CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com Research Article

FORMULATION AND *IN-VITRO* EVALUATION OFKETOCONAZOLE PATCHES FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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Article Received: September 2022 Accepted: September 2022 Published: October2022

Abstract:

Transdermal drug delivery is an alternative route for systemic drug delivery which increases bioavailability and minimizes absorption. Orally ketoconazole (KTC) causes serious liver injury, increases dosing frequency, undergoes first pass hepatic and gastrointestinal metabolism. The purpose of this research work was to formulate and evaluate the matrix type of transdermal drug delivery system of ketoconazole. KTC patches were developed by using polymers HPMC (E15LV), Eudragit-L-100, PVP, Eudragit-S-100 by employing solvent casting method and reducing toxic effects. Oleic acid and Tween 80 were selected as permeation enhancer and PEG400 as plasticizer. F1-F9 formulations were prepared and evaluatedfor physicochemical characteristics (Thickness, flatness, uniformity of weight, moisture content, moisture loss, swelling index, folding endurance), drug content and in-vitro drug release studies. Based on the drug release and physicochemical values obtained, the formulation KTC4 showed a high percentage of drug release of 97.1% in 12 hr and was considered as an optimized formulation. FTIR and DSC studies indicated that there was no interaction between drug and excipients. From the present study it was concluded that KTC4 formulation followed zero order mechanism of drug release, promoting controlled release of the drug and successfully avoiding first pass hepatic and gastro intestinal metabolism.

Keywords: *Solvent casting method, Ketoconazole (KTC), Permeation enhancer, Matrix transdermal patch and FTIR.*

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Please cite this article in Mamatha Kolaet al., ***Formulation And In-Vitro Evaluation Of Ketoconazole Patches For Transdermal Drug Delivery System.,*** *Indo Am. J. P. Sci, 2022; 09(10).*

INTRODUCTION:

TDDS are extended-release dosage forms that offer a stable systemic drug concentration and avoid first pass metabolism. They can even avoid gastrointestinal problems associated with drugs and low absorption. (1) This system is enabled in the rate-controlled administration of drugs through intact skin by employing an appropriate combination of hydrophilic and lipophilic polymers. (2) This route of administration is unsuitable for drugs that irritate or sensitize the skin. The penetration enhancers are used to penetrate the drug into systemic circulation via skin. (3,4) The transdermal drug delivery system has gained popularity over the past decades. Most of the drug molecules penetrate through the skin through intercellular micro route and therefore the role of permeation or penetration enhancers in TDDS is vital as they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells.(5,6)

Nicotine patches became the first transdermal success, raising the market of transdermal delivery in medicine and for the public in general. Transdermal delivery systems are currently available containing Scopolamine for motion sickness, Nitroglycerin for cardiovascular disease, Fentanyl for chronic pain, Nicotine to aid smoking cessation, Testosterone patches for hypogonadism in males, Clonidine for hypertension, Estradiol for hormone replacement therapy and Lidocaine as anaesthetic. (7)

KTC is a synthetic broad spectrum antifungal agent and belongs to the class of phenylpiperazine. (8) KTC blocks the synthesis of ergosterol, a key component of the fungal cell membrane by inhibiting cytochrome P-450 dependent enzyme lanosterol 14ὰ-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. KTC is included in Class II of Biopharmaceutical Classification System means, including a class of low solubility and high permeability, the increased solubility of this drug is of concern to pharmaceutical researchers. The absorption of ketoconazole orally is not maximal due to the solubility and the side effects it causes; to overcome the deficiencies of this conventional system a new drug delivery system is required. (9,10)

In the present investigation, an attempt was made to develop and evaluate transdermal formulation of Ketoconazole. KTC was selected as a drug candidate for the present study to treat fungal infections of the skin more efficiently. KTC transdermal patches were developed to promote controlled release and to avoid hepatic and gastro intestinal metabolism.

