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Permeation Enhancement of Transdermal Patches Using Penetration Enhancer and Different Concentration of Polymers

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Abstract – Transdermal drug delivery system is becoming more popular in the field of modern pharmaceutics. In the present work, an attempt has been made to develop a transdermal therapeutic system of drug Fluconazole with different concentration of hydrophilic (HPMC) and hydrophobic (ERS 100) polymeric system by solvent evaporation technique by using 30% w/w of Dibutyl phthalate incorporated as plasticizer and DMSO as a penetration enhancer. The physicochemical compatibility of the drug and the polymers was studies by Fourier transform infra-red (FTIR) spectroscopy analysis shows that there is no interaction between drug, HPMC and ERS 100. All the prepared formulations were subjected to physical studies (Weight Variation, Thickness, Folding endurance, Drug content determination, Flexibility or Tensile strength, Flatness, Percentage of moisture uptake, Percentage moisture loss, and Stability studies). Based on the physicochemical and In-vitro dissolution study formulation P2 (ERS/HPMC, 2:8) were the best formulation. The release profile of optimized formulation indicated that the permeation off the drug from the patches was showed diffusion controlled mechanism. Hence, it can be concluded that Fluconazole with the high concentration of hydrophilic polymer showed the better release.

Keywords: Fluconazole, Physiolochemical Incompatibility, Dibutyl Phthalate, DMSO, FTIR Spectroscopy

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INTRODUCTION

Transdermal systems are a desirable form of drug delivery because of the obvious advantages over other routes of delivery. Transdermal delivery provides convenient and pain-free self-administration for patients.[1] Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism. [2]

Fluconazole belongs to a group of medicines called azoles antifungal. The triazole fluconazole inhibits the fungal cytochrome P450 3A enzyme, lanosine 14α-demethylase, which is responsible for converting lanosterol to ergosterol, the main sterol in the fungal cell membrane. Triazoles thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the cascade of membrane abnormalities in the fungus and accumulation of 14-α methylsterols. The fluconazole is absorbed from the gastrointestinal tract and is excreted largely unchanged by the kidney. It is used prophylatically in a variety of conditions predisposing to systemic Candida infections. There are so many unwanted effects; it may cause gastrointestinal discomfort, abdominal pain, headache, elevation of liver enzymes and allergic rash. Therefore, the search continues for an effective antifungal with reduced adverse gastrointestinal reaction. Fluconazole possess appropriate physicochemical properties for potential transdermal delivery. It has low molecular weight (306.271 g/mol), low melting point, and low daily therapeutic dose. Moreover, it has been reported that fluconazole formulations exhibits good local tissue tolerability (e.g., dermal, rectal and thus, they appear to be suitable for dermal administration.[3-8]

Now days the fungal infection of skin is the common dermatological problems. The physicians have a wide choice for treatment from transdermal and to liquid formulations. So the transdermal drug delivery system is chosen an alternative route to deliver the drug directly to systemic circulation. [9-13]

MATERIALS AND METHOD:

Fluconazole (Symbiosis Pharmaceutical Pvt. Ltd. Kala Aamb (H.P)), Eudragit RS100 (Evonik Roehm Pharma, Mumbai), HPMC (Lobal Chem, Mumbai), Dibutylpthalate (Qualigens, Lobal Chem, Mumbai), DMSO (Lobal Chem, Mumbai), Dichloromethane and Methanol (Merck, Mumbai), Electronic

weighing balance (Afoset (ER – 200 A) Ahembdabad), Melting point apparatus (Lab india (MR-VIS) Mumbai), Double beam UV Spectrophotometer (Systronic (2202) Mumbai), FTIR Spectrophotometer (Bruker FTIR spectrophotometer, Mumbai), Magnetic stirrer (Remi Udyog, Mumbai), Hot air oven (Sudheer Scientific, Ambala), pH meter (Systronic (802), Ahemdabad), Dissolution apparatus (Electro Lab Tablet dissolution Tester USP (TDT 06P), Mumbai).

ANALYSIS OF THE MODEL DRUG

Description: Fluconazole was physically examined for color, clarity, flexibility etc.

