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Formulation and Evaluation of Transdermal Patches of Clotrimazole

Yelamanda Jagadeesh*[1], Hari Kiran[2], Reddy Naveena B[2], Chandra Prakash D[2], Bhagya Lakshmi G[2], Vaishnavi P[2], Varshini S[2], Vadamala Prudhvi Raj[1]

[1]Department of Pharmaceutics, Seven Hills College of Pharmacy (Autonomous) accredited A grade by NAAC. Venkatramapuram, Ramachandrapuram mandal, Tirupati district – 517561, Andhra Pradesh, India

[2]Seven Hills College of Pharmacy (Autonomous) accredited A grade by NAAC. Venkatramapuram, Ramachandrapuram mandal, Tirupati district – 517561, Andhra Pradesh, India

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ABSTRACT

The aim of the present research work was to formulate Transdermal patches of Clotrimazole and to enhance effectiveness and to avoid side effects of the drug. Transdermal patch of clotrimazole was prepared with EC and HPMC in different ratios in order to improve the drug diffusion. Clotrimazole has formulated Transdermal patches were prepared by solvent evaporation technique. Drug and polymers has been characterized by FT-IR. The FTIR spectra of formulation shows that no interaction between drug and excipient. The evaluation of Transdermal patches of Clotrimazole were performed mainly for their Physical parameters such as Weight variation, Thickness, Folding endurance test And also for their Drug content and In-vitro Drug diffusion studies. The patch prepared by solvent evaporation technique passes the prepared patch were found to be non irritant, weight variation was found in the range of 39±5.81 to 48±2.90mg, thickness in the range of 0.08±0.09 to 0.04±0.08 mm, Folding endurance of patches was found to be in the range of 98 ±0.57 to 128±0.59, The tensile strength of the patches was ranging from 1.95±1.2to 3.98±1.9, The percentage elongation ranges from 10.6 to 18.6, drug content uniformity was in between 78.25 to 89.76 %. The in-vitro drug diffusion profiles of the formulations in pH 7.4 show differences depending on their composition. A Tran's dermal patches of all the preparations were observed by the diffusion test. It was also observed that F6 showed highest drug release.

*Corresponding Author

Name: Yelamanda Jagadeesh
Phone: +91 9493100673
Email: jagadeeshlakshmi.16@gmail.com

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INTRODUCTION

One of the most dependable, appealing, and efficient techniques is the transdermal drug delivery system (TDDS), which has gained widespread acceptance [1]. Drug delivery through the skin has been both an intriguing and difficult study topic. Transdermal drug delivery has developed over the past two decades into an alluring and well-accepted technology because it minimises and avoids the drawbacks associated with conventional and parenteral drug administration, such as peak and valley phenomena, which show fluctuation in plasma drug concentration levels, pain and inconvenience from injections, and both routes' limited controlled release options [2, 3].

Transdermal drug delivery systems are topically applied medications within the form of patches that release medications for systemic effects in a set

and regulated rate. Transdermal drug delivery systems (TDDSs) make it possible for therapeutic doses of pharmacological compounds to be administered through the skin and into the bloodstream for systemic effects [4]. Stoughton came up with the idea for chemical material absorption through the skin for the first time in 1965. The U.S. Food and Drug Administration approved the first motion sickness patch that was commercially accessible on a prescription in December 1979.

There is a developing understanding that continuous medication delivery into the systemic circulation can be achieved using the intact skin as the port of drug administration, closely duplicating the advantages of intravenous infusion without any of its risks [5, 6]. This is referred to as transdermal administration, and the drug delivery methods are referred to as "transdermal therapeutic systems" or more commonly as "transdermal patches". A transdermal patch, also known as a skin patch, is an adhesive patch that is applied to the skin and contains medication that is intended to be absorbed into the bloodstream through the skin [7, 8]. Transdermal therapy systems are described as discrete, self-contained dosage forms that, when applied to healthy skin, transport drugs to the bloodstream at a controlled rate through the skin. A predetermined amount of medication is delivered to the surface of healthy skin at a predetermined pace through transdermal drug delivery systems, which are adhesive drug-containing devices with a defined surface area. These systems eliminate many issues with oral dosing, including product stability, bioavailability, and the peaks and troughs of pulse dosing, by providing the medicine consistently at a predictable rate and maintaining the rate for an extended length of time [9, 10].

