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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF SERTACONAZOLE NITRATE

B. Suma Deepthi*, M. Prasad Rao, M. Rama Kotaiah, K. Ratna Rajeev
M.A.M. College of Pharmacy,
Kesanupalli, Narasaraopet, Guntur District, Andhra Pradesh-522601, India.

ABSTRACT

The present work was designed to develop suitable transdermal matrix patch of sertaconazole nitrate, which is of the imidazole class used for antifungal medication, using Hydroxy Propyl methyl cellulose (HPMC), Polyvinyl pyrrolidone (PVPK-30) and Dibutyl phthalate. The aqueous insolubility of the drug inspires for the formulation of controlled release transdermal patches. Different batches developed using HPMC K15M and Polyvinyl pyrrolidone in different ratios by solvent evaporation technique. Drug excipient interaction study was further carried out using Fourier Transform Infrared (FTIR) spectroscopic technique. Physical evaluation performed such as moisture content, moisture uptake, thickness and folding endurance. In vitro diffusion studies were performed using cellulose nitrate membrane (pore size 0.45µ) in modified Franz's diffusion cells in buffer of pH 7.4. Permeation studies illustrated that the ratio of polyvinyl pyrrolidone and ethyl cellulose 1:5 shows good controlled release. Higuchi and Korsmeyer-Peppas models were used for optimizing the formulation.

Keywords: PVP K30, Hydroxy propyl methyl cellulose, Sertaconazole nitrate, modified Franz's diffusion cell.

Correspondig Author:
K. Ratna Rajeev,
M.A.M. College of Pharmacy,
Kesanupalli, Narasaraopet,
Guntur District, Andhra Pradesh-522601
pr.ratnarajeev@gmail.com

INTRODUCTION

Throughout the past two decades, the Transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Increasing number of drugs is being added to the list of therapeutic agents that can be delivered to systemic circulation via skin. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches [1,2]. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile resulting in reduced systemic side effects and sometimes, painless and offer multi-day dosing. It is generally accepted that they offer improved patient compliance. Although Transdermal drug delivery patches have a relatively short regulatory history compared to other, more traditional dosage forms, the technology has a proven record of FDA approval. Since the first Transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, throughout the past 22 years, more than 35 Transdermal patch products, spanning 13 molecules[3,4].

Sertaconazole Nitrate is for Treatment of interdigitaltineapedis (athlete's foot) caused by Epidermophytonfloccosum,Trichophytonmentagro phytes, or T. rubrum in immunocompetent adults and children ≥12 years of age. Treatment of tineacorporis (ringworm of the body),tineacruris (jock itch),or tineamanuum(hand ringworm)caused by E. floccosum, Microsporum (including M. canis), or Trichophyton(including T. mentagrophytes, T. rubrum, and T. schonleinii).

The present study aimed to formulate and evaluate the Transdermal Drug Delivery system[5,6]. Most of the drugs are reported a risk of undesirable side effects when given orally. Since skin is an excellent barrier for drug transport the various therapeutic agents are administered as TDD for systemic effect. There are various chemical and physical methods to promote Transdermal drug permeation through the disruption of the skin barrier. The main challenge for many Transdermal formulations is to effectively increase the permeability of the active ingredient through the stratum corneum. While avoiding skin irritation.

MATERIALS AND METHODS

Materials: Sertaconazole Nitrate gift sample obtained from Dr.Reddy's Laboratories,Hyderabad. Hydroxy propyl methyl cellulose, PVPK-30, polyvinyl alcohol and Dibutyl phthalate from Colorcon Asia Pvt.Ltd.,Goa and other chemicals were analytical grade from S.D. Fine-Chem Ltd., Mumbai.

