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Formulation and characterization of Liposomal Fluconazole Transdermal Patch

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KEYWORDS

metabolic degradation, liposomal formulation, antifungal medication, liposomal fluconazole transdermal patch

ABSTRACT:

Introduction

Fluconazole, a prominent triazole antifungal medication, is utilized to manage a broad range of Candida infections. It has been approved by the FDA for various systemic and superficial fungal conditions, including vaginal, oropharyngeal, and esophageal candidiasis. The effectiveness of fluconazole can be significantly improved through innovative drug delivery systems.

Objectives

The main objective of this study is to develop and characterize a liposomal fluconazole transdermal patch aimed at enhancing drug delivery. This involves improving systemic absorption, reducing gastrointestinal side effects, and preventing metabolic degradation.

Methods

This research involved the development of a liposomal formulation using a thin film hydration method and its subsequent incorporation into a transdermal patch. The patch was made using a matrix composed of glycerine, gelatin, and hydroxypropyl methylcellulose (HPMC). Key parameters measured included drug content, moisture content and uptake, uniformity of weight, thickness, antifungal activity, and in-vivo drug release.

Results

The developed transdermal patches demonstrated promising pharmacokinetic properties. Key findings include: Uniformity of Weight: Patches showed high uniformity with percentages ranging from 93±0.4% to 96±0.3%. Thickness: The patches maintained consistent thickness measurements, varying from 4.1±0.03 mm to 4.3±0.04 mm. Moisture Content and Uptake: Moisture content was low, with percentages around 0.57±0.005% to 0.82±0.006%, and moisture uptake also remained under 1%. Drug Content: Drug content was robust across different formulations, ranging from 84±0.5% to 89±0.4%. In-vitro Drug Release: Drug release showed increasing absorbance over time, with significant releases observed at 30 minutes, 1 hour, and 2 hours, confirming a sustained release profile. Antifungal Activity: The patches displayed effective antifungal properties, with zones of inhibition indicating fungistatic activity against Candida albicans.

Conclusion

The liposomal fluconazole transdermal patch represents a significant advancement in antifungal medication delivery. It not only reduces the side effects associated with oral administration but also enhances bioavailability and effectiveness. The patches demonstrated a consistent and controlled release of fluconazole, improved drug content uniformity, and effective antifungal activity, making them a viable alternative to traditional fluconazole treatment methods. This innovation is expected to improve patient compliance and overall treatment outcomes for fungal infections.

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1. Introduction

Globally, there has been an increase in frequency of superficial fungal infections of skin, hair, and nails. It was anticipated that 40 million or more individuals in developing and emerging nations are susceptible to fungal diseases. Due to a compromised immune system, a rapid and deadly succession of fungus infections can occur. "Mycoses" is another name for fungal skin infections. They are common and usually gentle. However, fungi can occasionally result in significant illness in extremely ill or immune-suppressed individuals. A fungal infection known as candidiasis is brought on by yeasts from genus Candida [1,2].

More than 20 different types of Candida yeasts can infect humans, with Candida albicans being the most common. Among the most common superficial cutaneous fungal infections are candidal infections. Cutaneous candidiasis is usually caused by endogenous, saprophytic Candida blastospores that selectively colonize the oral, gastrointestinal, vaginal, and cutaneous epithelium.Under diverse environmental conditions, Candida blastospores can transform into mycelium, penetrate epithelial tissue, and trigger an acute inflammatory response that is neutrophil-mediated, complement-dependent, and characterized by subcorneal pustules. The early stages of cutaneous candidiasis involve blastoconidia adhering to the surface of epithelial cells, fungal colonisation and growth, and invasion of epithelial tissue. According to in vitro investigations, pathogenic species are typically linked to adhesion to mucosal and corneocyte cells. It has been demonstrated in rodent models that the same species is capable of infecting stratum corneum and corneocytes by hyphal invasion.

Patients with significant immunosuppression from underlying illnesses or chemotherapy are developing fungal infections at an increasing rate. Such infections are frequently fatal, especially those that affect neutropenic cancer patients and people with AIDS. Although aspergillosis usually affects neutropenic cancer patients and cryptococcosis regularly affects AIDS patients, candidiasis is the most frequent fungus infection in both immunocompetent and immunocompromised hosts. Systemic candidiasis can be fatal when deeper tissues and blood are infected by candida when the immune system is weak. Both oral and topically administered medications can be used to treat the fungal infections[3–6].