MATERIALS AND METHODS

The following are the list of materials used in the formulation of Transdermal Patches of Clotrimazole with the sources from which the products are obtained according to the specifications.

Preformulation Studies

Pre-formulation is the initial phase of a drug's rational dosage form development. Pre-formulation is the study of the physical and chemical characteristics of the pharmacological ingredient, both on its own and when mixed with excipients. Pre-formulation testing's main goal is to provide the formulator with data that will help them create stable, bioavailable dosage forms that can be mass-produced [11].

Spectroscopic Studies:

Determination of Lambda max:

A 10mg of Clotrimazole was precisely weighed and dissolved in 35 ml of phosphate buffer at a pH of 7.4. The answer was then diluted using pH 7.4 into 100ml. the dilutions were made from these stock solutions to obtain the concentration of 10 μg/ml by using pH 7.4 UV spectrum was recorded in the wavelength range 261nm [12].

Drug-Excipient Interaction Studies:

1. FTIR spectroscopy; 2. Differential scanning Calorimeter.

FTIR Spectroscopy:

FT-IR spectra of Clotrimazole, HPMC, and PVP-K30 were documented. 2.5 mg of the sample was thoroughly combined with 100 mg of potassium bromide IR powder before being compressed under a vacuum. The resulting disc was mounted in a suitable holder in a thermo-electro-infrared spectrophotometer (Model Schimadzu 8400S), and IR spectrum measurements were taken between 4,000 and 400 cm^{-1}. Comparing the resulting spectrum for [13] any spectral alterations and the results were tabulated.

Preparation Of Clotrimazole Transdermal Patches By Solvent Evaporation Method:

Preparation Of Clotrimazole transdermal Patches:

The solvent evaporation method was used to create transdermal patches containing Clotrimazole. Chloroform, methanol, and EC were dissolved to create the drug reservoir. For each formulation, the polymer ratio was changed while maintaining the overall weight constant at 700 mg. As a plasticizer, PG was included.

Under slow stirring with a magnetic stirrer, the medication Clotrimazole was incorporated into the homogenous dispersion. On a PVA backing membrane, the uniform dispersion was cast, and it was allowed to air dry.

Desiccators were used to preserve the films for future research [14]. The prepared transdermal patches were shown in Figures 1 and 2.

Evaluation Studies of Transdermal Patches:

Weight Variation:

The individual weights of randomly to selected films are determined. The weight of the can be measured. It is not differ from the individual weight [15].

The Patch weight can be measure using analytical balance. Limit of Weight Variation is 30-49.

Thickness:

The Patch thickness can be measure by micrometer screw gauge at five different point of the Patch i.e. central and four corners that mean thickness can be calculated. Sample with air bubble, tear having means thickness variation of greater than 5%are excluded from analysis. It is essential for the uniformity of thickness is directly related to the accuracy of dose in the Patch. Limit of Thickness is 0.05-0.09 [16].

Folding Endurance:

It can be measured manually for the Transdermal Patch. The Patch can be until it breaks, fold it in the same spot repeatedly. The frequency of Patch could be folding the value of folding endurance at the same location without breaking. Limit of Folding Endurance is 98-128 [17].