MATERIALS AND METHODS:

Materials

Ketoconazole (KTC) was received as a generous gift sample from Aurobindo Pharma Labs Hyderabad, India. HPMC, Eudragit-L-100 & Eudragit-S-100 were procured from S. D. Fine Chemicals, Mumbai, India. All other laboratory chemicals and reagents used in the study were of pharmaceutical analytical grade.

Methods:

Before formulation of drug substance into a transdermal patch (dosage form), Preformulation studies were carried out to establish the physicochemical characteristics of a drug and its compatibility with different excipients. Compatibility study of drugs with the excipients was determined by Fourier transform infrared (FTIR) spectroscopy (Shimadzu 1800) and differential scanning calorimetry.

FTIR spectra of pure ketoconazole (KTC) and mixture of drug and polymers were recorded on FTIR. Sample and KBr were triturated and compressed using motorized pellet press which were analysed between wave number of 400-4000cm $^{-1}$. The spectra obtained for KTC, polymers and physical mixtures KTC with polymers were compared. (11)

DSC thermogram was recorded with a differential scanning calorimeter and it was performed on an optimized transdermal patch for possible interaction between drug and polymer. Initially, moisture was removed by heating sample and then sample was accurately weighed and sealed in flat bottomed platinum crucible 40-µl aluminium pan, where ὰ-alumina powder used as reference. Thermo grams were recorded from 25°C - 300°C at the heating rate of 5°C/min under a constant flow of an inert N_2 gas atm. at a flow rate of 10ml/min

Formulation of transdermal patch

Solvent casting technique was used for development of transdermal patches (TDD). Matrix type transdermal patches were prepared according to formula (Table-1).Casting solution was composed of different ratios of HPMC, Eudragit-L-100, Eudragit-S-100, PVP, methanol and dichloromethane. Accurately weighed polymers were dissolved in suitable solvents (methanol: dichloromethane) using a magnetic stirrer. To this solution, the selected model drug (KTC), plasticizer (PEG 400) and permeation enhancer (oleic acid, tween 80) was

added slowly with continuous stirring. The uniform dispersion obtained was poured in the Petri plate and the rate of evaporation of solvent was controlled by inverting the cut funnel over the patches. The patches were dried at room temperature for 24 hours and kept in a desiccator. (12,13)

Table-1: Composition of Transdermal Patches

S.No	Ingredients	KTC 1	KTC 2	KTC 3	KTC 4	KTC 5	KTC 6	KTC 7	KTC 8	KTC 9
1	Drug(mg)	200	200	200	200	200	200	200	200	200
2	HPMC(mg)	50	75	50	50	25	75	100	50	25
3	Eudragit-L-100(mg)	-	-	-	400	300	200	-	-	-
4	Eudragit-S-100(mg)	-	-	-	-	-	-	250	200	150
5	PVP(mg)	25	50	75	-	-	-	-	-	-
6	PEG 400(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
7	Oleic acid(ml)	1	1	1	1	1	1	1	1	1
8	Tween 80(ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
9	Methanol(ml)	7	7	7	7	7	7	7	7	7
10	Dichloromethane(ml)	7	7	7	7	7	7	7	7	7

Evaluation of patches

Physical appearance:

All the transdermal patches were visually inspected for colour, flexibility, clarity and smoothness.

Thickness of the patch:

The thickness of the drug loaded patch was calculated at 3 different points using verniercallipers and for each formulation, 3 patches were selected. The average thickness and standard deviation was determined.

