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Original Research Article

"Bioavailability enhancement of drugs for therapeutic approaches and future trend"

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Abstract

Global incidence of superficial fungal infections caused by dermatophytes is high and affects around 40 million people. It is the fourth most common cause of infection. Clotrimazole,a broad spectrum imidazole antifungal agent is widely used to treat fungal infections. Conventional topical formulations of clotrimazole are intended to treat infections by effective penetration of drugs into the stratum corneum. However, conventional have drawbacks such as poor dermal bioavailability, poor penetration,and variable drug levels limit the efficiency. The present study aims to formulation and evaluation of Clotrimazole dermal film. Clotrimazole loaded film were prepared using HPMC and HEC by solvent casting method and evaluated for drug content, % flatness, folding endurance, drug. Skin diffusion studies were performed using to determine the amount of clotrimazole accumulated in different layers of the skin. Results showed that the optimized formulation had good thickness higher drug content and slow diffusion with time. No permeation was observed through the skin up to 12 h following the permeation studies. Clotrimazole in the skin compared to marketed formulation and give better controlled release and good antifungal activity. Overall, results revealed the capability of dermal film in provide control release of clotrimazole film.

Keywords: Dermal film, Skin diffusion, Antifungal agent, Control release

INTRODUCTION

Transdermal therapeutic systems are defined as self-contained discrete dosage form which when applied to the intact skin delivers the drugs, through the skin, at a controlled rate to the systemic circulation. or Transdermal drug delivery systems (TDDS) are systems that utilize skin as a site for continuous drug administration into the systemic circulation.

A simple patch that you stick onto your skin like an adhesive bandages, which utilize passive diffusion of drugs across the skin as the delivery mechanism. Transdermal drug delivery offers an attractive alternative to the oral administration and injection.

Today about 74% of drugs are taken orally and are found not to be as effective as desired. Wound healing or wound repair is an intricate process in which the skin or organ or tissue repairs itself after injury. The best known and widely used approach for delivering drugs and mediation through the skin without using needles is dermal patch technology. The dermal patch technology has proven to be fastest, easiest, safest and most economical way to help wound to heal.

The firs transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness. The FDA has approved, till 2003 more than 35 transdermal patch products, spanning 13 molecules (In USA).

➢ Advantages:

1. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specification due to hepatic "First pass" effect formation of metabolites that causes side effects, short half-life necessitating frequent dosing etc.
2. Self-administration is possible with these systems.

3. The drug input can be terminated at any point of time by removing transdermal patch.
4. Allows effective use of drugs with short biological half-life.
5. Allow administration of drugs with narrow therapeutic window.
6. Provides controlled plasma level of very potent drugs.
7. Drug input can be promptly interrupted when toxicity occurs

➢ Disadvantages:

1. Drug that requires high blood levels cannot be administered Adhesive may not adhere well to all types of skin.
2. Drug or drug formulation may cause skin irritation or sensitization.
3. Uncomfortable to wear.
4. May not be economical.
5. The barrier function of the skin changes from one site to another on the same person or person to person and with age.

➢ USES:

- A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.Often; this promotes healing to an injured area of the body.

TRANSEPIDRERMAL ABSORPTION:

- It is now believe that the transdermal pathway is principally responsible for diffusion across the skin. The main resistance encountered along this pathway arises in the stratum corneum. Permeation by the Trans epidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue.

➢ **Transdermal permeation (percutaneous absorption):** The passage of substance from the outside of the skin through its various layers into the bloodstream. Transdermal permeation Drug Particles

Kinetics of transdermal permeation:

- Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps.
- Penetration of drug through viable epidermis,
- Uptake of the drug by capillary network in the dermal papillary layer
- Sorption by stratum corneum

➢ Fundamentals of skin permeation:

- Rate of permeation, dQ/dt, across a skin can be expressed as:

$dQ / dt = Ps (Cd – Cr)$

Where,

dQ/dt – Rate of permeation,

Ps – Permeability coefficient,

Cd – Concentration in donor compartment,

Cr – Concentration in receptor compartment

Component of film forming polymer:

1. Drug:

Drug For transdermal application of film forming systems, the drugs need to have suitable properties which are independent of the dosage form.

Generally the drugs which are applicable to these systems are highly potent which permeate the skin rapidly, which cause no skin irritation and which are relatively stable to the enzymes present in the epidermis.

Other properties of the drug like partition coefficient dictate the pathway a drug will follow through the skin. Second, the molecular weight of drug is an important factor in drug permeation as small molecules cross human skin than large molecules.