Moisture content (Loss on drying)

The intrinsic moisture present in a substance may affect how stable a dosage form is, particularly if it contains a medication that is water-sensitive. The moisture content is determined using the absolute approach, which results in a weight loss that is recorded throughout the procedure. Each patch (3.14 cm^2) from each batch was weighed separately, and the average weight was determined. This weight was taken into account as the starting weight. The patches were then all stored for 24 hours at room temperature in desiccators containing activated silica. When the weight of each individual patch remained unchanged, the final weight was recorded. The difference between the initial and final weights relative to the final weight was used to compute the % moisture absorption. Limit of Moisture content is 2.632-2.854 [18].

$$\% \, Moisture \; content = ((Initial \; weight - Final \; weight)/ Final \; weight) \times 100$$

Drug content

By dissolving the 2 cm2 Patch in 100 ml of pH 7.4 phosphate buffer using a magnetic stirrer for an hour, the drug concentration of the Patch was determined.

The drug concentration was then measured using spectrophotometry at a maximum wavelength of 261 nm.

For each formulation, the measurement was made in triplicate, and an average and standard deviation were reported and reported and results were tabulated in Table 3 Limit of content uniformity is 78-

Figure 1: Prepared Clotrimazole Transdermal Patches

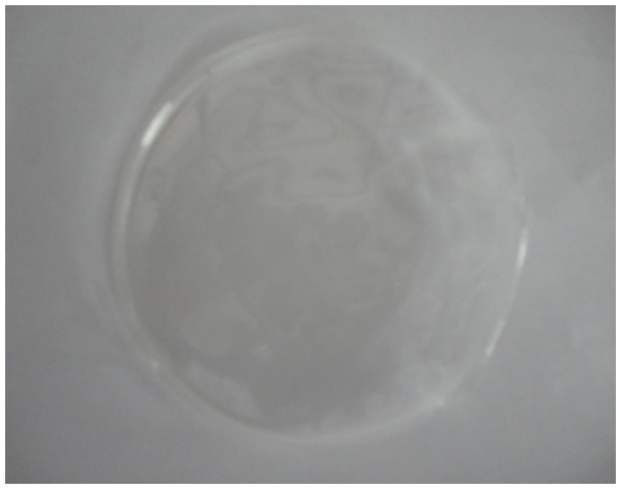

Figure 2: Prepared Clotrimazole Transdermal Patches

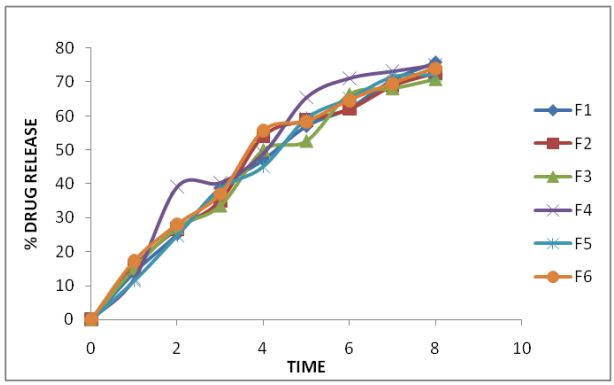

Figure 3: In-Vitro diffusion of Clotrimazole formulations (F_1-F_6) in pH7.4

Table 1: List of materials used

S. No.	List of materials	Supplier /Manufacturers
1	Clotrimazole(mg)	A-Z Pharmaceuticals, Chennai.
2	HPMC(mg)	S.D fine chem. limited, Mumbai.
3	EC(mg)	S.D fine chem. limited, Mumbai.
4	PG-(ml)	S.D fine chem. limited, Mumbai
5	Glycerin(ml)	Merck specialties Pvt., Ltd
6	Methanol: Chloroform(ml)	Merck specialties Pvt., Ltd

Table 2: Composition of Clotrimazole Transdermal Patch

S.No	Formulations	F1	F2	F3	F4	F5	F6
1	Clotrimazole(mg)	20	20	20	20	20	20
2	HPMC(mg)	6.0	6.5	7.0	7.5	8.0	8.5
3	EC(mg)	4.0	3.5	3.0	2.5	2.0	1.5
4	PG-(ml)	1	1	1	1	1	1
5	Glycerin(ml)	0.5	0.5	0.5	0.5	0.5	0.5
6	Methanol: Chloroform(ml)	10	10	10	10	10	10