Weight variation:

The test was done to ensure uniformity of weight and to check batch to batch variation. The patches were cut to a size of 2x2cm² and then weighed on electronic balanceand weresubjectedfor a weight variation test. The mean was calculated from the individual weights.(14)

Flatness:

Individual patches were taken and longitudinal strips were cut one at the centre and two from either side almost covering the entire patch surface. The variation in the length of each strip was measured by determining present constriction, considering 0% constriction equivalent to 100% flatness. (15)

Folding endurance:

The patch was folded repeatedly at the same place until it broke. Thus, the number of times the patch could be folded at the same place without breaking gives the value of folding endurance. (16)

Moisture content:

Individually weighed patches were kept in a desiccator having fused calcium chloride at room temperature for 24hrs. The patches were weighed and the percentage was calculated based on the difference between initial and final weights of the patches.

$$\%\ \text{Moisture content} = \frac{Initial\ wt - Final\ wt}{Final\ wt} \times 100$$

Moisture loss:

The patches were weighed and placed in the desiccator containing saturated solution of potassium chloride (200ml) in order to maintain 84%RH. After 24hrs, films were reweighed and percentage moisture uptake was calculated according to the formula. This test helps to check integrity and physical stability of patches.

$$\%\text{Moisture loss} = \frac{Final\ wt - Initial\ wt}{Initial\ wt} \times 100$$

Swelling study:

Weighed films were kept in a desiccator containing saturated solution of sodium chloride for 24hr and then reweighed. (16)The percentage degree of swelling was calculated from the given formula

$$\text{Degree of Swelling \%} = \frac{Ws - Wd}{Wd} \times 100$$

Where, W_s= the weight of the swollen patch
W_d= the weight of the dry patch

Drug content:

Patches were dissolved in 100ml of phosphate buffer pH 7.4. Then the above solution was stirred for 24hrs and filtered. Blank was prepared by using a drug free patch. Drug content was determined by measuring the absorbance at a specified wavelength after suitable dilution using a UV- Visible spectrophotometer. The measurements were made in triplicate. (17)

In-vitro permeation studies

Drug release study from dialysis membrane:

In-vitro permeation studies of the prepared transdermal patches were carried out by Franz diffusion cells using a dialysis membrane. It consists of two compartment i.e. Receptor compartment and Donor compartment. The receptor compartment is 5mm and holds a volume of 15ml which is filled with PBS pH 7.4 and it is attached to a collecting tube which allows easy collection of samples while the process is running. The dialysis membrane was prepared by using a semipermeable membrane from the egg andtied to an open tube. The prepared transdermal patch was placed on the dialysis membrane. The two compartments are held together with help of a clamp and the set up was placed over a magnetic stirrer at a temperature 37°C. Samples were withdrawn and replenished immediately from the receiver compartment at time intervals of 1, 2, 3, 4, 6, 8, 10 and 12h. Then the samples were analysed by UV- visible spectrophotometer at a wave-length of 278 nm to determine drug release from prepared transdermal patch.(17)

RESULTS AND DISCUSSION:

Preformulation studies

Fourier transmission infrared spectroscopy (FTIR):FT-IR techniques have been used to study the physical and chemical interaction between drug and excipients used. It was observed that there were no changes in the main peaks in IR spectra of mixture of drug and polymers, which shows there were no physical interactions. (Figure- 1,2,3)

