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Formulation And Evaluation Of Antifungal and Antibiotic Transdermal Patches

AKSHAY GOVIND SAJAGANE[1], Mrs. Khamkar S.P.[2]

[1] Department Of Medicinal Science Late. Narayandas Bhavandas Chhabada Institute Of Pharmacy, Raigaon, Satara. Dist: Satara, Maharashatra. 415020 Email Id: akshaysajagane200@gmail.com Mobile No : 7559106121

[2] M. pharm (Pharmaceutics) Assistant professor Late Narayandas Bhawandas Chhabada Institute of Pharmacy Raigaon, Tal:Jaoli, Satara. Dist: Satara, Maharashatra. 415020. Email Id: akshaysajagane200@gmail.com Mobile No : 7559106121

ABSTARCT :

Transdermal drug delivery systems (TDDS) offer an effective alternative to conventional dosage forms, providing sustained drug release and improved patient compliance. This study focuses on the formulation and evaluation of antifungal and antibiotic transdermal patches incorporating luliconazole and terbinafine as active pharmaceutical ingredients. The patches were developed using polymers such as polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC) to achieve optimal film-forming properties and controlled drug release. Chloroform and ethanol were employed as solvents, while polyethylene glycol (PEG) served as a plasticizer to enhance flexibility and adhesion.

The prepared transdermal patches were subjected to various physicochemical evaluations, including thickness, tensile strength, moisture content, folding endurance, and drug content uniformity. In vitro drug release studies were conducted using Franz diffusion cells to assess the permeation of luliconazole and terbinafine through synthetic membranes. The antifungal efficacy of the patches was evaluated against fungal strains to determine their therapeutic potential.

The results indicated that the optimized formulation exhibited satisfactory mechanical properties, sustained drug release, and potent antifungal activity. These findings suggest that transdermal patches containing luliconazole and terbinafine could serve as a promising alternative for the treatment of fungal infections, offering enhanced drug penetration and prolonged therapeutic action.

Keywords : Transdermal patches, antifungal therapy, luliconazole, terbinafine, PVA, PVP, HPMC, drug release, permeability, formulation, evaluation, polymeric film, chloroform, ethanol, PEG, sustained release, topical drug delivery.

INTRODUCTION

At present, the most common route of delivery of drugs is the oral route. Because it has the main advantage of easy administration, it also has disadvantage like-- poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for frequent dosing, which may be both cost prohibitive and inconvenient. To overcome such difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs , Improved patient compliance and effectiveness are very important aspects of new drug delivery systems. Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. One highly successful alternative drug delivery method is the transdermal. Skin of an average adult body covers a surface of approximately 2 m^2 and receives about one third of the blood circulating through the body. To deliver a drug into the body through transdermal layer of skin, it is necessary to understand about the skin. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intra patient variation.(1)

Transdermal Drug Delivery System (TDDS) involves the topically administered medications in self-contained, discrete dosage forms of patches, which on application to the skin deliver the drug into the bloodstream through the skin portal at a pre-determined and controlled rate over a prolonged time period to increase the therapeutic efficacy and reduce the side effect of drug.A transdermal or skin patch is a medicated adhesive patch that is applied on the skin to deliver a specific dose of drug into the systemic circulation through the skin. TDDS maintains the drug concentration within the therapeutic window for prolonged time period to ensure that the drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration TDDS are preferred over injectables and oral routes as they increase patient compliance and avoid first-pass metabolism.(2)

Transdermal route has competed with oral route as the most successful innovative research area in drug delivery. This is because treatment through oral route aims to attain and maintain drug concentration in the body within a therapeutically effective range. This is done by introducing a fixed dose at regular intervals, due to which the drug concentration in body follows a peak and trough profile, and result in a greater chance of adverse effects or therapeutic failure; large amount of drug is lost in the surrounding area of the target organ and the therapy should be monitored to avoid overdosing

.Currently transdermal delivery is one of the most 6 promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application.(3)

SKIN AND DRUG PERMEABILITY

For understanding the concept of transdermal drug delivery systems, it is important to review the structural and biochemical features of human skin and those characteristic which contribute to the barrier function and the rate of drug access into the body via skin.

