IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
January 2021 Vol.:20, Issue:2

Formulation and *In-Vitro* Evaluation of Transdermal Patches of Econazole for Anti-Fungal Activity

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

A. Geethalakshmi*[1], Lucky Gyani[1], Yamuna[1]

[1]Department of Pharmaceutics, R.R. College of Pharmacy, Bengaluru, Karnataka, India.

Submitted: 10 December 2020
Revised: 30 December 2020
Accepted: 20 January 2021

www.ijppr.humanjournals.com

Keywords: Transdermal drug delivery, Econazole, HPMC, EC, PEG400, PVP, Solvent evaporation technique

ABSTRACT

Transdermal drug delivery is an alternative route for systemic drug delivery which minimizes absorption and increases bioavailability. Orally Econazole has a short elimination half-life (2.5-6 hrs), low oral bioavailability (50%) undergoes extensive first-pass metabolism (85%) and frequent doses (15 mg) are required to maintain the therapeutic level as a result, dose development toxic effect. The purpose of this research work was to formulate and evaluate the transdermal drug delivery system of Econazole using various polymers such as HPMC, PVP, Carbopol, and Ethylcellulose by solvent evaporation technique for the improvement of bioavailability of drug and reducing toxic effects. The prepared 12 formulations were evaluated for different physicochemical characteristics like thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss, and weight uniformity. The *in vitro* release studies were performed by using modified Franz diffusion cells. The IR studies revealed that the drug and polymer were compatible with each other and all the batches prepared and evaluated F5 showed promising results. The developed and the best formulation F5 transdermal patches increase the therapeutic efficacy and reduced the toxic effect of Econazole. The most satisfactory formulations had shown no significant change in the Physico-chemical parameters and *in-vitro* parameters after storage at 40 ± 2 °C / 75 ± 5 % during short term accelerated stability studies as per ICH guidelines. Thus, the principle of formulating transdermal systems for an anti-fungal drug has been achieved with success.

1. INTRODUCTION

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. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive[1].

Antifungal medicines are used to treat fungal infections, which most commonly affect the skin, hair, and nails. Econazole is an imidazole with antifungal properties. It was patented in 1968 and approved for medical use in 1974. Econazole is used to treat skin infections such as athlete's foot, tinea, ringworm. Econazole has a short elimination half-life (2.5-6 hrs), low oral bioavailability (50%) undergoes extensive first-pass metabolism (85%) and frequent doses (15 mg) are required to maintain the therapeutic level as a result, dose development toxic effect. Like other imidazoles, Econazole exerts its effect by disrupting normal fungal cell membrane permeability. Ergosterol is an essential component of the fungal cell membrane. Econazole may inhibit ergosterol synthesis by interacting with 14-α-*lanosterol demethylase*, a cytochrome P-450 enzyme necessary for converting lanosterol to ergosterol. Inhibition of ergosterol synthesis results in increased cellular permeability, causing leakage of cellular contents such as phosphorus-containing compounds and potassium. Econazole prevents fungal organisms from producing vital substances required for growth and function. This medication is effective only for infections caused by fungal organisms.[2]

Fungal diseases like athlete's foot and ringworm are all types of fungal skin infections known collectively as tinea. They are caused by fungi called dermatophytes that live on skin, hair, and nails and thrive in warm, moist areas. Symptoms of these infections are erythema, itching can vary depending on where they appear on the body[3,4]. The purpose of this research work was to formulate and evaluate the transdermal drug delivery system of Econazole using various polymers such as HPMC, PVP, Carbopol, and Ethylcellulose by solvent evaporation technique for the improvement of bioavailability of drug and reducing toxic effects.

2. MATERIALS AND METHODS

2.1. Material

Econazole was purchased from Bangalore fine chemicals. Ethyl Cellulose, HPMC, Carbopol, PVP, Propylene Glycol, Chloroform, and Methanol were obtained from S.D. Fine Chemicals. Pvt. Ltd, Mumbai, India. All chemicals and solvents used were of analytical grade.