Figure 1: FTIR spectrum of pure drug

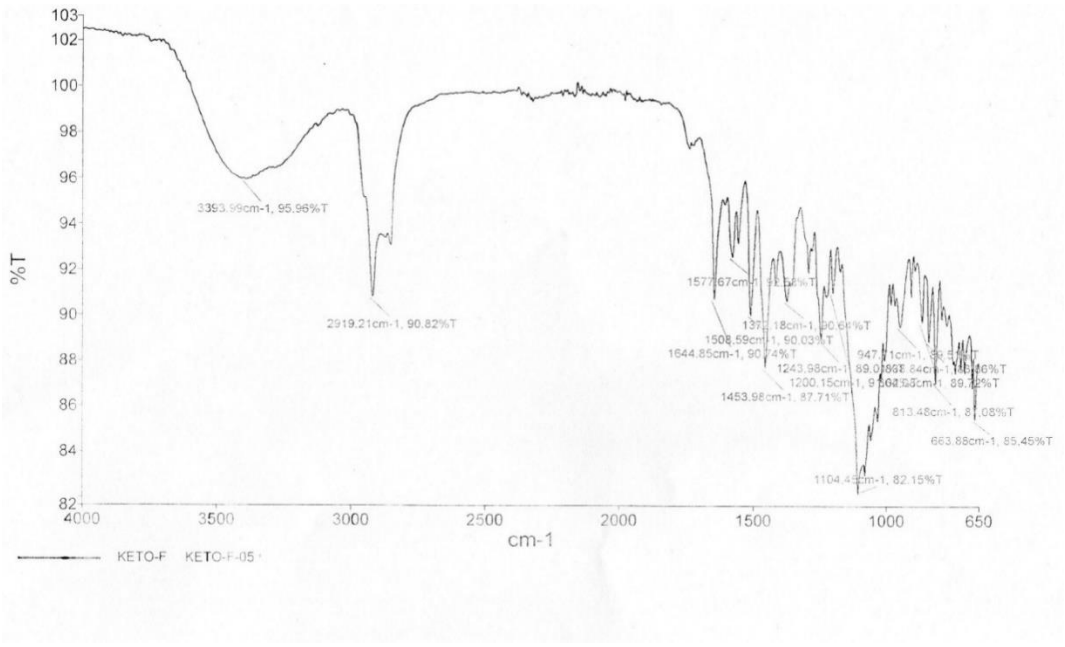


Figure-2: FTIR spectrum of physical mixture of Drug and polymers