Table 3: FT-IR interpretations of pure drug and excipients

Functional group	Clotrimazole	Clotrimazole & HPMC	Clotrimazole &EC
C=H (Aromatic)	749.50	751.51	751.08
C=H (vinyl)	822.85	824.33	824.05
=C–H(bending)	902.38	912.00	903.02
C–O(Stretching)	1080.26	1081.20	1081.06
C–N (Stretching)	1275.57	1277.07	1276.87
C=C (Stretching)	1432.79	1434.03	1433.45
O–H (Stretching)	2638.47	2830.70	2736.97

Table 4: Evaluation of Transdermal Patches

Formulations	Weight variation (%)	Thickness(mm	Moisture content (%)	Folding endurance	Drug content (%)
F1	48±2.90	0.07±0.02	2.84±0.12	98±0.57	89.76
F2	40±1.31	0.05±0.06	2.85±0.23	124±0.59	82.65
F3	41±2.32	0.08±0.09	2.64±0.35	122±0.81	82.44
F4	39±5.81	0.07±0.07	2.75±0.35	114±0.51	78.25
F5	45±5.62	0.06±0.09	2.85±0.56	126±0.81	83.40
F6	44±4.62	0.04±0.08	2.54±0.46	128±0.59	85.25

Table 5: In-Vitro Diffusion Of Transdermal Patches F1-F6

Time(Hr)	F1	F2	F3	F4	F5	F6
1	13.92±0.22	15.79±0.25	15.11±0.35	12.04±0.16	11.41±0.25	17.28±0.25
2	25.20±0.35	26.78±0.24	27.09±0.25	39.21±0.17	24.75±0.30	28.05±0.21
3	38.91±0.12	35.15±0.12	33.53±0.21	40.36±0.22	38.42±0.18	37.02±0.10
4	47.09±0.38	54.18±0.19	49.98±0.35	49.01±0.28	45.06±0.16	55.68±0.10
5	57.02±0.20	58.81±0.20	52.61±0.22	65.49±0.26	59.21±0.15	58.41±0.16
6	62.35±0.25	62.12±0.35	66.35±0.14	71.21±0.29	65.11±0.11	64.65±0.29
7	70.62±0.30	68.98±0.28	68.08±0.24	73.25±0.25	71.45±0.15	69.61±0.16
8	74.12±0.25	72.78±0.18	70.81±0.25	75.11±0.25	72.12±0.19	75.85±0.23

Table 6: Correlation coefficient (R^2) Values for different kinetic models for all formulations

Formulation	R2	R2	R2	R2	R2
	Zero order	First order	Higuchi	Korsemeryer papers	Hixson Crowell
F1	0.9992	0.9998	0.9844	0.9988	0.9995
F2	0.9947	0.9983	0.991	0.9992	0.9973
F3	0.9978	0.9998	0.9898	0.9934	0.9847
F4	0.9766	0.986	0.9763	0.9581	0.9995
F5	0.9999	0.9964	0.9766	0.9992	0.9977
F6	0.9999	0.9962	0.9946	0.9922	0.9947

Table 7: Microbial Studies of Transdermal Patches

Name of the Organisms	Cavity-1		Cavity-2		Average	
	Zone of Inhibition		Zone of Inhibition		Zone of Inhibition	
	Stranded	Stranded	Test	Test	Stranded	Test
E.coli(-ve)	18 mm	17 mm	15 mm	13 mm	18 mm	14 mm
S.aurens(+ve)	19 mm	21 mm	14 mm	12 mm	20 mm	13 mm
P.valgaris (+ve)	17 mm	15 mm	13 mm	11 mm	16 mm	12 mm
Candida Albicans (Fungi)	17 mm	18 mm	16 mm	16 mm	18 mm	16 mm
Bacillus Subtius(-ve)	13 mm	11 mm	9 mm	10 mm	12 mm	10 mm
Name of the Organisms	**Cavity-1 Zone of Inhibition**		**Cavity-2 Zone of Inhibition**		**Average Zone of Inhibition**	
	Stranded	**Stranded**	**Test**	**Test**	**Stranded**	**Test**
E.coli(-ve)	18 mm	17 mm	15 mm	13 mm	18 mm	14 mm
S.aurens(+ve)	19 mm	21 mm	14 mm	12 mm	20 mm	13 mm
P.valgaris (+ve)	17 mm	15 mm	13 mm	11 mm	16 mm	12 mm
Candida Albicans (Fungi)	17 mm	18 mm	16 mm	16 mm	18 mm	16 mm
Bacillus Subtius(-ve)	13 mm	11 mm	9 mm	10 mm	12 mm	10 mm