2. Polymer:

A variety of polymers are available for preparation of fast Filming system. The polymers can be used alone or in combination to obtain the desired film properties.

The film obtained should be tough enough so that there won't be any damage while handling or during transportation.

The robustness of the strip depends on the type of polymer and the amount in the formulation.

These polymers should from a flexible film at skin temperature.

The list of polymer along with their molecular weight and properties are mentioned in table as follows:

Characterization and Properties of Polymers used in Formulation Consideration

Polymer	Properties
Hydroxypropyl Methylcellulose (HPMC)	• Produce a light, non-greasy uniform film with good texture • Do not interact significantly with other ingredients • Surface active agent, therefore adsorbs water providing easy dispersion, lubricity and comfort feel in occlusive state on application to skin
Ethyl cellulose (EC)	• Nontoxic, nonirritating, non-allergic material • Good film forming properties that form tougher films
Hydroxypropyl cellulose	• Nonionic, pH insensitive polymer • Water soluble
Polyvinyl pyrrolidine (PVP)	• Solubility in water and other solvents • Adhesive and binding property • Acts as a bioavailability enhancer
Polyvinyl alcohol (PVA)	• Water soluble •Excellent film forming and adhesive properties • Nontoxic and biocompatible
Chitosan	• Excellent film forming ability •Opens the tight junctions of mucosal membrane, thereby enhancing the para cellular permeability and penetration of drug • Controls drug release
Eudragit RS 100, RL 100	• Transparent, elastic, self-adhesive • Good adhesion to the skin
Silicones Polydimethylsiloxane (PDMS)	• Water vapor permeable film • Adequate substantivity and durable film
Acrylates copolymer Avalure® AC 118, AC 120	• Tough, breathable, abrasion resistant films

3. Solvent:

The solvents form an important component in film formution. The solvent used in film forming systems help in solubilizing the drugs as well as have an impact on drug permeation.

Commonly used solvents for topical and transdermal use are listed in Table.

As these solvents are widely used,the safety of these has been established on long term use.

Characterization and Properties Solvent used in Formulation

Category	Examples
Glycols	Propylene glycols, polyethylene glycols
Alcohols	Ethanol, butanol, isopropanol, benzyl alcohol, lanolin alcohols, fatty alcohols
Other solvents	Ethyl acetate, oleic acid, isopropyl myristate

4. Plasticizers:

- Plasticizers are used in the film forming systems to impart flexibility to the film and improve the tensile strength of the film formed.
- The plasticizer used should be compatible with the polymers used and should have low skin permeability.

- Commonly used plasticizers are glycerine, polyethylene glycol, sorbitol, dibutyl phthalate, propylene glycol, triethyl citrate etc.

❖ Here solvent casting method to perform dermal film

Drug dissolved in alcohol by stirring for 5 min

↓

PEG in distilled water in end the film forming polymer (HPMC or HEC)
Successively added under constant stirring

↓

Continuously stirring for 25-30 min after dispersion preparation avoiding Evaporation

↓

Filmare obtained and drying for 48 hours for 20 c
Determination of Ingredient used trial in Experiment

Primary trial batch is as follows

Ingredient	N1	N2	N3
Clotrimazole	1.25 gm	5 gm	5 gm
Hydroxyethyl cellulose (HEC) 250 M	-	3 gm	2 gm
Polyethylene glycol (PEG)400	-	1 ml	1 ml
HPMC 15,000	1 gm	-	-
Prpelene glyol	10 ml	-	-
Polysorbate 20	1 ml	-	-
Ethanol	30 ml	10 ml	10 ml
Make up by Distilled water	100 ml	100 ml	100 ml

From above batches N1: Translucent film slightly rough, N2: Opaque film shiny smooth, N3 : Opaque film shiny smooth.