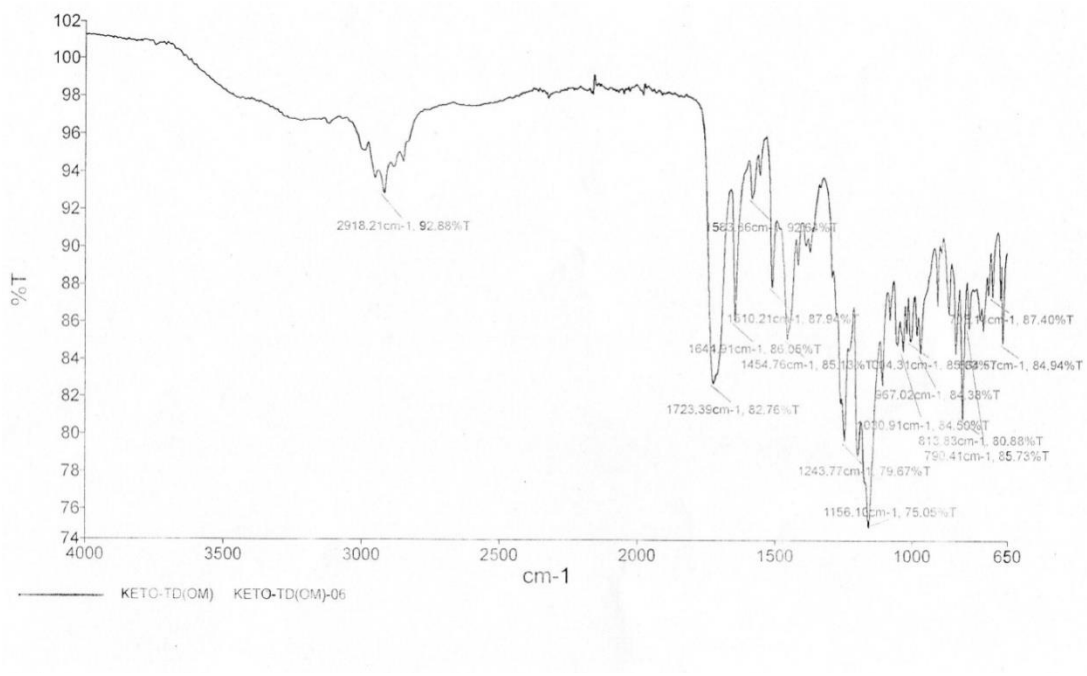
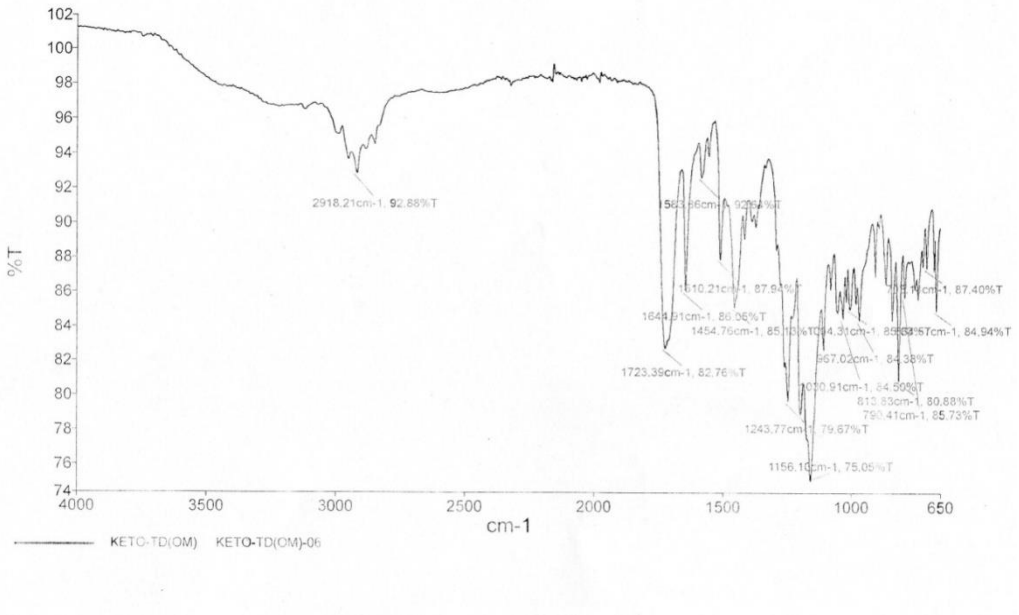
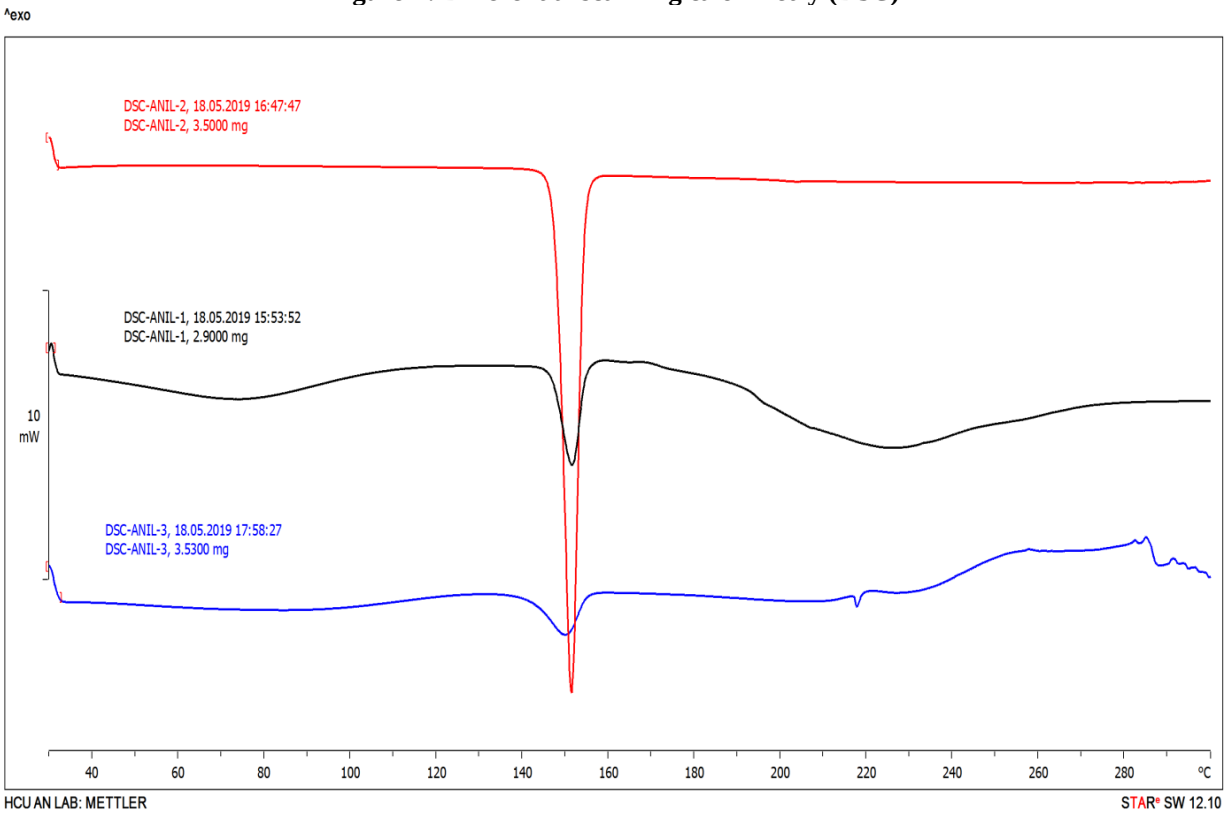