Solubility determination:

In distilled water and methanol:

An excess amount of drug was taken and dissolved in measured amount of distilled water and methanol in glass beaker to get a saturated solution. The solution was taken intermitentillely to assist the attainment of equilibrium with the undissolved particles. The measured quntitity of the filtered drug solution was withdrawn after 24 hours and successively diluted with distilled water suitably, and the concentration was measured in a UV spectrophotometer.

Melting point determination

Melting point is determined by the capillary tube method. In this method note the temperature at which the drug is melt, by placing the capillary tube which is fused from one side in to melting point apparatus this is its melting point.

Fourier transform infra-red (FTIR) spectroscopy

There is always possibility of drug excipients interaction in any formulation due to their intimate contact. The presence of any drug-polymer interaction was recorded in FT-IR spectroscopy. The scanning range was 400– 4000 cm−1.

Λ_{max} Scanning

Λ_{max} scanning help in identifying the purity of drug. Spectrum of Fluconazole was obtained in methanol solution, observed wavelength maxima was 260 nm.

Reagents preparation:

Preparation of pH 7.4 phosphate buffer

1.3606gm of KH_2PO_4 and 0.3128 gm of NaOH were taken and dissolved in 100 ml of distilled water. Then solution was made up to 200ml with distilled water.

Preparation of primary stock solution:

The powder equivalent to 100 mg of Fluconazole was accurately weighed and transferred into a 100 ml volumetric flask. To this, 50 ml of 7.4 pH phosphate buffer solution was added and occasional shaking to disperse and dissolve the contents. The volume was made up to 100 ml with 7.4 pH phosphate buffer solution to give 1000 µg/ml of Fluconazole solution.

Preparation of calibration curve in 7.4 pH phosphate buffer:

Calibration curve of Fluconazole was developed in 7.4 pH phosphate buffer at 260 nm wave length. From the stock solution, aliquots of 1 ml were pipette out into a series of 10 ml volumetric flask and volume was made up to 10 ml with 7.4 pH phosphate buffer get a concentration of 10µg/ml. From this dilution further dilutions were made as 2, 4, 6, 8, 10µg/ml. Absorbance of each solution was measured by using UV double beam spectrophotometer at 260 nm using 7.4 pH phosphate buffer as a reference standard.

Preparation of working standard solution:

Working standard solution having concentration of 10 to 100 µg/ml were prepared by appropriately diluting the stock solution with 7.4 pH phosphate buffer. The absorbance of each working standard solution was measured at 260nm on UV spectrophotometer using 7.4 pH phosphate buffers as blank. Average of triplicate reading was taken.

Fabrication of Transdermal patches:

Matrix type transdermal patches containing Fluconazole were prepared by solvent evaporation method, using different ratios of polymers ERS 100 and HPMC. The polymers were weighed dissolved in the mixture of solvents i.e. ethanol: acetone. Dibutylpthalate was added as plasticizer (30% w/w of polymers), DMSO as a penetration enhancer (5%v/w of polymers). The drug was added to the polymeric solution, and then they were stirred and poured in to the petridish. The rate of evaporation of solvent was controlled by inverting the funnel over the petridish. After the 24 hrs the dried patch were taken out and stored in a desiccator. The patches with different ratios of Eudragit RS 100: HPMC. The formulation A1 to A4 having different ratio of polymers without penetration enhancer, other formulations from P1 to P4 is having different concentration of polymers with penetration enhancer.

Table 1: Composition of transdermal patches:

Code	Drug (mg)	ERS:HPMC	%w/w Dibutylpthalate	Penetration enhancer
F1	100	1:4	30%	-
F2	100	2:8	30%	-
F3	100	4:6	30%	-
F4	100	8:4	30%	-
P1	100	1:4	30%	5%
P2	100	2:8	30%	5%
P3	100	4:6	30%	5%
P4	100	8:4	30%	5%

Evaluation of Transdermal Patches

Weight Variation: [4]

Cut 1-3 films from each patch then the patches was weighed directly on the digital balance for the determination of weight variation.

Thickness: [6]

Thickness of each patch at five different locations was done by using digital caliper.

Folding endurance: [7, 8]

Folding endurance was determined by repeatedly folding the patch at the same place until it breaks.