Fluconazole is one of the most frequently used antifungal drug. The FDA has approved this medicine for the treatment of vaginal, oropharyngeal, and oesophageal candidiasis as well as systemic Candida infections, including disseminated candidiasis, pneumonia, and cryptococcal meningitis.Fluconazole is a polar bis-triazole antifungal medication that shows specificity in inhibiting fungal-mediated processes, rather than those mediated by mammalian cytochrome P-450, such as those involved in drug metabolism and steroid biosynthesis. Fluconazole is a triazole that is commonly used to treat opportunistic infections in individuals with HIV, severe fungal infections, and candidiasis. Its good absorption, tolerance, and side-effect profile make it a popular choice. Of all microbiological diseases, mycoses have proven to be the most challenging to cure, in part due to the dearth of accurate diagnostic techniques and the scarcity of effective therapeutic medicines. Despite its effectiveness against many mycoses, amphotericin B necessitates parenteral administration and is frequently poorly tolerated. Furthermore, it has been reported that certain strains of C. guillermondii, C. lusitaniae, and Candida albicans show resistance to amphotericin B.

Commercially available fluconazole comes in oral and parenteral dosing forms, both of which have the potential to cause major side effects such nausea, vomiting, bloating, diarrhoea, rash, a decrease in red blood cell production, and stomach pain. Compared to topical preparations, conventional forms have a lower bioavailability [7–12].

The fundamental goals of drug delivery systems are to administer a medicine more efficiently than with conventional drugs, especially to the site of action, and with fewer harmful side effects. In the early stages of their development, liposomal vesicles were made from different lipid classes that are the same as those found in the majority of biological membranes.

Liposomes are generally understood to be lipid bilayers enclosing an aqueous cavity.

When a phospholipid is exposed to water, it becomes hydrated and forms liposomes, which are colloidal particles with a diameter of 0.01 to 0.5 µm. They are made up of one or more phospholipid bilayers made of

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synthetic or natural phospholipids encasing an aqueous core. Because they are made of a naturally occurring phospholipid, liposomes are immune-system inert, non-toxic, and physiologically inert.

Liposome classification according to structural characteristics:

1. Multilamellar Large vesicles > 0.5um

2. Oligolamellar vesicles (0.1-1um)

3. Uni-lamellar vesicles (All size range)

    a) Small uni-lamellar vesicles 20-100nm

    b) Medium sized uni-lamellar vesicles

    c) Large uni-lamellar vesicles >100nm

    d) Giant uni-lamellar vesicles >1um

4. Multivesicular vesicles >1um

A lipophilic medication is entrapped within lipid bilayers by liposomes, whereas a hydrophilic drug is encapsulated within an aqueous component. Hence, within liposomes medications that are lipophilic or hydrophilic can be delivered. Liposomes are microscopic lamellar structures can be prepared from components like soya lecithin, cholesterol and aqueous phase by reverse phase evaporation. Numerous studies have been conducted on the regulated and targeted delivery of drugs to treat microbial diseases, cancer, and viral infections using liposomes.

Liposomes have proven to be helpful for localizing drugs applied topically at or around the application site because of their capacity to act as slow-releasing vesicles. Although liposomes are utilised as vehicles to transport the medications they have caught into the skin, their liquid nature makes them difficult to use topically. Liposomes administered topically may leak from the application site. The solution to this problem is to incorporate the vesicles into an appropriate vehicle that maintains vesicle's original structure while modifying its rheological and/or mucoadhesive qualities. To do this, gelling agents can be used in liposomal dispersions to create liposomal hydrogels. Liposomes can also be entrapped in hydrogels. Drugs such as griseofulvin and calcein can be released in a manner determined by the stiffness of the liposomal membrane when liposomes are entrapped in hydrogels based on Carbopol and hydroxyethyl cellulose. Thus, it is possible to create a drug-in-liposomes-in-gel complex formulation. [13–16].