Figure-3: FTIR spectrum of optimized formulation



DSC studies: DSC studies were performed to study the interactions between drug and excipients. The DSC thermograms for the pure drug, drug and excipients, formulationwereobserved (Figure-4). Thus ketoconazole was found to be compatible with all polymers (HPMC, Eudragit-L-100, Eudragit-S-100, PVP) suggesting that combination of Ketoconazole and polymers could be used for the preparation of the various transdermal patches.

Figure-4: Differential scanning calorimetry (DSC)



Physical appearance:
All the formulated transdermal patches were visually inspected for clarity, flexibility and colour.

Flatness:
All the prepared transdermal patches were found to be uniformly flat without any foam development.
Weight variation:

The weight variation results of various transdermal patches were calculated and found to be within limits.
Folding endurance:

The patches did not show any sign of cracks even after folding more than 40 times and different patch numbers are presented in table.
Percent moisture content:

The prepared patches showed minimal moisture content ranging from 3.14 to 12.4% thus ensuring general stability and are found to be within limits
Moisture loss studies:

Moisture loss studies were carried out in order to determine the stability of the prepared patches under dry ambient conditions. The results for all the prepared transdermal patches reflected a low moisture loss for all the prepared transdermal films.

Drug content:
Drug content analysis was performed for all the prepared transdermal systems by following standard method, uniform drug content was noted for the prepared transdermal films ranging from 98.31 to 99.11%(Table-3)

In vitro permeation studies
The formulation with KTC1 exhibited an overall lower drug release in 12 h Patches formulated with PVP as polymer exhibited less drug release compared to patches prepared with EUDRAGIT L-100 and EUDRAGIT S-100.(Table-4). Among all the 9 formulations, KTC4 formulation containing HPMC and Eudragit-L-100 exhibited greatest cumulative percentage of drug release (97.1%) with in 12hr.(Figure-5)

Table2: Evaluation of Ketoconazole Transdermal Patches

Formulation	Weight variation (mg)	Folding endurance	Thickness(mm)
KTC 1	1.459	47	0.351
KTC 2	1.347	58	0.343
KTC 3	1.305	56	0.247
KTC 4	1.295	64	0.350
KTC 5	1.319	79	0.286
KTC 6	1.433	69	0.332
KTC 7	1.412	75	0.349
KTC 8	1.295	84	0.277
KTC 9	1.332	81	0.341