Method:

Preparation of Transdermal Patches

Matrix type transdermal patches composed of different ratios of Hydroxy propyl methyl cellulose and PVPK-30 were prepared by solvent evaporation technique in a petri dish. The bottom of the ring was wrapped with aluminum foil on which backing membrane was cast by pouring 4% w/v polyvinyl alcohol solution followed by drying at 60oC for 6h. Dibutyl phthalate was incorporated as a plasticizer at 30% w/w of dry weight of polymer. Backing membrane was casted by pouring and allowing evaporating 4% aqueous solution of polyvinyl alcohol in petri dish at 60oC for 6h. The matrix was prepared by pouring the homogenous dispersion of drug (2%)with different blends of Hydroxyproplylmethyl cellulose with PVPK-30 in chloroform on the backing membrane in petri dish. The above dispersion was evaporated slowly and uniformly at 40oC for 2h with inverted funnel on the dispersion to achieve a drug polymer matrix patch. The patches were again dried at 60oC for 30 min for complete drying. The dry patches were kept in desiccators until use.

Evaluation of Prepared Transdermal Films:

Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance.

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Percentage of Moisture Uptake

A weighed film kept in desiccators at room temperature for 24 hrs was taken out and exposed to 84% relative humidity (a saturated solution of aluminium chloride) in a Desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Water Vapour Transmission (WVT) Rate

The film was fixed over the brim of a glass vial, containing 3 g of fused calcium chloride as desiccant, with an adhesive type. The vial was weighed and kept in desiccators containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs intervals for a period of 72 hrs. The water vapour transmission rate was calculated from the plots of amount of water vapour transmitted versus time.

Drug Content Analysis

The patches (n = 3) of specified area were taken into a 100 ml volumetric flask and dissolved in methanol and volume was made up with phosphate buffer pH 7.4. Subsequent dilutions were made and analyzed by UV spectrophotometer at 260.nm.

In Vitro diffusion study

Franz's diffusion cell was used for the study of in vitro release patterns of the prepared patches. The diffusion medium is prepared of buffer of pH 7.4. A cellophane membrane is used as a barrier between the donor and receptor compartment. The films were placed between the donor and receptor compartment in such a way that the drug releasing surface faced the receptor compartment. Thereceptor compartment was filled with the buffer having pH 7.4 and a small bar magnet was used to stir the medium with the help of a magnetic stirrer.

The temperature of the diffusion medium was maintained and controlled at 37oC± 1oC by a thermostatic arrangement. A sample of5ml was withdrawn at predetermined intervals, being replenished by equal volumes of diffusion medium, withdrawal of samples was carried out for a period of 24h. The drug concentration in the sampled diffusion medium was determined spectro photometrically and was calculated with the help of a standard calibration curve.

Differential Scanning Calorimetry (DSC)

The physicochemical compatibility between Sertaconazole and polymers used in the patches was studied by using differential scanning Calorimetry (DSC; Shimazu DSC-60 Calorimeter, Tokyo, Japan).

Scanning Electron Morphology (SEM)

The external morphology of the Transdermal patches was analyzed using a scanning electron microscope (JSM 6100 JEOL, Tokyo, Japan). The samples placed on the stubs were coated finely with gold palladium alloy and examined under the microscope.

Stability Studies

Stability of a drug has been defined as the stability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications throughout its shelf life.

RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES

Melting Point

Melting point of Sertaconazole nitrate was determined by capillary tube method and it was found to be 165ºC (n = 3). This value is same as that of the literature citation.

Solubility Study

In the present study, an attempt was made to learn whether the media phosphate buffer, pH 7.4, was able to maintain sink conditions in permeation studies. From the solubility studies, the drug concentration was found to be 0.116 mg/ml in phosphate buffer pH 7.4. Thus, phosphate buffer was chosen as the permeation media because sufficient amount of drug dissolved in it, which is necessary to maintain sink condition.

Partition Coefficient Determination

Octanol and in vitro study fluid (phosphate buffer, pH 7.4) are considered to be the standard system to determine drug partition coefficient between skin and in vitro study fluid. The logarithmic value of partition (log P) value was experimentally found to be 0.57 ± 0.008. The results obtained also indicate that the drug possesses sufficient lipophilicity, which fulfils the requirements of formulating it into a transdermal patch.

The results of I.R spectral analysis showed 3309.06, 2934.94, 1689.53, 1636.78 and 1214.70 wave numbers as major peaks for Sertaconazole. The drug–polymer interaction was ruled out as there were no major shifts in the absorption bands of drug in presence of either polymer combinations.