Drug content determination: [9]

For a drug content uniformity, patch was dissolved in a 100ml of isotonic phosphate buffer saline pH 7.4 for 12 hours under occasional stirring. The contents were filtered by whatman filter paper and then filtrate was analysed by U.V spectrophotometer at a specific λ_{max}.

Flexibility or Tensile strength: [11]

The pulley system is used to determine the flexibility and tensile strength. With the help of two small catchers the patch was pulled in opposite direction by gradually increasing the force until the patch was broken. The tensile strength was noted from the scale of pulley in kg/cm^2.

Flatness: [12]

The strips were cut out longitudinally from each film i.e. one from center and two from either side. The length of each strip was measured and the variation in the length because of nonuniformity in flatness was measured by determining percent constriction, considering 0% constriction is equivalent to 100% flatness:

% Constriction = L_1-L_2/L_2×100

Where L_1= initial length of each strip

L_2= final length of each strip

Percentage of moisture uptake: [13]

To check the physical stability of film in high humidity condition the film were placed in a desiccator containing a solution of aluminium chloride at room temperature for 24 hrs and exposed to 85% relative humidity until a constant weight of film was obtained. The film was reweighed and the percentage moisture uptake was determined by following formula.

Percentage moisture uptake = Final weight – Initial weight/Initial weight×100

Percentage moisture loss: [14]

To check extend of moisture loss the films were weighed accurately and kept in the desiccators containing anhydrous calcium chloride. After 24 hr the film were taken out and reweighed.

Percentage of moisture loss = Initial weight – Final weight/Initial weight×100

***In-vitro* dissolution study:** [15]

The *in-vitro* dissolution test was performed using USP type 2 test apparatus. The patch was tied with paddle of apparatus then drug release study was carried out for 8 hr in 900 ml of pH 7.4 phosphate buffer dissolution media, maintained at 37±0.5°C and agitated at 50 rpm. Periodically 10ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The absorbance of Fluconazole was measured UV/Visible spectrophotometrically at 260 nm. The percentage cumulative drug release was calculated and amount of drug released from patches was determined.

Stability studies: [16]

The patches were exposed to two selected temperatures of 37°C and 45°C in two different hot air ovens. The transdermal patches were kept in the oven for one week. The patches were analysed for the drug content at the end of the day.

RESULTS:

Identity of Drug

Table 2: Organoleptic Properties of Pure Drug:

Drug	Test	Observation
Fluconazole	Color	White or almost white powder
	Odor	Odorless
	Taste	Slightly bitter

MELTING POINT DETERMINATION: Observed melting point of sample is approx. near to reported data which confirm the authenticity of obtained sample.

Table 3: Melting point of Fluconazole:

Method used	Experimental value	Literature value
Capillary method	142° C	138-142° C

λ_{max} Scanning of pure drug:

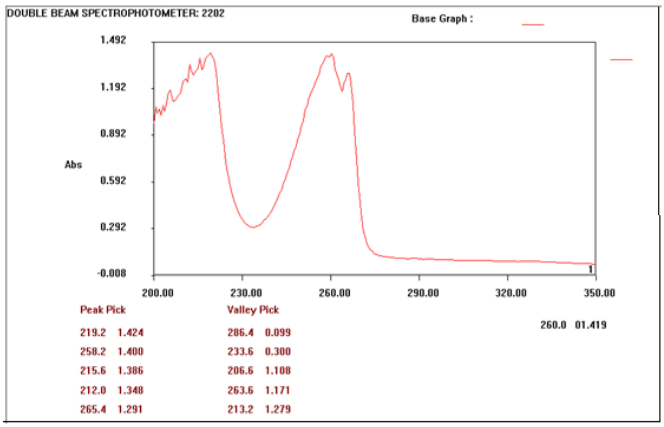

Fig 1: λ_{max} Scanning plot of Fluconazole

The absorption maximum of the drug solutions was found to be 260 nm by using double beam spectrophotometer at pH 7.4 buffer solution in Fig. 1. Hence this test supported the other identification testes, providing the fact that the obtained sample is pure Fluconazole.

SOLUBILITY STUDIES OF PURE DRUG:

The drug is very high soluble in alcohol, DMSO, Slightly soluble in water and sparingly soluble in pH 7.4 phosphate buffer.