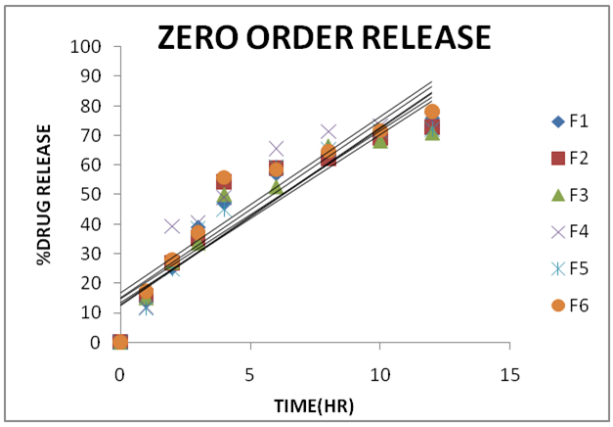

Figure 4: Zero-order release of formulations (F_1-F_6)

Figure 5: First-order release of formulations (F_1-F_6)

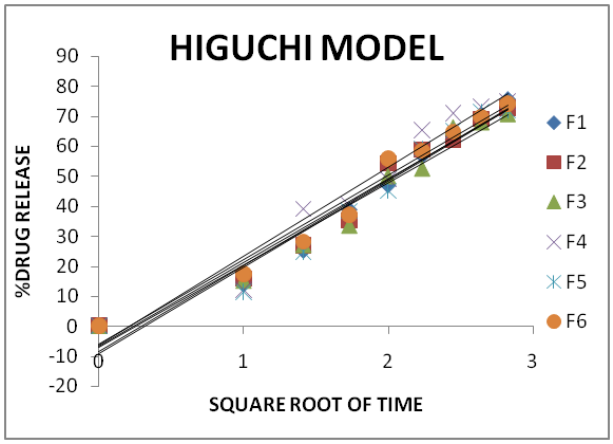

Figure 6: Higuchi model release of formulations (F_1-F_6)

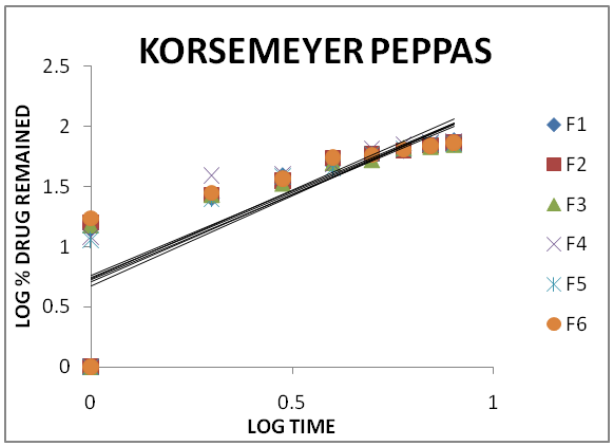

Figure 7: Korsemeyer peppas release of formulations (F_1-F_6)