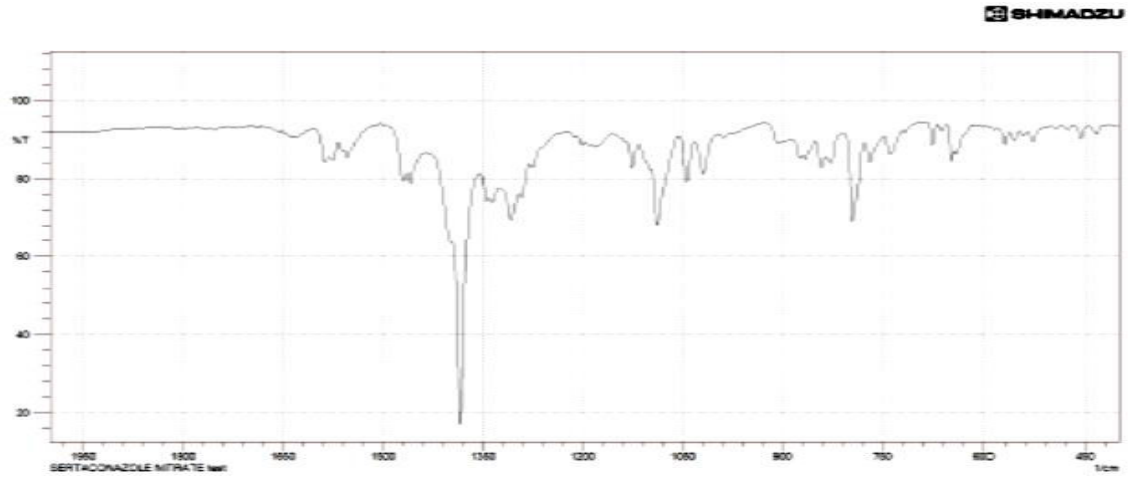

Fig-1 FTIR Spectrum of Sertaconazole

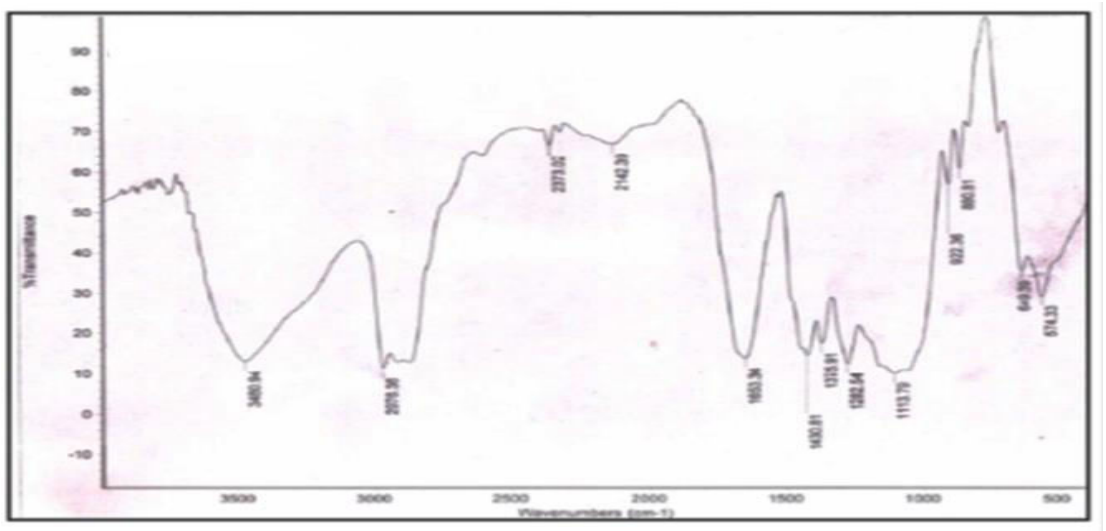

Fig-2 FTIR Spectrum of Sertaconazole, HPMC K15M and PVP K30

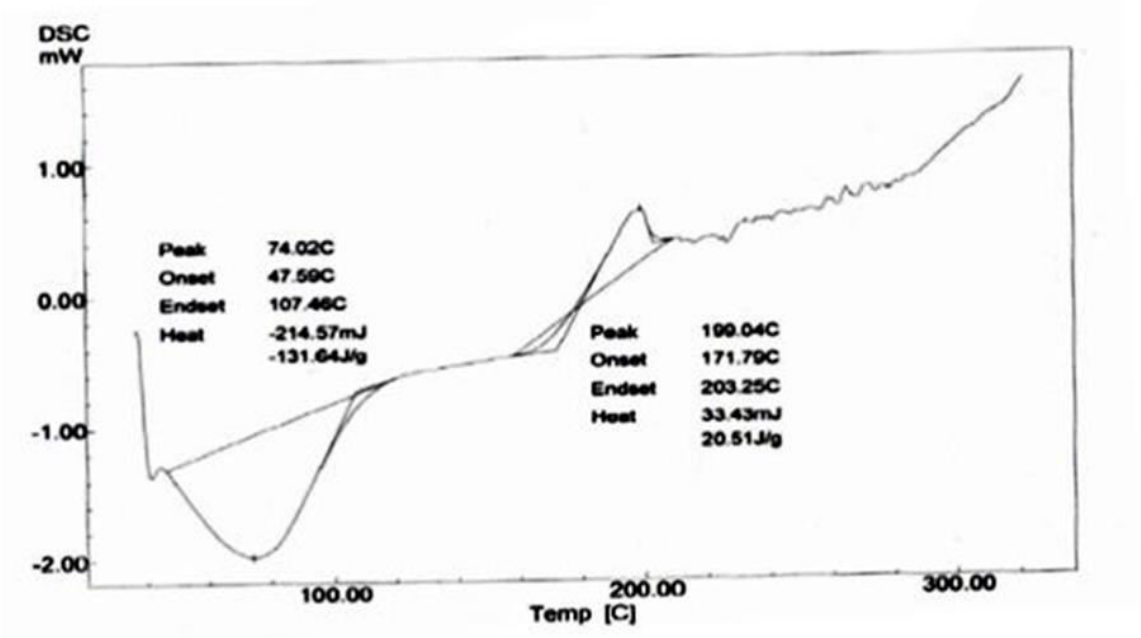

Fig-3 DSC of Formulated Sertaconazole Patches

Thickness

The thickness of each film was measured at 3 different points and S.D values were calculated and are tabulated below. The thickness varied from 0.16 to 0.20 mm. The thickness of the film was found to increase with the increase in HPMC K15M content. The orders of thickness for various films were:

F8>F7> F6>F5>F4>F3>F2>F1

Folding Endurance

The folding endurance was measured in triplicate, according to procedure and the results are shown in The folding endurance for F series formulations was found to be from 98 to 154. Formulation F5 showed greater folding endurance.and HPMC K15M shown in table-1

Table-1 Thickness and Folding Endurance of Different Formulations

Sl.No	Formulation Code	Thickness (µm)	Folding endurance.
01	F1	0.16±0.04	101±3
02	F2	0.17±0.02	116±3
03	F3	0.17±0.03	124±4
04	F4	0.18±0.04	138±4
05	F5	0.18±0.02	154±2
06	F6	0.19±0.04	098±2
07	F7	0.19±0.05	103±3
8	F8	0.20±0.02	114±4

Moisture Content

The moisture content was determined by keeping patches in a desiccators containing activated silica. The percentage moisture uptake was calculated as the difference between initial and final weight with respect to final weight. The results of the moisture content studies for different formulations are shown in Table 5.3.2 and Fig. 5.3.1. Percentage moisture content ranged from 2.54 to 3.24. % for HPMC K15M series patches. However higher content of PVP K30 in the patches showed more moisture content in them.

The order of moisture content for various films was found to be:

F8>F7> F6>F5>F4>F3>F2>F1

Moisture Uptake

The percentage moisture uptake was calculated as the difference between final and initial weight with respect to initial weight shown in table-2.

