively uniform in composition when used
- Reasonable system size
- Specified application site
- Highly reproducible application technique
- Delivery is usually zero order
II. MATERIALS AND METHOD

PLANT PROFILE

- NEEM

Scientific Classification
Kingdom: Plantae
Order: Sapindales
Family: Meliaceae
Genus: Azadirachta
Species: indica
Common name: Neem
Synonyms
- Azadirachta indica

Uses:
Azadirachta indica, or neem, is a plant whose beneficial values have made it popular throughout the world in recent years. Neem has been widely utilized in Ayurvedic, Unani, and Homoeopathic medicine has emerged as a prominent field in contemporary medicine. Neem elaborates a wide range of structurally complex and chemically diverse physiologically active chemicals. Several neem components have yielded the isolation of over 140 chemicals. Traditionally, neem leaves, blossoms, seeds, fruits, roots, and bark have all been used to cure fever, infections, inflammation, skin conditions, and dental problems, illnesses. The therapeutic benefits of neem leaf in particular have been documented. Immunomodulatory, anti-inflammatory, antihyperglycemic, antiulcer, antimalarial, antifungal, antibacterial, antiviral, antioxidant, antimutagenic, and anticarcinogenic qualities have been shown for neem leaf and its compounds.

Pharmacological activity
- Analgesic agent
- Antipyretic agent
- Antimicrobial activity
- Antibacterial activity
- Antifungal activity
- Antiviral activity
- Anti-hyper glycemic agent.

Formula for transdermal patches of azadirachta indica

<table>
<thead>
<tr>
<th>Sr no</th>
<th>Ingredients</th>
<th>Quantity</th>
<th>Pharmacological Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Aqueous Extract of neem</td>
<td>40 mg</td>
<td>Antibacterial activity, Antifungal activity</td>
</tr>
<tr>
<td>2.</td>
<td>Gelatine</td>
<td>242 mg</td>
<td>Gelling agent, Thickening agent</td>
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</tbody>
</table>

Figure 2:
3. Sodium Alginate 240 mg Stabilizing agent, Suspending agent
4. DMSO 0.3 ml Penetration enhancer
5. Glycerine 0.3 ml Antimicrobial preservative, emollient, Plasticizer
6. Water q.s Solvent

Methodology

**Procedure for extraction of leaves of azadirachta indica (by Soxhlet apparatus)**
- The size of the shade-dried leaves was reduced.
- Using a Soxhlet device, about 100g of the dry powder were continually extracted.
- After removing the waxy ingredients using petroleum ether for 24 hours, it was extracted using distilled water for 72 hours.
- The water material was allowed to evaporate for 72 hours in order to extract the crude extract.
- The extract was vacuum-dried in an oven.

**Procedure for preparation of transdermal patches**

Weigh the amount of sodium alginate and gelatine, dissolve them in water, and heat them on a water bath.

Continuous stirring after extract addition to create a homogeneous mixture.

Mix in glycerine and DMSO, then transfer to a Petri dish.

Dry by air at room temperature for a full day.

Using a knife, remove patches from petri dishes and store in a desiccator.

**Figure 3:**

**Formulation of transdermal patch**

**Physico-chemical evaluation of azadirachta indica Transdermal patch:**

**Weight Uniformity**
This was achieved by randomly weighing five different patches from each batch and finding the three-weight average. The patch used for the tests has been dried at 60°C for four hours before to testing.

**Thickness of patch**
A digital vernier calliper was used to measure the thickness of the patch at various points. A random selection of three patches was made from every formulation. A single patch's thickness was measured, and the average value was discovered.

**Drug Content**
After being removed, the patches were put in a beaker containing 100ml D.W. The liquid was stirred with a magnetic bead for five hours. After filtering, the solution was assessed using spectrophotometry. Evaluated for drug concentration.

**Percentage Moisture Content**
The patches were weighed and stored in calcium chloride-filled desiccators. The patches were removed and weighed after 24 hours. The moisture content as a percentage was computed with the aid of the subsequent formula.
Percentage moisture content = \( \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \)

**Determination of surface pH**

The patches were allowed to swell for two hours at room temperature in contact with one milliliter of distilled water, and the pH was measured by bringing the electrode in contact with the patch’s surface, allowing it some time to adjust.