Table 4: Solubility data of Fluconazole in different solvent:

Solvent	Concentration	Solubility
Water	0.9mg/ml	lightly soluble
Methanol	25.0mg/ml	reely soluble
DMSO	20.5mg/ml	reely soluble
Ph 7.4 Phosphate buffer	11.2 mg/ml	paringly soluble

COMPATIBILITY STUDIES: FTIR spectral studies: The FTIR spectra of drug and polymers were obtained with FTIR spectrophotometer. The drug was identified and compatibility was confirmed by confirmed by FTIR spectrum from Fig, 2, 3.

Table 5 FTIR spectral data of Fluconazole

Functional Group	Literature frequency (cm^{-1})	Observed value (cm^{-1})
O-H Stretch	3500-3700	3566
N-H Stretch	3300-3500	3345
C-F Stretch	1000-1400	1054
Aromatic distribution	680-860	733
C=C (Blend)	1560-1680	1617

The peaks shown in obtained spectra were compare with spectrum reported in the literature to confirm the authenticity of the given sample. The matching of IR spectra proves the identity of pure drug.

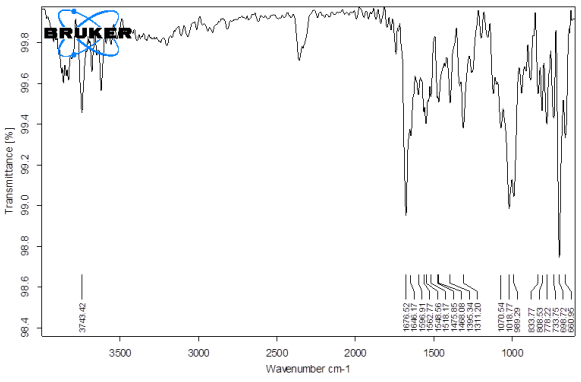

Fig 2: FTIR spectra of pure Drug

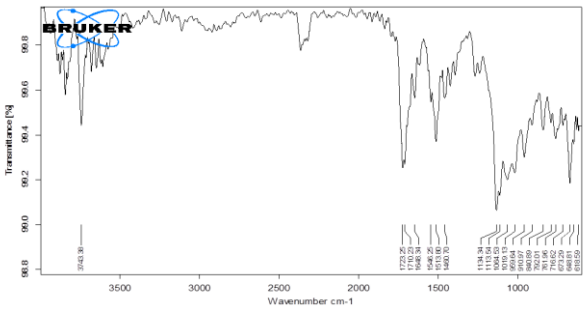

Fig 3: FTIR spectra of physical mixture (pure Drug + HPMC + ERS100)

Calibration curve of Fluconazole: The calibration curve of Fluconazole was prepared in phosphate buffer having pH 7.4 at 260 nm and the absorbance values at different Concentrations of Fluconazole in pH 7.4 phosphate buffer solution are shown in Table and graphically represented in figure.

Table 6 Calibration data of Fluconazole in pH 7.4 phosphate buffer.

S. No.	Conc. (µg/ml)	Absorbance
1	2	0.324
2	4	0.463
3	6	0.593
4	8	0.683
5	10	0.791

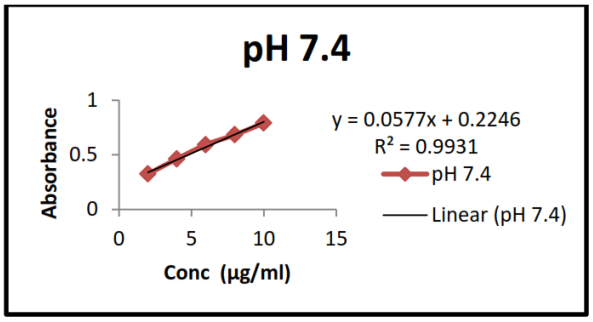

Fig 4 Standard curve of Fluconazole in pH 7.4 phosphate buffer (Slope= 0.057, Regression analysis= 0.993)

CHARACTERIZATION AND EVALUATION OF TRANSDERMAL PATCHES:

Description: The prepared patches were clear and smooth.