Table-2 % Moisture Content and Moisture Uptake of Different formulations

Sl. No	Formulation Code	%Moisture content	% Moisture uptake
01	F1	2.54±0.12	4.76±0.15
02	F2	2.61±0.31	4.81±0.21
03	F3	2.68±0.42	4.89±0.52
04	F4	2.73±0.32	5.14±0.40
05	F5	2.79±0.08	5.39±0.16
06	F6	3.02±0.16	5.03±0.31
07	F7	3.13±0.24	5.11±0.43
08	F8	3.24±0.10	5.22±0.22

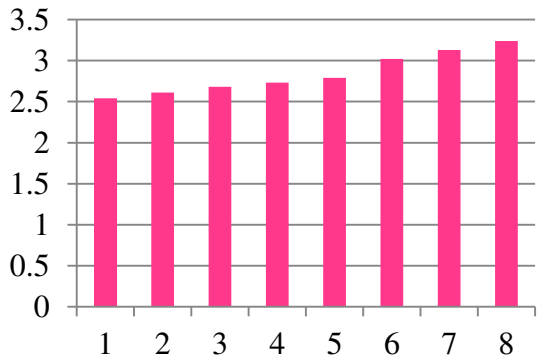

Fig-4 % Moisture Content of various formulations

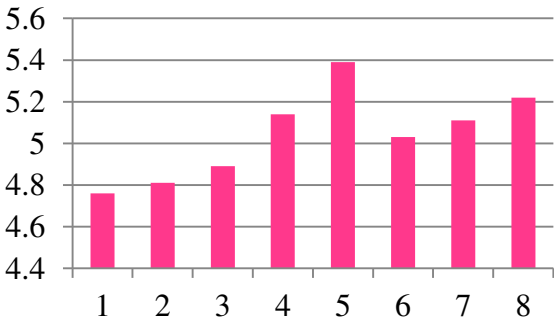

Fig-5 % Moisture Uptake of various formulations

Table-3 In-vitro diffusion characteristics of various formulations of sertaconazole (higuchi)

Sl.No	SQRT	F5
01	0	0
02	1.0000	26.41±1.19
03	1.4142	34.17±1.24
04	1.7320	44.28±1.03
05	2.0000	56.40±1.17
06	2.2360	71.05±1.06
07	2.4494	74.57±1.07
08	2.6457	78.54±1.14
09	2.8284	81.73±1.12
10	3.0000	86.11±1.24
11	3.1622	89.82±1.28
12	3.4641	93.77±1.34
13	4.8989	99.63±0.45

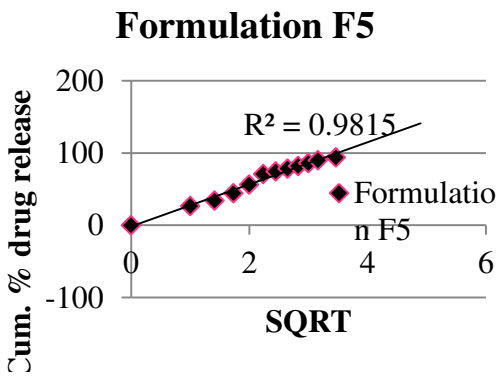

Fig-6 Graphical representation of In-vitro diffusion characteristics of various formulations of sertaconazole (higuchi)

SUMMARY AND CONCLUSION

In the present study, an attempt was made to deliver a novel anti fungal drug, Sertaconazole through Transdermal route in the form of Transdermal patches. Transdermal patches of both matrix and membrane controlled type were prepared out of which matrix type of patches were found to be satisfactory. Among the different formulations of matrix type(F1 to F8), the formulation F5 containing HPMC K15M and PVP K30 was selectedas best formulation, after considering its low percentage moisture content,percentage moisture uptake, water vapor transmission rate, better %drug content (99.238%) and maximum 99.63 % drug permeated through the skin at the end of 24 hrs. The drug permeation profile was also found to follow Higuchi kinetics. The patches were thin, flexible and transparent. The drug–polymer interaction results suggested no interaction between drug and polymers was observed.

The best formulation F5 showed negligible change in % drug content and permeation profile for a period of 90 days study. Based on the in vitro characterization, it was concluded that Sertaconazole could be administered transdermally through the matrix type TDDS. The Present study showed that matrix Transdermal patches of sertaconazole exhibited better in vivo performance than oral sertaconazole administration in mice as well as reversing the fungal complications.

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