Prepared Film

- Evaluation of parameter of dermal film is as follow:

Organoleptic property

Melting point range Melting point of drugs

Experiment	Observation
Melting Point Range	147-149 °C

Optical properties of drugs

Properties	Results
State	Solid
Description	White powder
Taste	Tasteless
Odour	Odourless
Colour	White

Compatibility studies:

1. **Differential Thermal Analysis :No change melting point of drug**

- Compatibility study:Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.
  Differential Thermal Analysis(DTA): In lab by melting point

1) Analytical method:

Determination of wavelength of Clotrimazole phosphate buffer pH 7.4: A stock solution having 1% Clotrimazole was prepared in Ethanol. It was further diluted to obtain second 2000 µg/ml. From second stock prepare test solution range 10-90 µg/ml and measure absorbance

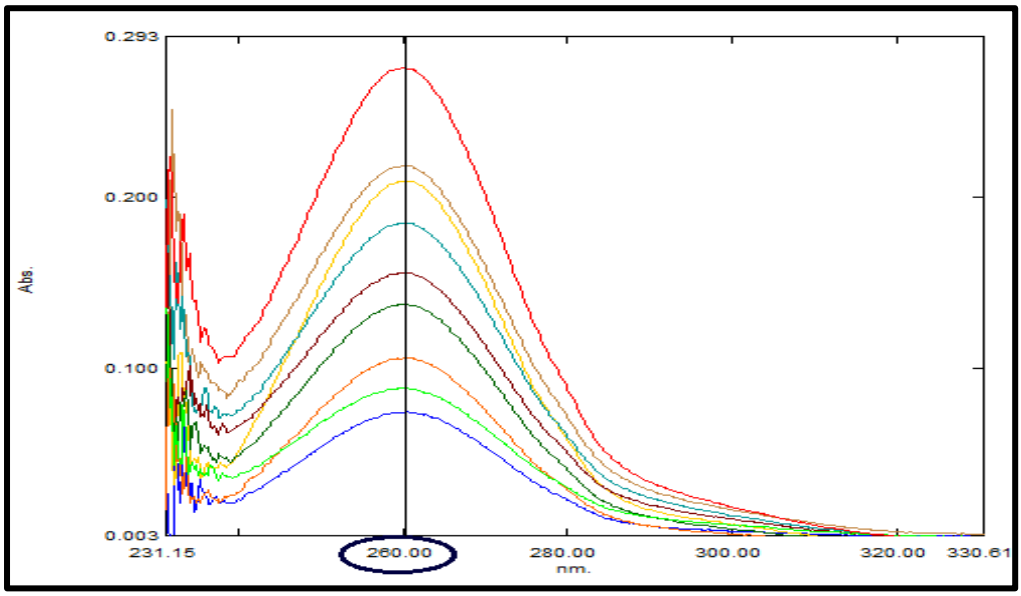
Determination data of wavelength of Clotrimazole in phosphate buffer pH 7.4

Table No. 6.3: Wavelength of Clotrimazole in phosphate buffer pH 7.4

SR. NO.	CONCENTRATION (µg/ml)	ABSORBANCE
1	10	0.055 ± 0.00057
2	20	0.089 ± 0.001
3	30	0.106 ± 0.001
4	40	0.137 ±0.000577
5	50	0.156 ± 0.001155
6	60	0.185 ± 0.00057
7	70	0.209 ± 0.001
8	80	0.238 ± 0.000577
9	90	0.275 ± 0.001

2) Analytical method:

(1)Standard curve of Clotrimazole in phosphate buffer pH 7.4



Overlay spectra of Clotrimazolein phosphate buffer pH 7.4

3) Analytical method:

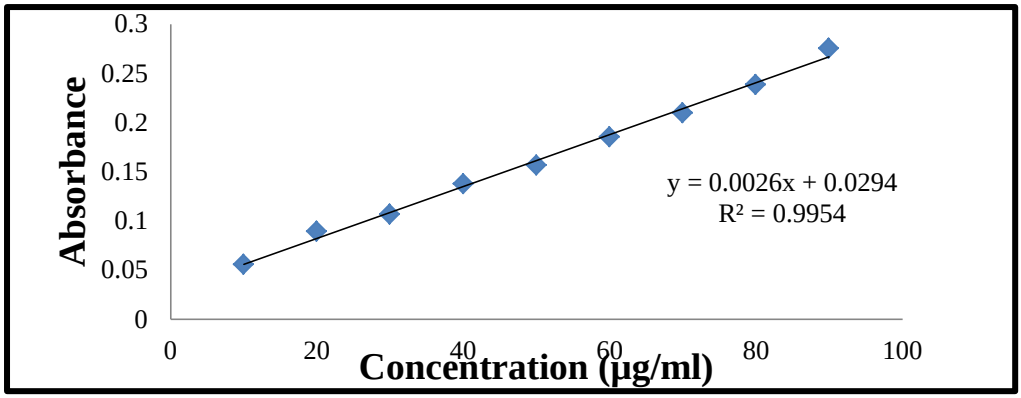
1) Standard curve of Clotrimazole in phosphate buffer pH 7.4

y= mx + c

y=0.0026x+0.0294

R^2=0.9954

Phosphate buffer pH 7.4



Calibration curve of Clotrimazole in phosphate buffer pH 7.4

2) Weight Variation:

The patches were subjected to weight variation by individually weighing twenty selected patches randomly and the average was calculated.Cut film 2cm to 2cm and weight 20 films and average total film. Average weight= Total weight of film/ No of film

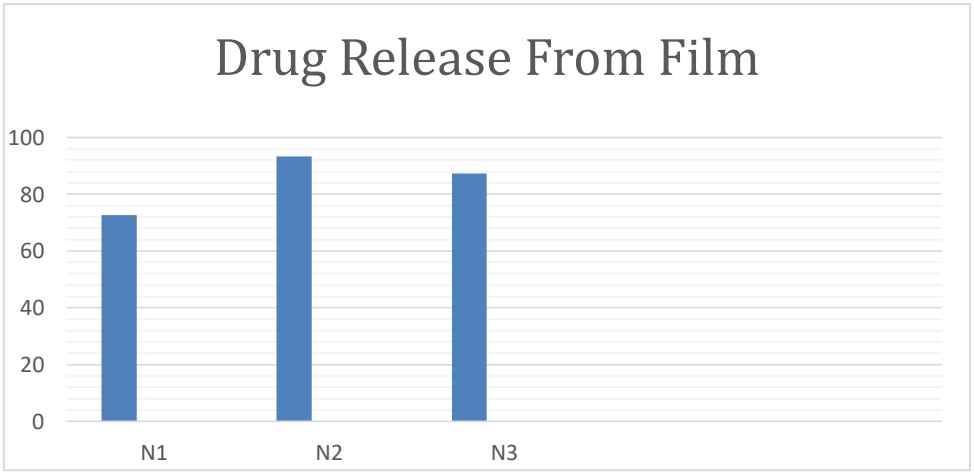
Weight Variation (* Mean ± SD; n=3)

Formulation	Weight of average film
N1	1.56 ± 0.5
N2	2.00 ± 0.2
N3	3.00 ± 0.7

From above study F1 very thin film, F2 average weight and F3 very hard film

3) Drug content:
Each patch from different formulations (patch size of 2 cm2, equivalent to 10 mg of drug) was dissolved in phosphate buffer (pH 7.4) and shaken continuously for the 24 h using a magnetic stirrer to extract the drug from the patch. After filtration and dilution with phosphate buffer, % drug content was measured spectrophotometrically at a wavelength of 260 nm.weight one film equivalent to 10 mg of drug properly mixed with 25 ml ethanol prior to filter and absorbance measured at 260 nm using ethanol as blank reagent.

Drug content studies of Clotrimazolefilm : (* Mean ± SD; n=3)



Drug content studies of clotrimazole drug
From above study F2 give high drug release

4) Film Thickness:
The thickness of the prepared transdermal films was measured by screw gauge or varnier calipers with least count at five different sites, and the average was calculated with an SD .Cut film 2cm to 2cm and and measure thickness by varnier calipers

Determination of Film Thickness

Formulation	Thickness
N1	2mm ± 0.03
N2	4mm ± 0.04
N3	7mm ± 0.04

From above study F1 very thin film, F2 average and F3 very thick film

5) % Flatness: Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

Cut 3 strips of 7cm form film (2 form corners + 1 center) Length measured without applying pressure…% Flatness= average% length

Determination of Flatness

Formulation	% Flatness
N1	87.58 ± 0.03
N2	94.42 ± 0.07
N3	83. 14 ± 0.04

From above study F2 have good flatness compare to other

6) Folding endurance:

The folding endurance of patches was determined by repeatedly folding a strip of film at the same place till it tends to break. It is determined as the number of times the film is folded at the same place either to break the film or to develop visible cracks repeatedly folding small strips of film (2cm to 2cm) at the same place until it breaks. Count no. of the time the film is fold.

Determination of Folding Endurance

Formulation	Folding endurance
N1	30 ± 0.03
N2	45± 0.07
N3	60± 0.04

From above study F2 have high folding endurance

7) Film adhesion:

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured.