Table 7 Weight Variation data of fluconazole transdermal patches

Formulation Code	Weight variation (gm)			SD	Average	Average ±SD
	Sample 1	Sample 2	Sample 3			
F1	0.04	0.06	0.03	0.0152	0.043	.043±.015
F2	0.07	0.05	0.08	0.0152	0.066	.066±.015
F3	0.06	0.09	0.08	0.0152	0.076	.076±.015
F4	0.1	0.13	0.15	0.0251	0.126	.126±.025
P1	0.06	0.07	0.08	0.01	0.07	.07±.01
P2	0.15	0.11	0.1	0.0264	0.12	.12±.02
P3	0.13	0.16	0.13	0.0173	0.14	.14±.017
P4	0.17	0.15	0.18	0.0152	0.166	.166±.015

All values are expressed as mean ± SD; n = 3

Table 8 Thickness data of fluconazole transdermal patches

Formulation Code	Thickness(mm)			SD	Average	Average ±SD
	Sample 1	Sample 2	Sample 3			
F1	0.06	0.13	0.12	0.037	0.103	.103±.037
F2	0.2	0.22	0.18	0.02	0.2	0.2±.02
F3	0.24	0.32	0.29	0.040	0.283	0.28±0.04
F4	0.45	0.3	0.32	0.081	0.356	0.35±.081
P1	0.17	0.18	0.14	0.020	0.163	0.16±.021
P2	0.28	0.25	0.26	0.015	0.263	0.26±0.015
P3	0.26	0.34	0.29	0.040	0.296	0.29±0.04
P4	0.35	0.38	0.32	0.03	0.35	0.35±0.03

All values are expressed as mean ± SD; n = 3

Table 9 Folding Endurance data of fluconazole transdermal patches

Formulation Code	Folding Endurance			Average	SD	Average ±SD
	Trial 1	Trial 2	Trial 2			
F1	84	85	86	85	1	85±1
F2	86	87	86	86.33	0.577	86.33±0.5
F3	75	78	76	76.33	1.527	76.33±1.5
F4	65	64	67	65.33	1.527	65.33±1.5
P1	76	79	79	78	1.732	78±1.7
P2	98	99	98	98.33	0.577	98.33±0.577
P3	89	87	88	88	1	88±1
P4	65	67	68	66.66	1.527	66.66±1.527

All values are expressed as mean ± SD; n = 3

Table 10 Moisture uptake data of fluconazole transdermal patches

Formulation Code	Initial Weight (gm)	Final Weight (gm)	% Moisture uptake
F1	0.69	.81	8.695652
F2	1.34	1.42	17.91045
F3	1.23	1.36	13.00813
F4	1.08	1.19	10.18519
P1	0.86	1.02	12.7907
P2	1.45	1.51	22.75862
P3	1.41	1.48	18.43972
P4	1.42	1.47	15.49296

Table 11 Moisture loss data of fluconazole transdermal patches

Formulation Code	Initial Weight (gm)	Final Weight (gm)	% Moisture release
F1	0.69	0.64	7.8125
F2	1.34	1.28	4.6875
F3	1.23	1.12	9.821429
F4	1.08	0.98	10.20408
P1	0.86	0.82	4.878049
P2	1.45	1.4	3.571429
P3	1.43	1.35	5.925926
P4	1.42	1.34	5.970149

Table 12 Flatness study data of fluconazole transdermal patches

Formulation Code	Initial length (cm)				Final length (cm)				% Constriction	% Flatness
	Trial 1	Trial 2	Trial 3	Avg.	Trial 1	Trial 2	Trial 3	Avg.		
F1	6.5	9	6.8	7.433	6.5	9	6.8	7.433	0	100
F2	7.5	9.8	7.2	8.166	7.5	9.8	7.2	8.166	0	100
F3	7.4	9.5	7	7.966	7.4	9.5	7	7.966	0	100
F4	7.3	9	6.9	7.733	7.3	9	6.9	7.733	0	100
P1	7.3	9.2	6.8	7.766	7.3	9.2	6.8	7.766	0	100
P2	7.8	9.8	7.3	8.3	7.8	9.8	7.3	8.3	0	100
P3	6.9	9.4	6.2	7.5	6.9	9.4	6.2	7.5	0	100
P4	7.6	9.2	6.5	7.766	7.6	9.2	6.5	7.766	0	100