2.2. METHODOLOGY

2.2.1. Preformulation Studies

It is one of the important prerequisites in the development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility, and compatibility studies.

Solubility: The solubility of the selected drug was determined in Methanol, DMF, and DMSO using the standard method.

Melting point: Fine powder of Econazole was filled in a glass capillary tube (previously sealed at one end) and kept in electrical melting point apparatus. The melting temperature was found with the help of the melting point apparatus.

Estimation of Econazole: A Spectrophotometric method based on the measurement of extinction at 260 nm in methanol was used for the estimation of Econazole.

Fourier Transform Infrared Radiation (FTIR): The FTIR spectroscopy studies were carried out for pure drug alone and along with polymers to check the compatibility between drug and HPMC, EC, Carbopol, and PVP which are used to formulate transdermal patches. The drug spectrum peaks were compared with the drug and polymer mixture spectrum peaks. The instrument from Sipra Ltd was used for the study using the KBr pellets method. The major sharp and significant peaks (functional groups) of the drug and drug-polymer mixture was noted.

Method of preparation of Transdermal patches: Transdermal films of Econazole were prepared by solvent casting technique. A solution of PVP with EC, HPMC, and Carbopol was dissolved in a 10 ml mixture of methanol as per the formulation table. PEG 400 added in required amounts as per the formulation chart to the prepared solution and stirred well. The accurately weighed drug was mixed with the above mixture and mixed well to obtain a

homogenous mixture.

After proper mixing, the solution was kept for stabilization and complete removal of air bubbles. Then the above mixture was cast in a glass mould of 9 cm^2 previously coated with a thin layer of glycerine to prevent the adhesion of the formed patch to the mould. The rate of evaporation was controlled by inverting a glass funnel over the glass mould. The mould was kept aside for drying at room temperature for 24 hrs. After 24 hrs the dried films were carefully removed from the mould and stored in a desiccator.

Table No. 1: Formulation chart for Econozole transdermal Patch

Sr. No	Ingredients	Purpose	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Econazole (mg)	Anti-fungal agent	15	15	15	15	15	15	15	15	15	15	15	15
2	HPMC (mg)	Thickening agent	200	100	-	-	-	-	-	200	100	-	200	100
3	EC (mg)	Control release	100	200	100	200	-	-	-	-	100	200	-	-
4	Carbopol (mg)	Stabilizing agent	-	-	-	-	200	100	-	-	200	100	100	200
5	PVP (mg)	Film former	-	-	-	-	200	100	-	-	200	100	100	100
6	PEG-400 (mL)	Plasticizer	5	5	5	5	5	5	5	5	5	5	5	5

2.2.2. EVALUATION OF TABLETS

Thickness: The thickness of the transdermal patch is measured using a digital micrometer screw gauge at three different points of the patch and the average of the three is taken as the thickness of the patch. A uniformly thick patch will have an equal thickness at every point and the variation of thickness within the patch and patch to patch can be calculated.[5]

Folding Endurance: A strip of a specific area (2 cm x 2 cm) was cut evenly and repeatedly folded at the same place until it breaks up to 300 times. The number of times the film was folded at the same place without breaking gave the value of the folding endurance.[6]

Drug Content determination: A specified area of the patch (2 cm X 2 cm) was dissolved in 100 mL methanol and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically at a wavelength of 260 nm and determined the drug content.[7]

Weight variation: The prepared patches were dried at 60°C for 4 hrs before testing. A specified area of the patch was cut in different parts of the patch and weigh in a digital balance. The average weight and standard deviation values are to be calculated from the individual weight.[8]

Moisture Content: The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature (25^0C) for 24 h. The films were weighed again after a specified interval until they show a constant weight. The percentage moisture content is calculated using the formula:

% Moisture content = Initial weight – Final weight X 100

Moisture Uptake: The weighed films were kept in a desiccator at room temperature for 24 h containing a saturated solution of potassium chloride to maintain 84% relative humidity. After 24 h, the films were weighed again and the percentage moisture uptake was determined from the below-mentioned formula:

% Moisture uptake =Final weight − Initial weight× 100.[9]

Percentage Elongation Break Test: The percentage elongation break was determined by noting the length just before the breaking point, the percentage elongation was determined from the below-mentioned formula.