The skin

The skin is the largest organ of the human body which covers a surface area of approximately 2 sq. m and receivers about one third of the blood circulation through the body. It serves as a permeability barrier against the deal absorption of various chemical and biological agents. It is one of the most readily available organs of the body with thickness of few millimetres (2.97 0.28 mm) which,

• Acts as a thermostat in maintaining body temperature.
• Serves as a barrier against physical chemical and microbiological attacks
• Plays role in the regulation of blood pressure
• Separates the underlying blood circulation network from the outside environment

Anatomy of Skin:

The structure of human skin can be categorized into four main layers:
categorized into four main layers:

- The epidermis
- The viable epidermis
- A non-viable epidermis (Stratum carenum)
- Dermis (4)

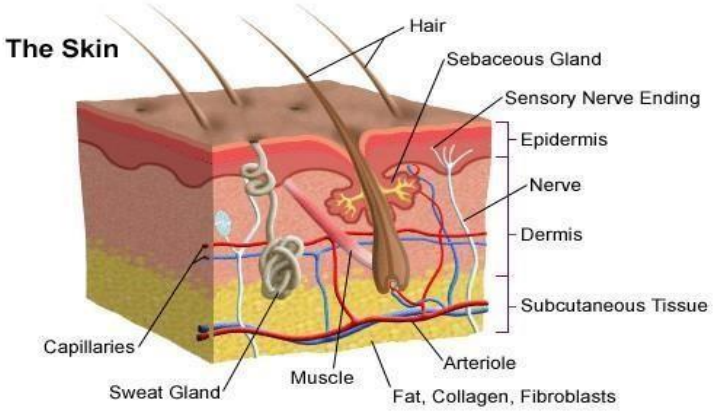


fig1:structure of skin

The Epidermis:

The epidermis is a continually self-renewing, stratified squamous epithelium covering the entire outer surface of the body and primarily composed of two parts: the living or viable cells of the malpighian layer (viable epidermis) and the dead cells of the stratum corneum commonly referred to as the horny layer .Viable epidermis is further classified into four distinct layers as shown in figure

- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basale (5)

Stratum corneum:

The stratum corneum or the horny layer is the rate-limiting barrier that restricts the inward and outward movement of chemical substances. Over most of the body, the stratum corneum is composed of 15 to 25 layers of acutely flattened, metabolically inactive, somewhat polygonal cells having a dry weight density of 1.3-1.4 g/cm³. The thickness of individual cell layers varies from 0.2 um to 0.5 um depending on their location. The interior of these cells is

crisscrossed with densely packed bundles of keratin fibres. Due to this, the dry composition of the horny layer is 75-85% protein, most of which is the intracellular keratin and a part being associated with a network of cell membranes. The bulk of the remainder of the substance of the stratum corneum is a complicated mixture of lipids which lies between the cells. It appears to be organised into bilayers. The stratum corneum thus has two distinct chemical regions, the mass of intracellular protein and the intercellular lipoidal medium. These phases are isolated from one another by cell membranes which are themselves knit together by desmosomes adding a tough infrastructure to the horny mass. (6)

Viable epidermis:

This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basale layer move outward, they itself alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum. (7)

Dermis:

Dermis is the layer of skin just beneath the epidermis which is 3 to 5 mm thick layer and is composed of a matrix of connective tissues, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products .Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water, and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules. (8)

Hypodermis:

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection & carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drag has to pone through all three layers and reach in systemic circulation." (9)

Percutaneous absorption:

Before a topically applied drug can act either locally or systemically, it must penetrate through stratum corneum. Percutaneous absorption is defined as penetration of substances into various layers of skin and permeation across the skin into systemic circulation." Percutaneous absorption of drug molecules is of particular importance in transdermal drug delivery system because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general once drug molecule cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily."
The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process which involves:
•Dissolution within and release from the formulation
•Partitioning into the skin's outermost layer, the stratum corneum (SC)
•Diffusion through sc
•Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, uptake into the papillary dermis (capillary system) and into the microcirculation. (10)

Routes of drug penetration through skin:

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands as shown in figure 6. In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact Stratum corneum becomes the primary pathway for transdermal permeation"
For any molecules applied to the skin, two main routes of skin permeation can be defined:

1. Trans-epidermal route
2. Trans-follicular route

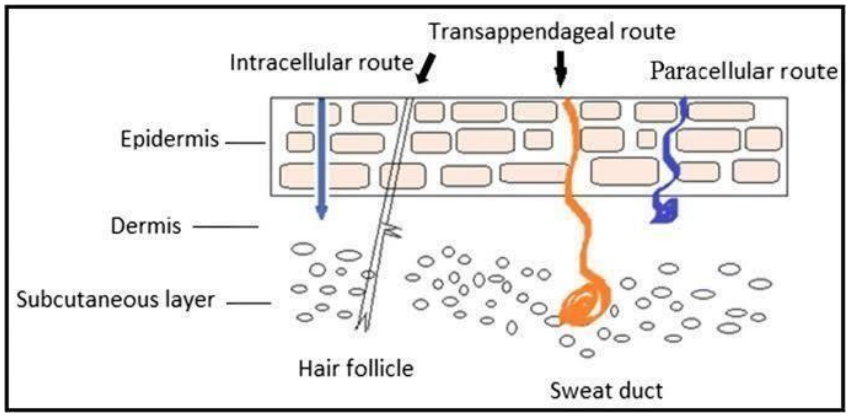


Fig 2: route of drug penetration through skin

Trans-epidermal route:

In trans-epidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathway as shown in Both polar and non-polar substances diffuse via transcellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated stratum corneum whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the stratum corneum. Thus the principal pathway taken by a penetrant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants (octanol/water log K > 2) traverse the stratum corneum via the intercellular route. Most molecules pass the stratum corneum by both routes."

Trans-follicular route (Shunt pathway)

This route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% area of the total skin. This seems to be most important for ions and large polar molecules.(11)

INTRODUCTION TO TRANSDERMAL

PATCHES:

Transdermal patches are medical patches that deliver medication through the skin and into the bloodstream. They are often used for continuous and controlled drug delivery over an extended period. The patch contains the medication, which is absorbed through the skin into the bloodstream, bypassing the digestive system. This method is commonly used for medications like nicotine replacement therapy, hormone therapy, pain relief, and motion sickness prevention.

TRANSDERMAL DRUG DELIVERY SYSTEM ADVENTAGES :-

1. It is a non invasive treatment.
2. Avoid GIT absorption problems for drugs.
3. Avoids first pass hepatic metabolism of drugs.
4. Self-medication is possible.
5. Maintains therapeutic level for 1 to 7 days.
6. Controlled delivery resulting in more reliable and predictable blood levels.
7. Reduce the peak plasma levels of drug this leading to decrease side effect Reduce the fluctuation in plasma levels of drugs.
8. Enhancement of patient compliance.
9. Reduction of dosing frequency.
10. Easy elimination of drug delivery in case of toxicity.

Disadvantages:-

1. Transdermal drug delivery system cannot deliver ionic drugs.
2. It cannot achieve high drug levels in blood.
3. It cannot develop for drugs of large molecular size.
4. It cannot deliver drugs in a pulsatile fashion as cause allergic reaction.
5. There is possibility of skin irritation due to the one or many of the formulation components..

6. Transdermal therapy is feasible for certain potent drug (12)

fig 3 : example of transdermal patch

Pathophysiology of Fungal Infection:

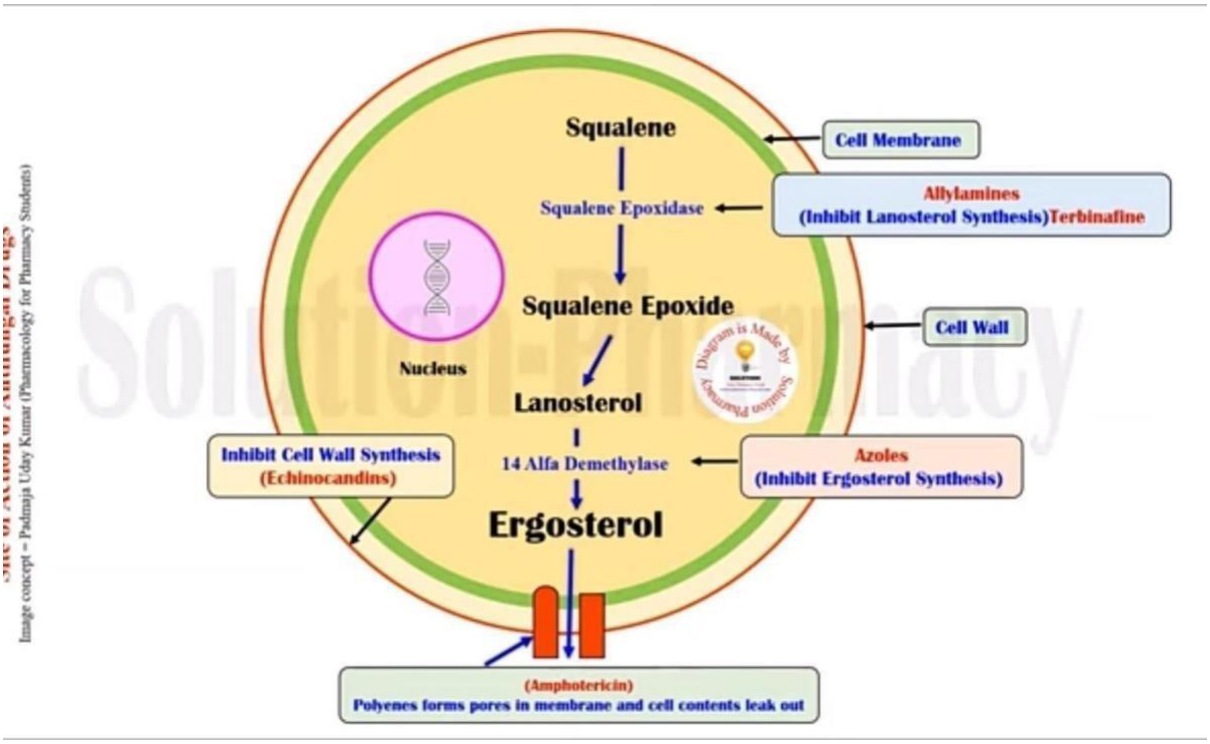


Fig 4 : Pathophysiology of fungal infection

Selection of drugs:

1. Drug should be non ionic.
2. Drug should have molecular weight less than 600 dalton .
3. MP should be less than 2000 C.
4. Drug should be lipophilic in nature.
5. Drug should be potent. (13)

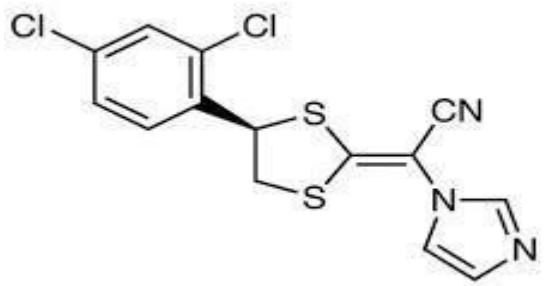
DRUG PROFILE

Luliconazole

Molecular formula: C14H9Cl2N3S2

Molecular Weight: 354.27 g·mol^{-1}

Melting point: 152 °C (14)

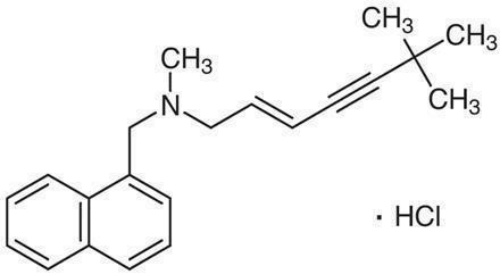


Terbinafine

Molecular formula: C21H26ClN

Molecular Weight: 291.438 g·mol^{-1}

Melting point: 195-198°C (15)



OPTIMIZATION METHODS

Method-[A]

Formulation:

Ingredients	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**Role**
Luliconazole	**75 mg**	**75 mg**	**75 mg**	**75 mg**	**75 mg**	**Antifungal**
Terbinafine	**50 mg**	**50 mg**	**50 mg**	**50 mg**	**50 mg**	**Antibiotic**

Glycerine	**1 ml**	**1 ml**	**1 ml**	**1 ml**	**1 ml**	**Plasticizer**
HPMC	**50 mg**	**60 mg**	**70 mg**	**-**	**-**	**Thickening agent**
Starch	**-**	**-**	**-**	**50 mg**	**60 mg**	**Thickening Agent**
Methanol	**20 ml**	**20 ml**	**20 ml**	**20 ml**	**20 ml**	**Solvent**

Table no 1:Method A

Procedure:

Methanol (solvent) + Drug.

↓

Dissolved.

↓

Add HPMC. Dissolve.

↓

Add 1 ml Glycerine.

↓

Make viscous solution and pour into petri dish.

↓

Cover petri dish with inverting funnel.

↓

Kept for evaporation at room temperature.

METHOD [B]

Formulation :

INGREDIENTS	**F1**	**F2**	**F3**	**F4**	**F5**	**ROLE**
Luliconazole	**75mg**	**75mg**	**75mg**	**75mg**	**75mg**	**Antifungal**
Terbinafine	**75mg**	**75mg**	**75mg**	**75mg**	**75mg**	**Antibiotic**

DichloromethanE	**10 ml**	**10 ml**	**10 ml**	**10 ml**	**10 ml**	**Solvent**
DMSO	**0.5 ml**	**0.5 ml**	**0.5 ml**	**0.5 ml**	**0.5 ml**	**Permeation enhancer**
PEG	**0.5 ml**	**0.5 ml**	**0.5 ml**	**0.5 ml**	**0.5 ml**	**Plasticizer**
HPMC	**750 mg**	–	–	–	–	**Thickening agent**
PVC	–	**0.54 ml**	–	–	–	**Thickening agent**
PVP	–	–	**0.63 ml**	–	–	**Thickening agent**
Gelatin	–	–	–	**1000 mg**	**750 mg**	**Gelling agent**
Methanol	**1.5 ml**	**1.5 ml**	**1.5 ml**	**1.5 ml**	**1.5 ml**	**Solvent**
Distilled water	**50 ml**	**50 ml**	**50 ml**	**50 ml**	**50 ml**	**Vehicle**

Table no 2: Method B

Procedure :

Polymer + distilled water.

Dissolved by using magnetic stirrer.

Add drug + solvent.

Stir by using magnetic stirrer.

Add methanol and PEG

.Dry the sample at 500 C and store in desicator.

Method [C]

Formulation table :

INGREDIENTS	F1	F2	F3	Role
Luliconazole	75mg	75mg	75mg	Antifungal
Terbinafine	50mg	50 mg	50 mg	Antibiotic
PVP	167 mg	177 mg	185mg	Thickening agent
PVA	167mg	177 mg	185mg	Thickening agnet
Methanol	10ml	10ml	10ml	Solvent
DMSO	0.1ml	0.1ml	0.1ml	Permeation enhancer
PEG	0.1ml	0.1ml	0.1ml	Plasticizer
Distilled Water	10ml	10ml	10ml	Vehicle

Table no 3: Method C

Procedure :

Take distilled water and methanol in the beaker.

↓

Add drug and dissolved by using magnetic stirrer.

↓

Add polymer slowely.

↓

Make it clear solution .

↓

Add plasticizer.

↓

Lubricate the petri dish with glycerine. Add the prepare solution in the petri dish.

Then evaporate the sample at room temperature for 24 hrs.

Then peeled of the sample and store in desicator.

Method [D]

Formulation Table:

Ingredients	**F1**	**F2**	**F3**	**Role**
Luliconazole	**75 mg**	**75 mg**	**75 mg**	**Antifungal**
Terbinafine	**50 mg**	**50 mg**	**50 mg**	**Antibiotic**
PVA	**1.5%**	**2%**	**1%**	**Adhesive**
PVP (k-30)	**150 mg**	**160 mg**	**155 mg**	**Binder**
HPMC	**150 mg**	**130 mg**	**120 mg**	**Thickening agent**
Chloroform	**30ml**	**10 ml**	**20 ml**	**Solvent**
Ethanol	**30 ml**	**10 ml**	**20 ml**	**Solvent**
PEG	**0.3 ml**	**0.3 ml**	**0.3 ml**	**Plasticizer**

Table no 4: Method D

Procedure:

Petri dish is lubricated with glycerine and dry it for 24 hrs at room temperature .