Table 3: Evaluation of Ketoconazole Transdermal patches

Formulation	Moisture content (%)	Moisture loss (%)	Drug content (mg)	Swelling study (%)
KTC 1	4.55	20.13	99.11	22.73
KTC 2	10.7	13.70	98.72	37.32
KTC 3	3.14	25.60	98.65	36.45
KTC 4	6.12	15.46	98.70	33.77
KTC 5	11.8	8.99	99.07	35.21
KTC 6	5.79	11.94	98.31	38.82
KTC 7	5.03	9.57	99.10	36.12
KTC 8	12.4	20.44	99.82	37.92
KTC 9	9.6	19.11	98.37	33.51

Table 4: *In-vitro* permeation studies of ketoconazole Transdermal patches

Time (hrs)	KTC1 (%)	KTC2 (%)	KTC3 (%)	KTC4 (%)	KTC5 (%)	KTC6 (%)	KTC7 (%)	KTC8 (%)	KTC9 (%)
0	0	0	0	0	0	0	0	0	0
1	11.4	15.1	14.2	19.9	7.3	16.4	13.0	10.3	15.7
2	28.6	22.3	25.9	25.7	21.8	23.5	23.7	29.2	24.4
4	35.2	31.4	34.3	38.6	40.1	34.7	37.4	33.7	38.2
6	46.1	47.6	44.7	55.7	59.6	43.2	53.2	49.6	42.9
8	57.2	55.1	53.8	74.2	62.3	66.9	60.5	51.4	56.1
10	61.8	68.5	65.4	87.2	71.4	71.1	74.6	67.3	64.5
12	69.2	78.3	79.2	97.1	89.2	82.3	87.2	78.7	75.4

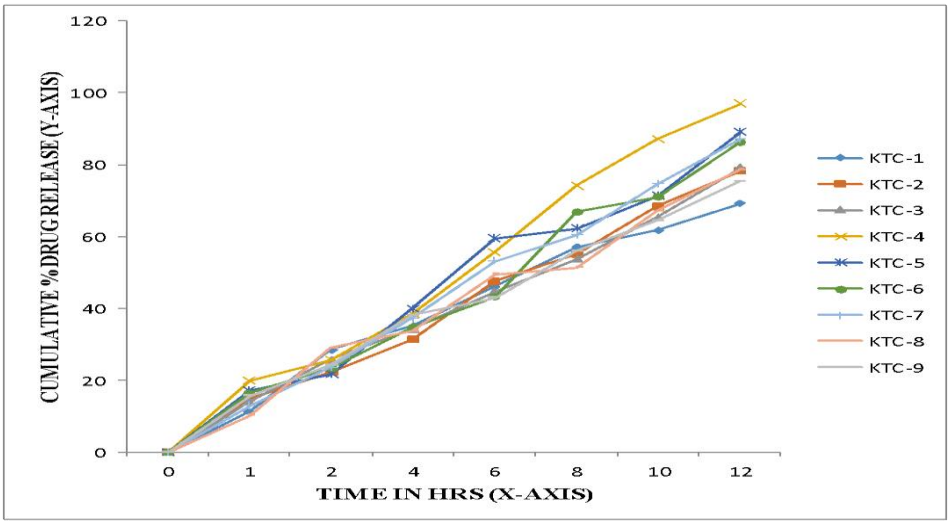


Figure:5- Comparative graph of release profile of *in-vitro* permeation studies of ketoconazole (KTC) transdermal patches KTC1-KTC9