An alternative method of delivering medication is offered by a transdermal drug delivery device, which can have an active or passive design. Pharmaceuticals can now be administered across the skin barrier thanks to these devices. Delivery of medications topically is a desirable method of local and systemic therapy. Adhesive drug-containing devices with pre-programmed drug delivery rates and a particular surface area that stick to the skin are known as transdermal drug delivery systems (TDDS). In 1979, the FDA gave the first transdermal patch products its approval. A topical formulation increases the drug's bioavailability, reduces GI side effects, and stops the liver from metabolising it. Medication applied topically acts precisely where it is needed. Transdermal patches operate quite simple. When a patch is worn on the skin for an extended length of time, a comparatively high amount of medication is administered to the body. Through a mechanism known as diffusion, the medication directly enters the bloodstream through the skin. Because of the high concentration on the patch and the low concentration in the blood, the medication will continue to diffuse into the blood for a significant amount of time, preserving the consistent concentration of drug in the blood flow.

Essential Elements of Transdermal Drug Delivery Systems

- Polymer matrix or matrices.
- The drug Permeation enhancers
- Other excipients

Factors affecting Transdermal Delivery

- The medication being released from the vehicle.
- Perforation through the barrier of the skin.
- Initiation of the pharmacological response

Advantages:

There are numerous benefits to this form of medicine delivery over conventional ones.

- An alternative to the oral route
- By using transdermal medication delivery, stomach absorption and its related pH and enzymatic problems can be avoided.
- Because the transdermal route has a shorter metabolization pathway than the gastrointestinal system, this approach also permits lower pharmacological dose.

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• Additionally, the patch allows for continuous dosing as instead of the peaks and valleys in medicine levels that are linked with taking pharmaceuticals orally.
• The ability to quickly stop the effects of the drug by removing the patch, as well as prompt medication notification in an emergency.
Disadvantages:
• It is impossible to provide the medication that demands high blood levels, and it may even irritate or sensitize the skin.
• The adhesives could be difficult to wear and might not stick well to all skin types.
• Another significant obstacle to the product's widespread acceptance is its high cost.[17–21].
Material and method:

Chemicals: Fluconazole was a gifted sample from Promea Therapeutics Pvt. Ltd., Hyderabad, Telangana. Cholesterol, Chloroform, Lecithin, DMSO, Glycerin, Gelatin, HPMC was procured from Department of pharmaceutics Of KGRDCP & RI, Karjat. Strips (Backing film) was purchased from local market.

Preparation of Phosphate Buffer (Saline pH 7.4): Mix 8.0 g of sodium chloride, 0.19 g of potassium dihydrogen phosphate, and 2.38 g of disodium hydrogen phosphate with enough water to make 1000 ml. Adjust the pH, if necessary.

Preparation of liposomes:

1. Liposomes were prepared by a thin film hydration method. Rinse the round bottom flask, (250ml) with Chloroform. Use immediately after rinsing.

2. Accurately weighted the amount of Lecithin and Cholesterol (6:4) in a round bottom flask. Dissolved in Chloroform and Methanol mixture (2:1 v/v).

3. Organic solvent was then evaporated to obtain thin film at the base of round bottom flask by Handshaking method at temperature 40-45°C (in water bath).

4. To make sure any leftover solvent was completely removed, this round-bottom flask was placed under vacuum for the whole night.

5. Add Phosphate Buffer (pH 7.4) to round bottom flask which contains the Fluconazole to rehydrate that film. Kept that dispersion undisturbed for 2 to 3 hours to allow complete swelling of lipids.

6. Sonicate suspension to remove all the precipitates to obtain the milky suspension containing vesicles.

7. Liposomal suspension of fluconazole was obtained [13,14,22–25].

Preparation of patch:

• The patch was prepared in batch of 3 with ratio of 6:1.5:0.5 of glycerine, gelatin and HPMC.

• Accurately weighed amount of gelatin, HPMC and liposomal suspension was added in beaker.

• A measured volume of glycerin was heated to 120°C in a different beaker.

Fig. 1 Prepared transdermal Patch

• Subsequently, the gelatin mixture was poured into a beaker filled with glycerin, and the mixture was heated until it became homogenous.

• Finally, mixture was poured into pre-cleaned Petri dish followed by cooling in ice bath. The prepared formulation was collected and stored at cool and dry place [15,26–31].