All values are expressed as mean ± SD; n = 3

Table 13 Tensile strength data of fluconazole transdermal patches

Formulation Code	Tensile strength (kg/cm²)			Average	SD	Average ±SD	% Elongation
	Trial 1	Trial 2	Trial 3				
F1	15.96	12.68	11.86	13.5	0.06	13.5±0.06	15
F2	18.62	17.23	14.36	16.73667	0.07	16.73±0.07	22.5
F3	14.36	13.45	10.36	12.72333	0.041	12.72±0.01	45
F4	20.32	16.88	15.72	17.64	0.078	17.64±0.07	62.5
P1	15.86	14.11	11.85	13.94	0.065	18.38±0.05	30
P2	24.63	23.65	19.85	22.71	0.04	22.71±0.04	67.5
P3	18.62	17.23	14.36	16.73667	0.07	16.73±0.07	60
P4	21.56	18.23	15.36	18.38333	0.055	18.38±.055	45

All values are expressed as mean ± SD; n = 3

Table 14 Drug content uniformity study of fluconazole transdermal patches

Formulation code	Absorbance	Drug content Uniformity %
F1	0.698	83.157
F2	0.759	93.859
F3	0.746	91.578
F4	0.725	87.894
P1	0.766	95.087
P2	0.782	97.894
P3	0.775	96.666
P4	0.76	94.035

All values are expressed as mean ± SD; n = 3

All the films were found to be uniform in their weight, thickness, flatness and folding endurance with low SD values.

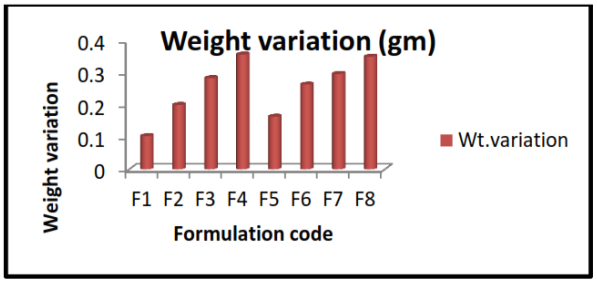

Fig. 6.5 Graphical representation of weight variation Fluconazole transdermal patches

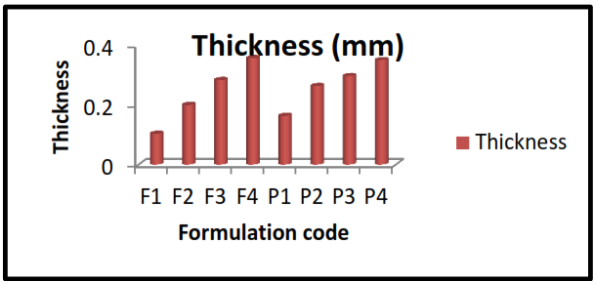

Fig.6.6 Graphical representation of thickness Fluconazole transdermal patches

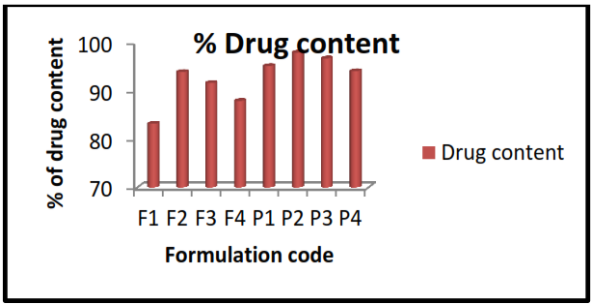

Fig. 6.7 Graphical representation of % drug content uniformity Fluconazole transdermal patches

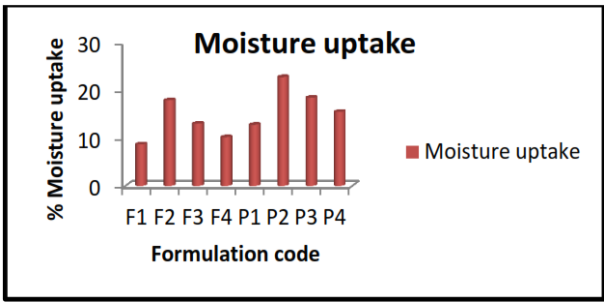

Fig. 6.8 Graphical representation of % moisture uptake uniformity of Fluconazole transdermal patches