Elongation percentage = (L1 − L2) L2 × 100, where L1 is the final length of each strip, and L2 is the initial length of each strip.[10]

***In Vitro* Drug Release Studies:** *In Vitro*, drug release studies were performed by using a Franz diffusion cell. The cellulose acetate membrane was used for the determination of the drug from the prepared transdermal matrix-type patches. The prepared transdermal film was placed on the cellulose acetate membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads, and the temperature was maintained at 37 ± 0.5°C.

The sample of 5 mL was withdrawn at different time intervals and analyzed for drug content spectrophotometrically at 260 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Kinetics of drug release: To study the release kinetics of *in-vitro* drug release, data obtained from the *in-vitro* release study were plotted in various kinetic models: Zero-order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer-Peppas as log % drug released Vs log time. By comparing the r^2-values obtained, the best-fit model was selected.[11]

Stability studies

A stability study is conducted to determine the period for which the patch remains viable and usable. In unstable patch formulations drug starts degrading gradually so stability is tested according to ICH guidelines at 40°C/75% RH for 6 months. Samples are taken at 0, 30, 60, and 90 days and tested for their stability.[12]

3. RESULTS AND DISCUSSION

3.1. PREFORMULATION STUDIES

Solubility studies

Econazole is soluble in water and freely soluble in Methanol, DMSO, DMF.

Table No. 2: Solubility profile of Econazole

SOLVENTS	SOLUBILITY	INFERENCE
Methanol	25mg/mL	Soluble
DMSO	0.3mg/mL	Slightly Soluble
DMF	25mg/mL	Soluble

Melting point

The melting point of Econazole was determined by the capillary method. The melting point was found to be 162°C.

Table No. 3: Melting point of Econazole

TRIAL 1	TRIAL 2	TRIAL 3	Average
162^0C	163^0C	161^0C	162^0C

FTIR Spectroscopy

FTIR of the Econazole was determined by FTIR spectra as mentioned below.