Weight one film (M) attach on smooth surface (S) generate vertical force on it which lead to epation of plate

$$St\ (N.cm^{-2}) = M\ (kg)_{x}\ 9.81\ (N.kg^{-1} / S\ (cm^{2})$$

Determination of Film Adhesion

Formulation	Film adhesion
N1	0.28 ± 0.02
N2	0.34 ± 0.03
N3	0.26 ± 0.03

From above study F2 have high film adhesion

8) In vitro diffusion study:

Diffusion cell (take beaker fill with buffer and take test tube cut second side and make both side open one end attach semipermeable paper put middle of beaker) put 1 film upper side of semipermeable membrane and measure absorbance particular time interval

Drug release kinetics were analyzed by various mathematical models such as a zero-order and first-order kinetic models; Higuchi and Korsmeyer–Peppas models to ascertain the kinetics of drug release.

Zero order kinetics: $Q_1 = Q_0 + K_0 t$

Where Q is the amount of the drug dissolved in time *t*, Q is the initial amount of drug in the solution (most times, Q_{50}) and *K* is the zero order release constant.

First order kinetics: $\ln Q_t = \ln Q_0 - K_1 t$

Where Q_t is the amount of drug released in time *t*, Q_0 is the initial amount of drug in the solution and *K* is the first order release constant.

Higuchi model: $Q_t = K_H t_{1/2}$

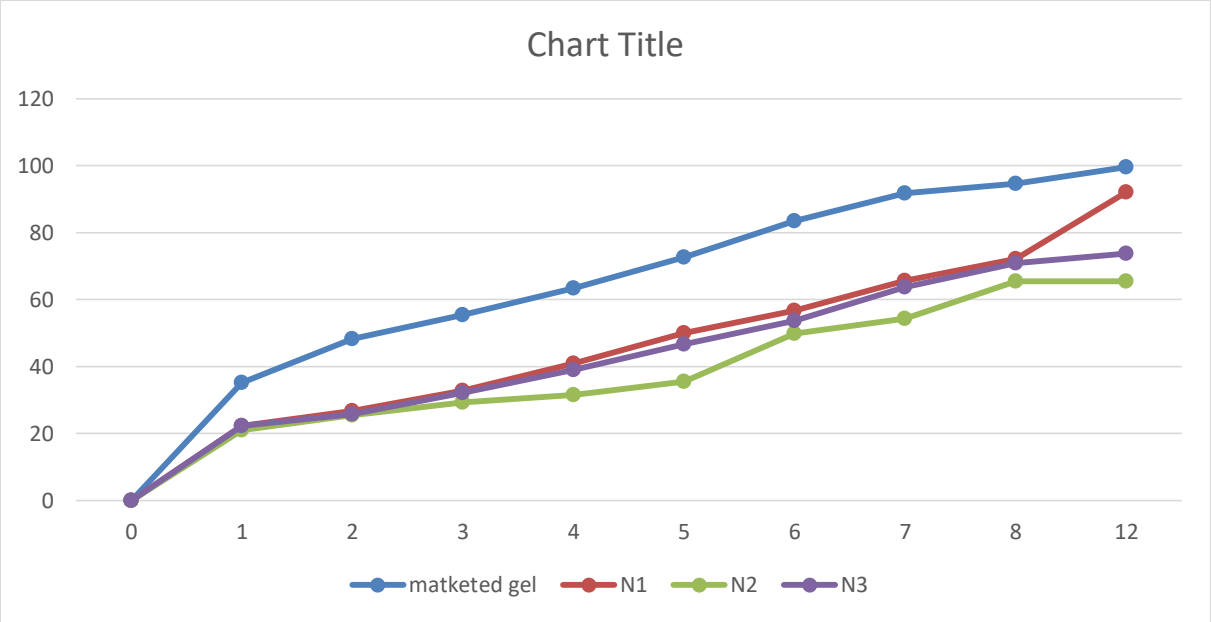
Where Q_t is the amount of drug released in time *t*, K_H is release rate constants.

Korsmeyer–Peppas model: $Q_t/Q_\infty = at^n$

Where *n* is the release exponent and the function of *t* is Q_t/Q_∞ (fractional release of the drug).

Determination of Invitro diffusion study

Sr. No	Time (hrs)	Maketed Preparation gel	N1	N2	N3
1	0	0	0	0	0
2	1	35.21	22.34	21.02	22.35
3	2	48.30	26.73	25.43	25.77
4	3	55.42	32.88	29.26	32.12
5	4	63.38	41.02	31.53	39.06
6	5	72.61	49.98	35.48	46.73
7	6	83.53	56.67	49.89	53.62
8	7	91.79	65.62	54.30	63.78
9	8	99.52	72.20	65.43	70.97
10	12	-	92.11	65.54	73.72



10) In vitro antifungal activity:

The results of drug release studies recorded as inhibitory zone diameter (IZD) using the agar diffusion method. The *in vitro* antifungal activity of the formulations was compared to the CTZpure sample. All batches of the transdermal films gave greater zones of inhibition than the CTZ pure sample against the clinical isolate of *C. albicans*. However, transdermal films prepared gave the greatest zone of inhibition against the test organism.Take microorganism culture pour on plate and then make bore on plate and compare zone of inhibition of true drug marketed and prepared film.