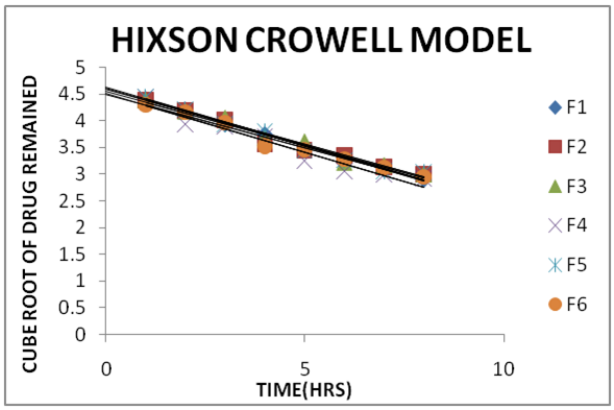

Figure 8: Hixson Crowell Model release of formulations (F_1-F_6)

89% [19].

In-vitro drug penetration studies protocol for patch

A customised Franz Cell apparatus (Perm Gear, USA) was created to evaluate the in vitro drug release of Clotrimazole from a transdermal patch. The artificial membrane/albino rabbit skin was first fixed within the Franz Cell apparatus's two donor compartments and receptor compartments. The pH 7.4 phosphate buffer was employed as the receptor solvent. 5 mL of the receptor solvent was put into every receptor compartment [20, 21].

The skin was divided into pieces with a 2 cm2 diffusion area. The transdermal patch was attached to the rabbit skin in such a way that the drug layer was towards the epidermis, and it was then secured in the Franz Cell apparatus's donor and receptor compartments. A steady stream of hot water was circulated to keep the temperature of the receptor solvent at 37 °C plus or minus 1 °C.

At predetermined intervals, samples of each 2 ml were taken out of the receptor compartments and

immediately replaced with new receptor solvent that had been kept at the same temperature. The samples were put through a 0.45-micron membrane filter before being tested for drug concentrations with a UV-Visible spectrophotometer with a 262-nm detection wavelength [22].

Kinetics of drug release

Using zero order as well as first order, the mechanism of drug release from the Clotrimazole transdermal patch during the dissolving test in dissolution media (pH-7.4 buffer) was identified [15].

Zero order equation

It depicts systems where the release rate is unaffected by the dissolved species' concentration. The zero-order equation is used to fit the dissolving data [23].

$Q = Q_0 - K_0 t$ (1)

Q = Amount of drug released at time's'

Q_0 = Amount of drug released initially (often considered zero)

K_0 = Zero order rate constant

A straight line with a slope equal to K0 and an intercept at the origin of the axes would appear on a concentration vs. time graph. Plotting the cumulative proportion of the medication dissolved over time leads to zero-order plots.

First order equation

The first order equation addresses the release from systems where the concentration of the dissolving species affects the rate of dissolution.

$\text{Log } C = \text{Log } C_0 - Kt / 2.303$ (2)

C_0 = Initial concentration of the drug

C = Concentration of drug at time's

K = First order constant

t = Time

Higuchi model

Higuchi created models in 1961 (Higuchi 1961) and 1963 (Higuchi 1963) to analyse how pharmaceuticals that are water soluble and low solubility release when they are put into semisolid and solid matrices. The relationship discovered was; It was used to analyse the dissolution from a planer system with a homogeneous matrix.

$A = [D (2C-C_s) C_{st}] 1/2$ (3)

$A = D\varepsilon/\tau (2C-\varepsilon C_s) C_{st}$ (4)

Where the terms A, D, C, Cs, and t have the same meaning as in equation (4), is the capillary system's tortuosity factor, and is the matrix porosity. The Higuchi model, often known as the simplified Higuchi model, can be typically simplified as follows:

$A = KH\, t_{\frac{1}{2}}$ (5)

KH is the Higuchi dissolution constant in this scenario. According to Higuchi, drug release is a diffusion process that depends on square root time and is based on Flick's law. Example: The foregoing relationship, as shown in equation (5), is followed by drug dissolution from several modified release dosage forms, such as in the case of some transdermal systems and matrix tablets with water soluble drugs.

Korsmeyer-Peppas model

When diffusion was the primary drug release mechanism in 1983, Korsmeyeretal devised a straightforward, semi-empiric model that exponentially related drug release to elapsed time (t).