FTIR Spectroscopic Studies

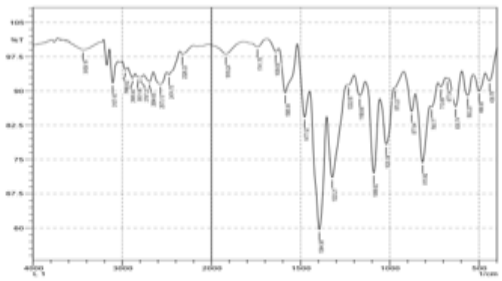

Figure 1: FTIR Spectra of Pure drug Econazole

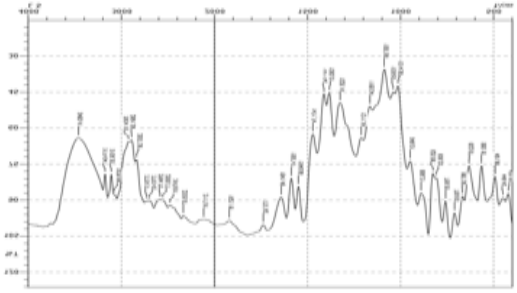

Figure 2: FTIR Spectra of Econazole + HPMC

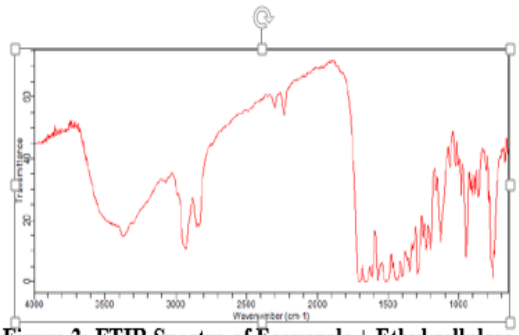

Figure 3: FTIR Spectra of Econazole + Ethyl cellulose

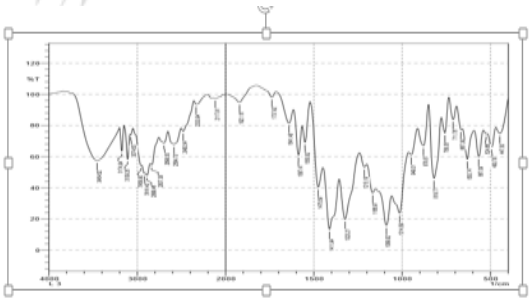

Figure 4: FTIR Spectra of Econazole + PVP

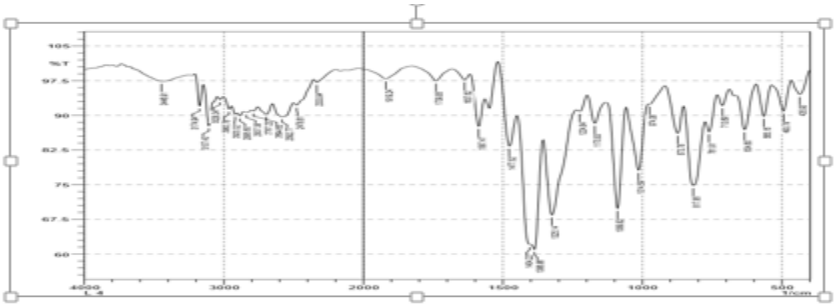

Figure 5: FTIR Spectra of Econazole + Carbopol

The absorption spectra and their principle peaks at or around the corresponding range of the pure drug was present when it is mixed with other additives. It is inferred that there was no interaction between drug and polymer and other additives. The integrity of the drug was maintained in all physical mixtures. The spectra showed no incompatibility between the polymer and the pure drug (Econazole).

3.2 PHYSICAL EVALUATION

Table No. 4: Physicochemical Evaluation of Transdermal Patches

Batch code	Weight variation [mean(mg)±SD]	Thickness [Mean(mm)±SD]	% Moisture uptake	% Moisture content
F1	0.012±0.04	0.14±0.06	4.18±0.04	2.41±0.08
F2	0.014±0.05	0.15±0.05	4.12±0.06	3.12±0.07
F3	0.009±0.06	0.12±0.08	4.29±0.05	3.08±0.06
F4	0.011±0.04	0.14±0.07	5.12±0.06	3.02±0.05
F5	0.015±0.03	0.16±0.06	5.28±0.03	3.45±0.04
F6	0.013±0.05	0.12±0.05	4.20±0.04	2.74±0.03
F7	0.012±0.06	0.11±0.04	4.25±0.05	3.28±0.06
F8	0.010±0.05	0.16±0.06	3.16±0.06	2.17±0.05
F9	0.014±0.02	0.14±0.05	4.11±0.05	2.04±0.01
F10	0.012±0.02	0.15±0.03	4.16±0.02	3.10±0.02
F11	0.013±0.03	0.13±0.02	3.18±0.09	2.78±0.03
F12	0.011±0.03	0.12±0.03	4.15±0.09	2.88±0.02

The thickness and Weight variation

All the films exhibited uniform weight and thickness and there was no much deviation in the weight of any formulation indicates that the polymeric solution of the drug is well dispersed in the patches. The results of thickness 0.11 – 0.16 and weight variation 0.009 – 0.015 were shown in Table No. 4.

Moisture uptake

The difference in the moisture uptake may be due to the increase in the concentration of hydrophilic polymers and the difference in resistance of matrix network structure to the

movement of water molecules through the formulation. The values obtained for all the formulations (3.16- 5.28) were given in Table No. 4.