Determination of in vitro antifungal activity using cup plate method

Organism	Formulation	Zone of inhibition diameter in mm
Gram Positive	Control (Plane gel)	-
Gram Positive	Pure drug	11.3± 0.04
Gram Positive	Clotrimazole film	9.6± 0.03
Gram Positive	Marketed Clotrimazole gel	6.3±0.06

In vitro antifungal activity using cup plate method

The Clotrimazole has more antifungal activity than marketed gel after 24 hr.

11) Stability Study:
Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.Pack film in aluminum paper film put in different temperature and after 10, 20 and 30 day check stability.

Stability testing of new drug substances and products [Q1A (R2)]

Determination of Stability testing study

Stability Condition	Physical Stability
	No. of Days
	10
25ºC/60% RH	No change in appearance
40º C/75%RH	No change in appearance

The Clotrimazole film was stable after 10 days.

Result: In this work, transdermal films containing CTZ were formulated by solvent casting technique using admixtures of HEC and HPMC and evaluated for physicochemical performance, stability and *in vitro* diffusion drug release properties. The films exhibited good organoleptic and physicochemical properties. The values of the thickness of the films indicated uniformity in thickness, while the weights of the different batches of the transdermal films were relatively similar. All the transdermal films had highly uniform drug content. The results showed that the process employed in the preparation of the CTZ films was capable of producing films with uniform drug content and minimal film variability, consistent with earlier studies on CTZ films. The little variation in the drug content may be as a result of API and matrix physicochemical and material characteristics. However, all the formulations did not cause any skin reaction within 24 h. Folding endurance results indicated that the films would not break and would maintain their integrity with general skin folding when applied. The implication of this is that the transdermal film could be placed in any part of the body involved in movement, and that that part of the body would have to be involved in a folding movement for approximately 300 times before the film could crack/break. This suggests a good capacity of the films to withstand folding on the body surface (skin). The result of bioadhesive strength confirms the observation made under folding endurance which suggested good adhesive films. The greater the bioadhesiveness of a transdermal film formulation, the better the skin adhesiveness of the formulation. The high bioadhesive strength developed may be due to the long contact time between the tissue and transdermal films. Swelling of polymers precedes bioadhesive interaction and drug release commences after swelling . This implies that within 5 min the polymer blends would have started releasing the drug. The moisture content of the prepared formulations was low, which is important for the formulations to maintain stability and reduce brittleness during long term storage

The *in vitro* diffusion release profile is an important tool that predicts in advance how a drug would behave *in vivo*. It is evident that there was controlled permeation of CTZ from the transdermal films without a burst effect in all the formulations. The flux data may be expressed by Fick's second law of diffusion, which takes into account the initial donor concentration, its partition coefficient between the donor solution and the membrane, the diffusion coefficient of the permeant in the membrane, and the thickness of the membrane. it implies that sustained release CTZ dosage form might be developed with this formulation. Antifungalas well as stability studies the improved *in vitro* performance reveal that facilitated the understanding in-vivo behaviour of CTZ in the polymeric matrices as well as the release of drug from the films.

Conclusion: Three compositions containing Drug and excipient Formulations N1, N2 and N3 were formulated and processed by casting solvent evaporation technique, in order to develop new antifungal dermal films in the form of a polymeric adhesive matrix containing Clotrimazole 10 mg/cm2.

The behaviour towards moisture vapour indicates that the Clotrimazole-HPMC film has control release period of 12 h. This formulation could eventually be improved through extending the drying period by increasing the amount of plasticizer (PEG400). The Clotrimazole-HEC films are elastic, resistant to stretching and have the ability to release more than 60% of their Clotrimazole content in vitro at pH 7.4.

Considering the difficultly of the drug dissolution (release) process due to its low solubility in aqueous media, the release of 70% from these new dermal films can be considered a very good percentage. The most appropriate composition for Clotrimazole dermal film preparation is represented by N2—obtained. Its breakage strength and high elasticity creates favorable prerequisites for the management of operations.

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