Figure6: Zero order release for KTC4 formulation

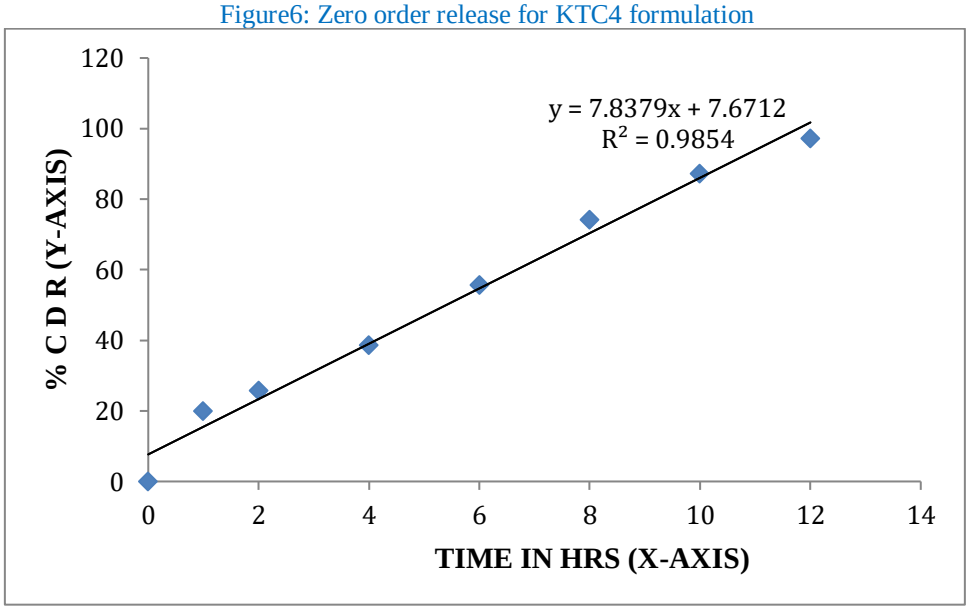


Table 5: Drug release kinetic model for optimized formulation

PARAMETERS	ZERO	FIRST	HIGUCHI	PEPPAS
	%CDR Vs T	*Log% Remain Vs T*	*%CDRVs√T*	*Log C Vs Log T*
Slope	7.8379	-0.0653	29.286	1.2223
Intercept	7.6712	2.0868	-9.1377	0.7626
Correlation	0.992652	-0.99135	0.979075647	0.821228
R²	0.9854	0.9828	0.9586	0.6744

CONCLUSION:

The transdermal patches containing ketoconazole (KTC) were successfully prepared by solvent casting technique. Various formulations were formulated and evaluated for physicochemical properties and *in-vitro* diffusion studies were performed with an aim of providing controlled release of drug for longer duration for improving patient compliance and reducing dosing frequency. Total nine (9) formulations of ketoconazole (KTC) patches were prepared using different polymers.

Compatibility studies of drug-excipients were carried out using FTIR & DSC and results revealed the absence of any interaction. KTC-1, KTC-2, KTC-3 were formulated using HPMC and PVP in various ratios. KTC-4, KTC-5, KTC-6 were prepared using HPMC and Eudragit-L-100 in various concentrations. KTC-7, KTC-8, KTC-9 were prepared using HPMC and Eudragit-S-100. Oleic acid and tween 80 are used as chemical enhancers for better penetration, PEG 400 was used as plasticizers and methanol & dichloromethane were selected as solvent. From various formulations of ketoconazole (KTC) transdermal films, KTC-4 containing HPMC and Eudragit-L-100 as polymers was found to be an optimized formulation.

The physicochemical properties results for the prepared transdermal films were within the pharmacopoeia limits such as moisture content, swelling study, drug content, folding endurance, etc. Cumulative % drug release profile of KTC-4 transdermal patch showed 97.1% drug release within 12 hrs. Data analysis of kinetic modelling of the optimised formulation was plotted and it followed zero order release with R^2 value of 0.9854(Table-5).Thus it was concluded that Ketoconazole transdemal patches were formulated efficiently and the results showed transdermal delivery of ketoconazole can have good applications in terms of reducing dosing frequency, improved patience

compliance avoiding hepatic and gastro intestinal metabolism, non-invasive characteristics and easy termination of therapy.

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