Moisture content

Moisture content can cause significant changes in properties such as reduced crushing strength, increased pore diameter in the patches containing hydrophilic polymer. The little moisture content helps the formulation to be stable and prevents them from becoming completely dried, brittle product. The values obtained for all the formulations (2.04-3.45) were given in Table No. 4.

Table No.5: Physicochemical evaluation of transdermal patches

Batch code	Folding endurance	% Elongation break test	% Drug content
F1	186±0.12	31.1±0.11	94.4±0.16
F2	194±0.14	32.2±0.10	95.9±0.19
F3	179±0.16	33.6±0.13	91.1±018
F4	189±0.15	28.1±0.14	93.4±0.19
F5	197±0.12	35.8±0.15	95.12±0.14
F6	179±0.11	33.5±0.16	94.1±0.16
F7	184±0.12	23.7±0.17	93.2±0.14
F8	181±0.14	25.3±0.15	92.41±0.16
F9	194±0.15	24.4±0.12	92.1±0.12
F10	179±0.18	31.1±0.12	93.4±0.15
F11	185±0.12	33.3±0.15	92.3±0.12
F12	187±0.16	28.7±0.16	93.1±0.15

Folding Endurance

The folding endurance was found to be in the range of 179 to 197. The values for all formulations were shown in Table No. 5. This data revealed that the patches had good mechanical strength along with flexibility.

Drug content uniformity

All the prepared formulations are found to have uniform drug content which is in the acceptable range of IP. The drug content of the formulations was found to vary between 91.1–95.9. The results are shown in Table No. 5.