$A_t/A_\infty = atn$ (6)

The function of 't' is At/A (fractional release of drug), and 'a' is the constant including structural and geometrical characteristics of the dosage form. n is the release exponent, which indicates the drug release mechanism.

The equation (6) changes when a burst effect is a possibility.

$A_t/A_\infty = atn + b$ (7)

'b' stands for the burst effect. The introduction of the lag period has been necessary to appropriately characterise the amount of medication released, making the Korsmeyer equation, or equation (6), incorrect. A calculation

$A_t/A_\infty = [k (t-l) n + k' (t-l) 2n]$ (8)

The best fit of the data was achieved by include a lag period (l), kinetic constants (k and k') for diffusion and erosion controlled release, and a diffusion exponent (n). The kinetic constants weren't often cumulative, and as the temperature rose, k' became increasingly negative.

Hixson – Crowell model

Hixson-Crowell recognised in 1931 that the particle regular area is proportional to the cubic root of its volume and sought an equation as a means of evaluating the drug release with changes in the surface area and the diameter of the particles/tablets.

$A_0^{1/3} - A_t^{1/3} = k_s t$ (9)

A0 represents the initial dose amount in the dosage form, At represents the dosage amount that is still present at different periods, and ks is a constant that takes the surface volume relation into account.

This model is applied under the presumption that drug particle dissolving rate, not diffusion, controls the release rate.

Antimicrobial Studies

Collection of Microorganisms

Micro organisms' like Staphylococcus aurous(MTCC 96), Progenies vulgaris (MTCC 435), Bacillus subtilis(MTCC 121) and Escherichiacoli(MTCC 443) The microorganisms were originally obtained from Microbial Type Culture Collection Centre, SreeVidyanikethan College of Pharmacy, Department of Pharmaceutical biotechnology, A.Rangampet, Chandragiri (M) Chittoor (d)AP. India. Cultures were kept in screw-capped bottles at 4 °C as nutrient agar slants. By routine plating, the viability and purity of all cultures were evaluated [24].

Test solution

Each extract's test solution was made by combining 1 gm of it separately with 10 ml of sterile distilled water in a bottle with a specific gravity and storing it in the refrigerator. One hour before each usage, the solution was taken out of the fridge to warm up at room temperature.

Standard solution

The standard antibiotic streptomycin (1 in 10 ml) was dissolved in sterile distilled water. This was used as a standard for standard drugs for gram-positive organisms. For gram-negative organism ampicillin was used as standard drug.

Preparation of medium

Inoculums of bacteria were prepared using nutrient broth. To prepare the medium for antimicrobial screening, nutrient agar was utilised. The nutritional agar medium has the following composition.

Peptone -5.0g

Beef extract - 1.5g

Yeast extract - 1.5g

Agar - 1.5g; Distilled water - 1000MI; PH adjusted -7.2

Preparation of inoculums

Inoculums' was created by adding an 80 millilitre loop of nutrient broth and a 150 millilitre Erlenmeyer to a loop of stock culture. With the exception of agar, the inoculums broth's composition was identical to that of the stock culture. The inoculum flasks were employed for tests after a 24-hour incubation period at 37°C.

Experimental protocol

Autoclaving at 1200 for 15 minutes sterilised the nutritional agar medium. The pipette and Petri plates were sterilised for one hour in a 150°C oven. Each of the sterilised Petri dishes received approximately 25ml of melting nutritional agar medium and 0.5ml of bacterium inoculum broth. The Petri dishes' contents were meticulously preserved while rotating. At room temperature, the inoculum-containing media was allowed to harden. Fine what's man filter paper discs were created at identical distances once the material had solidified. The various concentrated extracts of the test and standard solutions, as well as the blank, were placed in Petri dishes and left undisturbed for an hour at room temperature after being coated with what's man filter paper disc 6. The Petri dish was incubated for 24 hours at 370 degrees, and the zones of inhibition were measured in millimetres. The experiment was done three times, and the average readings are kept on file [25].