Preparation of egg membrane: Eggs were bought from the local departmental store. The outer layer of the egg's skin was delicately peeled off, revealing the membrane underneath. 0.1 N HCl was used to remove the egg's outer skin while swirling continuously. Following the complete membrane separation, phosphate buffer pH 7.4 was used to wash the membrane. The membrane was now employed for subsequent experiment work [32].

Identification of drug:

1.Ultra Voilet Spectroscopy:

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A 0.025 percent w/v solution in methanol exhibits absorption maxima at roughly 266 and 261 nm when analysed in the 190–450 nm range.

2. Fourier Transform Infrared Spectroscopy:

Using infrared absorption spectrophotometry, fluconazole was identified. Compare the spectrum to the one obtained using fluconazole RS or to the fluconazole reference spectrum. [33].

Characterization of prepared transdermal patches:

The following tests were run in order to assess the produced patches.

1.Thickness: The screw gauge was used to measure the thickness of the transdermal films at five distinct places using the least count method. An SD was used to compute the average.[34].

2. Drug content: The medicine is dissolved in 100 millilitres of a suitable solvent after a precisely weighed amount of the film (approximately 100 mg) is added. The mixture is then continuously shaken in a shaker incubator for a whole day. The entire mixture is then sonicated. Drug in solution by adequate dilution is evaluated spectrophotometrically following sonication and filtration.[35].

3. Percentage Moisture content: This test was also performed in dry conditions to verify the integrity of films. The individual transdermal films (of the designated area) were stored at room temperature in a desiccator filled with fused anhydrous calcium chloride. The films were weighed at regular intervals of 24, 48, and 72 hours during this time.

The following formula was used to determine percentage moisture content:

% Moisture content= (Initial weight - Final weight)/Initial weight×100[36].

4. Percentage of moisture uptake: A weighted film that had been held in a desiccator at room temperature for 24 hours was removed and exposed to 84% relative humidity (a saturated solution of aluminium chloride) in a desiccator until a consistent weight for the film was achieved. The difference between the final and initial weights in relation to the initial weight was used to compute the percentage of moisture uptake.

5. Uniformity of weight: Ten randomly chosen patches are weighed separately, and the average weight is then determined in order to study weight variation. The weight of each individual shouldn't differ greatly from the weight of the average[35].

6. Optical microscopy: An optical microscope, was used to examine the liposomal dispersion in order to determine the shape and lamellar nature of the vesicles. Using a 10X eye piece and 45X objective lens, a drop of liposomal dispersion was covered with a cover slip and examined under a microscope at 450 magnifications. A camera (13-megapixel) that was mounted on the microscope was used to take photomicrographs.

7. Antifungal Activity: The Kirby-Bauer smear method was utilized to test the antifungal activity of candida albicans utilizing disc paper. The process used to carry out this method is to pour 20 millilitres of Potato Dextrose Agar (PDA) agar media into each petri dish, let it settle, and then add 0.1 millilitres of inoculum. Using a loop needle, the media's surface is wiped until it is uniformly spread. Using tweezers, a sterile disc-shaped patch is applied over the agar plate. Every petri dish was incubated at 37°C for one 24-hour cycle. Around the disc paper, there is a zone of inhibition to growth is observed[37,38].

8. In vitro drug release:

I. Preparation of egg membrane: Eggs were bought from the local departmental store. The outer layer of the egg's skin was delicately peeled off, revealing the membrane underneath. 0.1 N HCl was used to remove the egg's outer skin while swirling continuously. Following the complete membrane separation, phosphate buffer pH 7.4 was used to wash the membrane. The membrane was now employed for subsequent experiment work

II. Drug diffusion through egg membrane: The produced patch was subjected to an in vitro permeation research using egg shell membrane, as this membrane's primary composition is similar to that of the human stratum corneum. As a result, the membrane was ready for usage before. Throughout the experiment, the water in the cell's outer jacket was heated to 37 ± 1°C to simulate skin temperature. In the receptor compartment, phosphate buffer solution with a pH of 7.4 was utilized as the dissolving medium. A patch of 1.5 by 1.5 cm2 was placed on top of the diffusion cell's installed membrane.