In vitro drug release profile

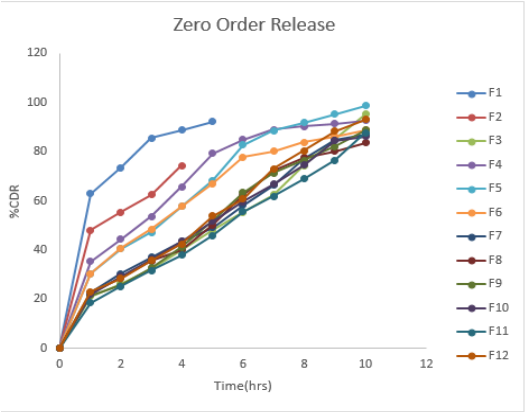

Figure 6: Zero order kinetics of Formulation F1 to F12

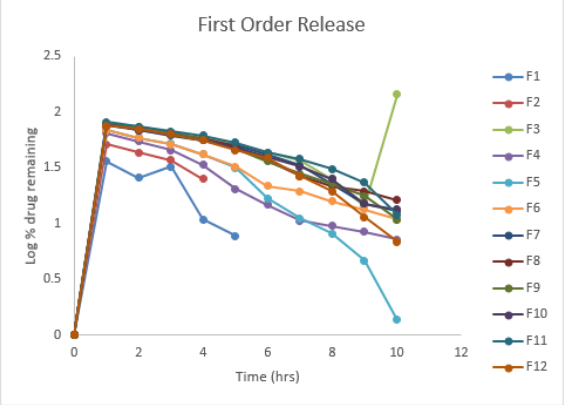

Figure 7: First order kinetics of Formulation F1 to F12

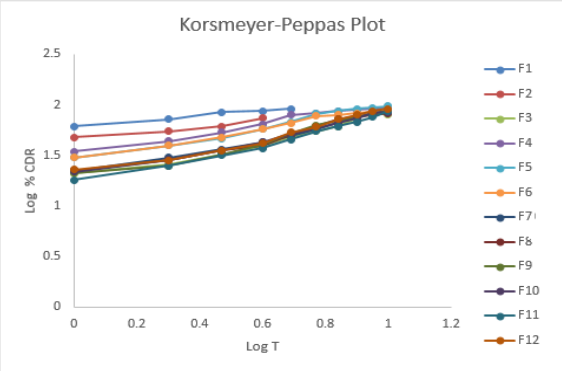

Figure 8: Korsrmeyer-peppas kinetics of Formulation F1 *to* F12

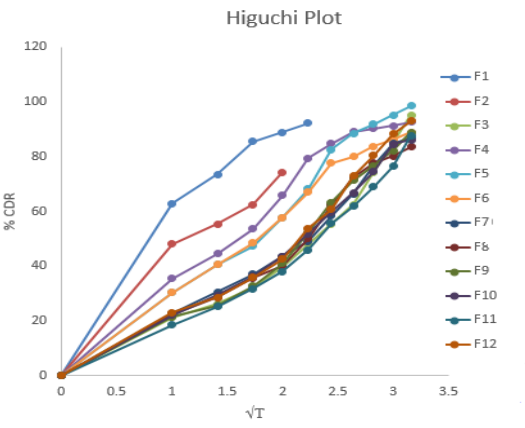

Figure 9: Higuchi kinetics of Formulation F1 to F1

The cumulative percentage of drug release from the various formulations was found between 83.70 to 98.78. Formulation F5 exhibited the greatest 98.68 percentage of drug release compared to other formulations and drug release was found to be less in formulations F7, F8, F10 and F11 showed in Figures 6-9.

Table No. 6: Curve fitting data of the release rate profile for selected formulations.

FORMULATION	ZERO ORDER(r^2)	1st ORDER(r^2)	HIGUCHI MATRIX(r^2)	KORSMEYER- PEPPAS	
				(r^2)	(n)
F1	0.7213	0.0739	0.9347	0.9751	0.254
F2	0.816	0.3451	0.9702	0.9391	0.2687
F3	0.9854	0.0945	0.9862	0.9614	0.3145
F4	0.8843	0.1404	0.9645	0.9636	0.4664
F5	0.9333	0.1497	0.985	0.9809	0.5533
F6	0.9312	0.0708	0.9892	0.9851	0.6895
F7	0.9789	0.0003	0.9492	0.9749	0.6645
F8	0.9838	0.0122	0.9447	0.9573	0.6845
F9	0.9863	0.0035	0.9514	0.9614	0.6687
F10	0.9837	0.0001	0.9646	0.9789	0.6954
F11	0.989	0.0063	0.9492	0.9788	0.6457
F12	0.9841	0.0078	0.9552	0.9636	0.6545

Kinetics of drug release

The results of drug release data were fitted to various kinetic equations to analyze the release mechanism. The selected F5 formulation was found to follow the Higuchi model and follows Non-Fickian diffusion because the 'n' value obtained from the Peppas equation was more than 0.5, which indicated that formulations showed drug release by the Non-Fickian diffusion mechanism.

Stability studies

Table No. 7: Stability studies on Physicochemical Properties of selected formulations F4, F5, F6 transdermal patches

Formulation code	% Moisture uptake	% Moisture content	Folding endurance	% Elongation break test	% Drug content
F4	5.08±0.06	2.98±0.05	188±0.15	28.3±0.14	96.4±0.19
F5	5.01±0.03	2.68±0.04	179±0.12	31.8±0.15	94.12±0.14
F6	4.32±0.04	2.74±0.03	179±0.11	36.55±0.16	95.1±0.16

Table No. 8: Release studies of Formulations F4, F5, F6 after stability studies.

FORMULATIONS	30 DAYS	60 DAYS	90 DAYS
F4	97.75±0.05	97.42±0.04	96.96±0.05
F5	98.68±0.06	98.33±0.06	98.10±0.08
F6	94.89±0.05	94.42±0.06	94.14±0.04