RESULTS AND DISCUSSION

Excipient Interaction Studies

1. FT-IR Spectroscopy
2. Differential scanning Calorimeters

FT-IR Spectroscopy

Fourier transforms infrared spectroscopy (FT-IR)

Fourier transforms infrared spectroscopy studies for Clotrimazole

FT-IR spectrum of Clotrimazole. The characteristic peaks of Clotrimazole spectrum are 2638.47 due to O–H (Stretching), 1432.79 due to C=C (Stretching), 1275.57 due to C–N (Stretching), 1080.26 due to C–O (Stretching), 902.38 due to=C–H (bending), 822.85 due to C=H (vinyl) and 749.50 due to C=H (Aromatic) (Figures 3, 4, 5, 6, 7 and 8).

Fourier transforms infrared spectroscopy studies for Clotrimazolewith the HPMC

FT-IR spectrum of Clotrimazole: HPMC was shown in Figure 3. Clotrimazole: HPMC spectrum shows characteristic absorption peaks 2830.70 due to O–H (Stretching), 1434.03 due to C=C (Stretching), 1277.07 due to C–N (Stretching), 1081.20 due to C–O (Stretching), 912.00 due to =C–H (bending), 824.33 due to C=H (vinyl) and 751.51 due to C=H (Aromatic) (Tables 2, 3, 4, 5, 6 and 7).

Fourier transforms infrared spectroscopy studies for Clotrimazolewith the EC

FT-IR spectrum of Clotrimazole with EC. Clotrimazole with EC spectrum shows characteristic

absorption peaks 2736.97 due to O–H (Stretching), 1433.45 due to C=C (Stretching), 1276.87 due to C–N (Stretching), 1081.06 due to C–O (Stretching), 903.02 due to =C–H (bending), 824.05 due to C=H (vinyl) and 751.08 due to C=H (Aromatic).

The FTIR spectra of Clotrimazole, excipients and Transdermal patches are compared. From the obtained spectra of Transdermal patches, it was observed that all characteristics peak of Clotrimazole were also present in the Transdermal patches indicating that there are no interaction between the excipients and the drug.

The procedure for FTIR of Clotrimazole pure drug and mixers of drug and polymers was discussed on chapter 6.6.1 and discussion is on chapter 8.2 and the results were shown here.

Evaluation of Transdermal Patches:

The procedure for Evaluation of Clotrimazole transdermal patches was discussed on chapter 6.7.1 and discussion is on chapter 8.4 and discussion is on chapter 8.5 and the results were shown here.

In-Vitro diffusion:

The procedure for in-vitro diffusion of Clotrimazole transdermal patches was discussed on chapter 6.8 and comparative diffusion of formulations was shown in Figure 7. The result has shown here.

Kinetics of Drug Release:

The procedure for kinetics of drug release of Clotrimazole transdermal patches was discussed on chapter 6.9 and the results graphs were shown here. Correlation coefficient (R^2) Values for different kinetic models for all formulations in Table 5.

Microbial Studies

The procedure for microbial studies of Clotrimazole transdermal patches results were shown here.

CONCLUSION

Transdermal patch is a promising approach with a view of obtaining long compared to currently existing methods, it would be advantageous to the drug's mode of action conventional forms. The main objective of the study was to formulate and evaluate Transdermal patch containing clotrimazole. Various polymers like HPMC and EC were employed for their film forming properties of HPMC it was selected for further studies. Prepared patches were smooth surfaces and acceptable mechanical properties. There was no interaction between drug and polymer. Drug release was found to be 75.85% in 8 hours. From the present investigation it can be concluded that Transdermal patch For paediatric and geriatric patients as well as the general public, formulation may represent a novel medicinal dosage form for various fungal infections. The finding of this result revealed that the problems of clotrimazole on oral administration like dissolution rate, limited absorption and gastric side effects can be overcome by applying clotrimazole topically in the form of Transdermal patch.

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