2% PVA solution dry at 60^0 C for 6 hrs in petri dish

· In 100 ml beaker add HPMC and PVP in the ratio of 1:1 was dissolve in chloroform and Ethanol (1:1)

↓

Dissolve above solution in Electro magnetic stirrer.

↓

Mix the solution and transfer into the petri dish .

↓

Evaporate the solution at room temperature for 24 hrs.

↓

Peel of the sample and store in desicator

↓

Add the drug in the above solution.

↓

Add 0.3 ml PEG .

Fig 10 : Petri dish kept for evaporation filled with solution

Fig 11: Peeling of the patch

fig 12: dried patch

Method [D] -F_2 was selected for further preparation of Antifungal Transdermal Patch as it exhibited better quality characteristics.

- Thin, flexible, smooth and transparent films were obtained withPVP (k-30), PVA, HPMC and EC polymers using PEG as plasticizers. • Thickness of all the formulations remained uniform.
- The systems containing PVP polymer showed better release of drug.
- The systems were found to be stable at 37 ℃ and 45 ℃.
- Studies have shown promising results.

EVALUATION OF TRANSDERMAL PATCH

Folding endurance:

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance. **Folding endurance = 312 (16)**

Uniformity of dosage unit test:

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2µm membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

Uniformity of dossge unit test = 0.4075 (17)

Thickness of patches:

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared.

Thickness of patch= 0.13 to 0.16 mm (18)

Percentage moisture content:

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula

Percentage moisture content = [Initial weight- Final weight/ Final weight] x100.

Initial weight= 900 mg
Final weight= 835 mg

Percent moisture content = (900 – 835 /835) 100

Percent moisture content = 7.7 % (19)

pH

pH should be acidic. The
pH was found to be 5.77
pH =
5.77 (20)

RESULT AND DISCUSSION:

Antifungal transdermal patch is formulated and Evaluated successfully.

Organoleptic Properties of patch:

Parameter	**Result**
Colour	**colourless**
Transparency	**Transparent**
Odour	**odourless**

Table no 6: Appearance of Patch

Test	Result
Folding endurance	**312**
Uniformity of dosage form	**0.4075**
thickness	**0.13 to 0.16 mm**
Percent moisture content	**7.7%**
pH	**5.77**
Drug content	**95.79%**

Table no 7: Evaluation parameters

Drug Diffusion :

Time	Absorbance	% of Drug Diffusion
30 min	**0.110**	**11%**
60 min	**0.231**	**35.2%**
90 min	**0.285**	**46%**
120 min	**0.341**	**79.2%**

Table no 8: Drug diffusion

CONCLUSION AND OUTCOME:

Luliconazole is antifungal drug now a days available in market in cream and gel form and terbinafine is antibiotic drug available in the form of tablet, cream , gel, etc. This two drugs in combination is novelty of our product which shows synergistic effect.

The formulation and evaluation of a transdermal antifungal patch have shown promising results. The patch demonstrated favourable physicochemical properties, including optimal drug release rates, adequate adhesiveness, and desirable mechanical strength, making it suitable for transdermal delivery.

In vitro permeation studies confirmed effective skin penetration of the antifungal agent, maintaining therapeutic concentrations over an extended period. Preliminary in vivo studies indicated that the patch is effective in treating fungal infections, with advantages such as reduced application frequency and enhanced patient comfort, potentially improving adherence to treatment.

While the initial findings are encouraging, further research is needed to ensure long-term stability, evaluate potential skin irritation, and assess effectiveness across different populations. Future studies should also consider the scalability and economic feasibility of large-scale production.

Overall, the transdermal antifungal patch presents a viable alternative to traditional treatments, offering improved convenience and therapeutic outcomes.

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