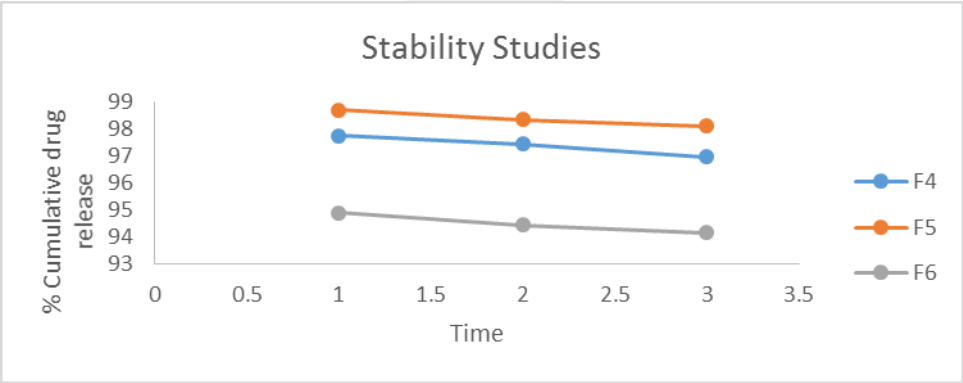

Figure No. 10: Stability Studies of Formulation F4 To F6

The stability studies were carried out on the most satisfactory formulations F5 at 40 ± 2°C /70 ± 5 % RH for three months to assess their stability as per ICH guidelines. At fixed time intervals of 30 days, 60 days, and 90 days, the formulation was evaluated for the physicochemical properties and in vitro drug release. There was no significant difference in the physicochemical parameters and *in vitro* drug release profiles and were found to be superimposable with the initial observation.

CONCLUSION

Thin, flexible, smooth, and transparent films were obtained with PVP, HPMC, EC, and carbopol polymers using PEG 400 as plasticizers. The thickness of all the formulations remained uniform with low SD values. The formulation containing Carbopol and PVP as a matrix-forming agent and PEG 400 as plasticizer will be the most suitable one for the transdermal systems of Econazole as these showed a sustained and complete release for 10 hours. Among all the selected formulations, F5 showed satisfactory results. Stability studies were carried out on the most satisfactory formulation F5 for six months as per ICH guidelines. There was no significant difference in the physicochemical parameters and *in-vitro* drug release profiles. So, the Econazole selected formulation F5 is stable, economical & acceptable for industrial use.

REFERENCES:

1. Zaid Alkilani, McCrudden.Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum. 2015; 7(4):438–470.
2. https://www.pdr.net/drug-summary/Econazole.
3. https://www.hopkinsallchildrens.org/PatientsFamilies/Health- Library/HealthDocNew/Tinea
4. Kanika Sahni, Sanjay Singh.Indian Dermatol Online J. 2018 May-Jun; 9(3): 149–158
5. Sankar V, Johnson DB, Sivanand V, Ravichandran V, Raghuraman S, Velrajan G, Palaniappam R, Rajasekar S, Chandrasekaran AK. Design and Evaluation of Nifedipine Transdermal Patch, Ind J Pharma Sci. 2003;65(5):510-515.
6. Shinde AJ, Garala KC, More HN. Development and Characterization of Transdermal Therapeutics System of Tramadol Hydrochloride. AAPS Pharm Sci Tec.2008; 2(4):265-269.
7. Sahu RK, Jain A, Nayak S. Development and Evaluation of Transdermal Patches of Colchicine. Der Pharmacia Lettre. 2012; 4(1):330-343.
8. Aarti N, Louk ARMP, Russel OP, Richard H.G. Mechanism of oleic acid-induced skin permeation enhancement in vivo in humans. J control Rel.1995; 37:299-306.
9. Shaila L, Pandey S and Udupa N. Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotine suitable for use in smoking cessation. Indian J Pharm Sci.2006; 68:179-18.
10. LecST,YacSH,KimSW,BernerB.OnewaymembraneforTransdermaldrugdelivery systems / system optimization. Int. J Pharm. 1991; 77:231-237.
11. WadeA,WellerPJ,HandbookofPharmaceuticalExcipients,WashingtonDC:Americ Pharma Pub Assoc.1994: 362-366.
12. http://www.pharmainfo.net/reviews/development-fabrication-and-evaluation-transdermal-drug- delivery-system-review.