**Percent Elongation**

Strain is the term used to describe the stretching that occurs in a patch sample under stress. In basic terms, strain is the patch’s deformation divided by the sample’s original dimension. Generally elongation of patch increases as the plasticizer content increases. This formula is used to calculate it.

\[
\text{percentage elongation} = \frac{\text{Increase in length of patch}}{\text{Initial length of patch}} \times 100
\]

**Tensile strength**

The maximum stress exerted to a patch specimen until it breaks is its tensile strength. It is computed by dividing the applied load at rupture by the cross-sectional area sectional area of the strip as indicated by the following equation.

\[
\text{Percentage elongation} = \frac{\text{Load at failure}}{\text{Patch thickness} \times \text{Patch width}} \times 100
\]

**Anti-microbial Assay**

**Principle** –

Antibiotic-impregnated discs with a known concentration Plates of agar are layered with discs that has been consistently seeded, or infected, with a culture of the microorganism under investigation. The plate is incubated for 18 to 24 hours at 37°C. The antibiotic medication diffuses into the agar during this period, possibly impeding the growth of the organism. The efficiency of susceptibility is related to the diameter of the inhibitory zone surrounding the disc. Growing to the edge of the disk, organisms become resistant.

**Procedure:**

A modified agar well diffusion method was used to evaluate the antibacterial activity of multiple formulations. 0.2 mL of a 24-hour broth culture containing Staphylococcus aureus and Candida albicans was seeded onto nutrient agar plates in this technique. Agar plates were allowed to firmly establish. A sterile 8 mm borer was used to cut two wells of equal distances in each plate. Randomly placed test solutions were placed in the first well of each petriplate and standard solutions in the second. The plates were incubated at 37°C for a whole day. The zones of inhibition (measured in millimeters) were used to determine the antibacterial activity.

### III. RESULT AND DISCUSSION

**Physical appearance** –
- Colour: Pale Yellow
- Texture: Fine
- Solubility: Freely soluble in Distilled Water

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Uniformity of weight (gm)</th>
<th>Thickness (mm)</th>
<th>Drug Content (%)</th>
<th>Moisture Content (%)</th>
<th>Surface pH</th>
<th>Percent Elongation (%mm)</th>
<th>Tensile strength (Kg/mm²)</th>
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<tbody>
<tr>
<td>Transdermal patch</td>
<td>0.46 ± 0.86</td>
<td>0.45 ± 0.23</td>
<td>85.69±0.56</td>
<td>3.422±0.22</td>
<td>7.3±072</td>
<td>91±1.11</td>
<td>6.361±0.87</td>
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</table>

**Table 3: Anti-microbial Assay**

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Formulation Code</th>
<th>Zone of Inhibition (in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>For Gelatine Patch</td>
<td>20 mm</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>For Gelatine Patch</td>
<td>32 mm</td>
</tr>
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</table>
An aqueous extract of Azadirachta indica transdermal patch was created using the solvent casting technique. Drug-Polymer ratios, permeability enhancers, and formulation characteristics were all adjusted to produce thin, clear, smooth, stable, and highly permeable transdermal patches examined. The drug and excipients are not incompatible, as evidenced by the lack of an additional peak or broadening of peaks in the FTIR graphs of the drug, excipients, and formulations. 0.3 cc of glycerin was used as a plasticizer to create a flexible patch without altering its diffusion characteristics. Should the amount be surpassed, the film loses its elasticity and turns stiff. As the plasticizer permeates the patch, it softens the polymer particles. This softening speeds up latex coalescence and patch development. Moisture absorption percentage, Moisture content as a percentage, thickness, folding endurance, Drug content as a percentage, and Each patch’s percent elongation was evaluated. Between the patch formulations, there was no discernible difference in the amount of drug. This suggests that during the patch’s creation, the medication was administered consistently. After three weeks at 40°C, the results of the stability tests showed that there has been no discernible change from its initial state. The Gelatine patch successfully prevented the growth of germs in the area around it, according to the results of the antimicrobial screening. The current work has succeeded in creating a transdermal patch containing Azadirachta by using a variety of polymers.

V. REFERENCES