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Following that, the samples were taken out of the receptor compartment at certain times. To keep the receptor cell solution at the same starting volume, one milliliter of the receptor solution was taken as a sample each time, and at the same time, one milliliter of phosphate buffer solution was introduced back to the receptor cell. A UV-Vis spectrophotometer was used to analyze the samples that were collected.[32].

Results and Discussion:

1.Ultra Voilet Spectroscopy:

UV spectra of Fluconazole is shown in fig. 2. The maximum absorbance (λmax) is present at 266 and 261 nm in spectrum, which confirms that the Fluconazole is in pure form.

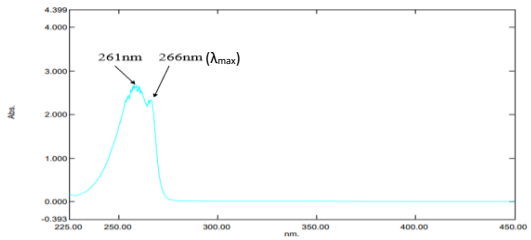


Fig. 2 UV Spectroscopy of Fluconazole

2. Fourier Transform Infrared Spectroscopy:

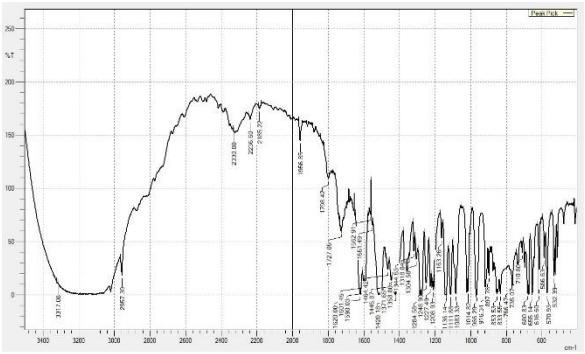
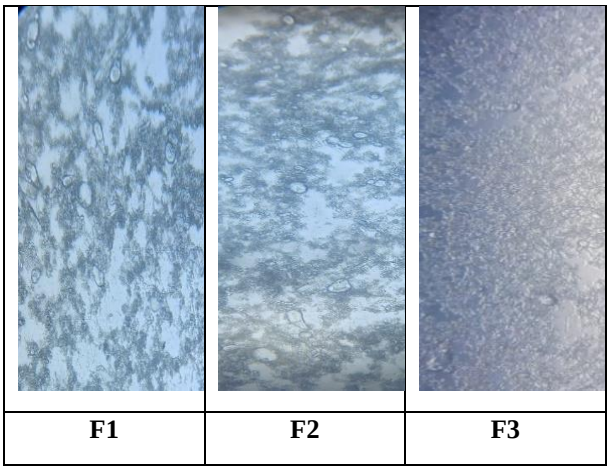


Fig. 3 FTIR Spectroscopy of Fluconazole

Figure 3 displays the characteristic peaks seen in the FTIR spectrum. A broad peak for the OH stretch can be found at 3317.08 cm-1 in the spectrum, indicating the presence of a hydroxyl group. The existence of a triazole ring in fluconazole is shown by the presence of a peak in the spectrum at 1620.00 cm-1 (C-N stretch). Aromatic C-H stretching is responsible for the peak at 2957.39 cm-1, NO2 stretching is responsible for the peak at 1285.58 per cm, N-H bending is responsible for the peak at 1551.49 cm-1, and C-F stretching is responsible for the peak at 655.14 cm-1. Fluconazole's FTIR spectrum interpretation confirms the drugs purity.

Optical Microscopy:

Photomicrographs verified that liposomal vesicles had formed



F1	F2	F3

Fig. 4 Photomicrographs of liposomes

Evaluation of uniformity of weight of patch:

Table 1. Results of percentage weight uniformity of patch

Formulation	Percentage weight uniformity (%)
F1	93±0.4
F2	96±0.3
F3	95±0.5

Evaluation of Thickness of Patch:

Table 2. Results of thickness of Patch

Formulation	Thickness (in mm)
F1	4.2±0.05
F2	4.1±0.03
F3	4.3±0.04

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Evaluation of Percentage Moisture content and percentage moisture uptake of patch:


Fig. 5 Dessicator

Table 3. Results of Percentage Moisture content and percentage moisture uptake of patch

Formulation	Percentage Moisture content (%)	Percentage moisture uptake (%)
F1	0.82±0.006	0.36±0.007
F2	0.57±0.005	0.28±0.005
F3	0.63±0.004	0.32±0.003

The F2 formulation's percentage moisture content and moisture uptake were found to be promising and acceptable, with values less than 1%.

Evaluation of Drug Content of patch:

Table 4. Results of drug content of patch

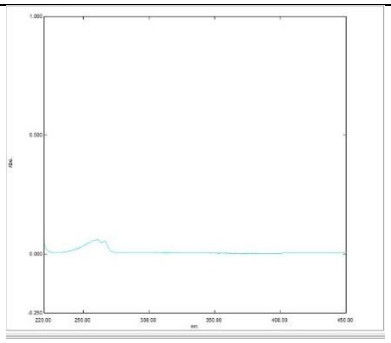
Formulation	Percentage Drug content (%)
F1	84±0.5
F2	89±0.4
F3	87±0.4

The drug content uniformity of F2 was determined to best match the homogenous distribution of the drug (entrapped in liposomes) throughout the jelly. The drug content was found to be between 80% and 90%, which is an acceptable range.

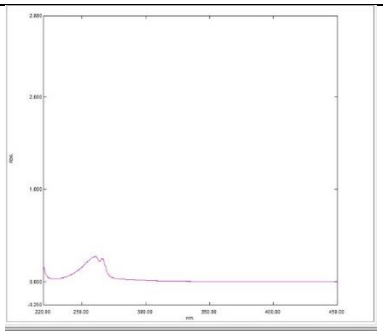
Evaluation of In-Vitro Drug release of patch:

For initial 0 and 15 min sample no peak for drug was seen for the wavelength between 261 nm and 266 nm as per given in IP. The first peak was seen for the sample taken at interval of 30 min and later seen for sample taken after 1 hour and same followed for other hourly samples too, at the wavelength of 261 nm and 266 nm.

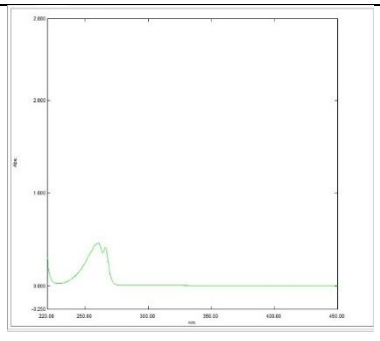
The absorbance seen for 1 hour sample was having comparatively more absorbance than that of 30 min sample. And the absorbance seen for 2 hours sample was having twice the absorbance then that of 1 hour sample showing us the drug release.



For 30 Min



For 1 hour



For 2 hours

Fig. 6 UV spectrum of Drug release.

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Table 5. Invitro diffusion study of patch formulation			
Formulation	DR For 30 min	DR For 1 hour	DR For 2 hour
F1	14.9±0.14	15.2±0.17	16.3±0.21
F2	15.2±0.16	15.7±0.18	16.5±0.19
F3	15.1±0.17	15.5±0.19	16.2±0.20

Evaluation of antifungal activity of patch:

Fig 7. Antifungal activity of Patch

Table 6. Antifungal study of Patch	
Formulation	**Zone of inhibition (in mm^2)**
F1	2.0
F2	2.3
F3	2.1

The anti-fungal activity was seen as the drug showed zone of inhibition. It showed fungistatic activity against the fungi (*Candida albicans).*

Summary and Conclusion:

Recent years have seen a rise in the importance of transdermal. delivery. A revolutionary medication delivery method that eliminates difficulties with drug therapy such as the requirement for assistance, intermediate dose, and painful administration is transdermal drug delivery. Compared to traditional methods of medicine administration, transdermal distribution has many benefits. The aim of this project was to formulate a transdermal patch using antifungal activity of fluconazole and incorporating the Liposomal suspension into a jelly and to evaluate this prepared patch on various parameters such as UV, optical microscopy, in vitro drug permeation, anti-fungal activity, etc. The prepared transdermal drug delivery system of fluconazole had shown good promising results for all the evaluated parameter.

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