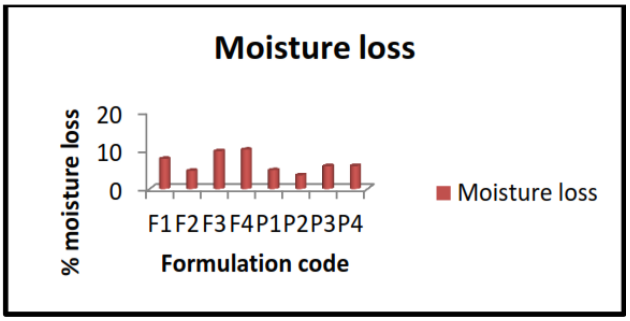

Fig. 6.9 Graphical representation of %moisture loss uniformity of Fluconazole transdermal patches

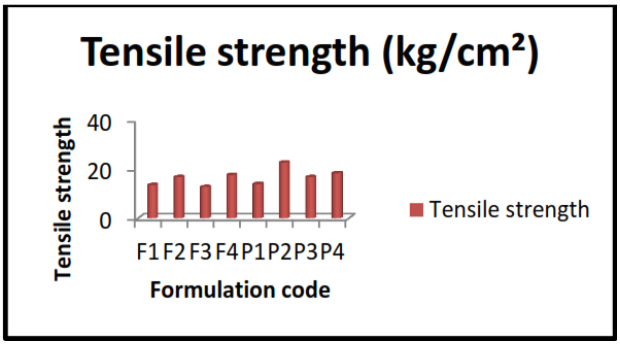

Fig.6.10 Graphical representation of tensile strength of Fluconazole transdermal patches

INVITRO DRUG RELEASE STUDY

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the controlled release performance.

Table 6.14 *In vitro* release study of Transdermal patch of fluconazole

S. No.	Formulation Code	% Drug release							
		1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
1	F1	13.8	15.68	26.4	32.8	38.6	41.5	42.6	51.8
2	F2	5.62	18.68	21.7	44.69	44.94	57.57	63.44	66.52
3	F3	11.2	18.6	27.8	38.6	39.6	42.3	46.2	51.3
4	F4	8.9	13.36	24.6	38.4	41.2	43.62	48.23	53.12
5	P1	14.25	20.39	41.3	49.1	58.6	62.5	71.82	78.71
6	P2	13.5	21.3	32.9	35.2	44.26	58.6	69.2	86.1
7	P3	10.28	25.81	27.9	33.06	47.25	55.75	64.9	84.2
8	P4	15.2	24.9	38.1	48.3	53.45	56.3	70.71	75.27

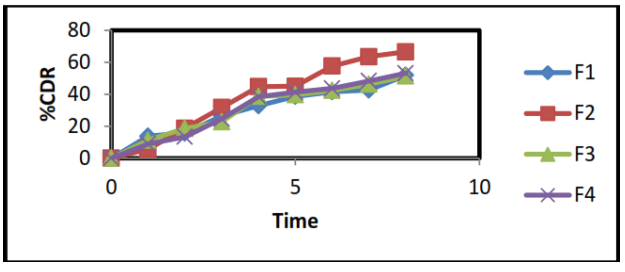

Fig. 6.11Graphical representation of % CDR of F1-F4 at different time intervals

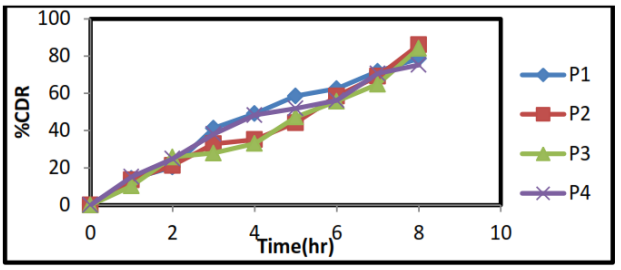

Fig.6.12 Graphical representation of % CDR of P1-P4 at different time intervals

Formulations P2 (ERS 100 & HPMC in 2:8) exhibited greatest (86.1 %) of drug release value, which are significantly different compared to the lowest value observed with the formulation F1 containing (ERS 100 & HPMC in 1:4) i.e. (51.8 %). In the present study it was observed that as the concentration of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially as compared to hydrophobic polymers ERS 100. This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of drugs molecules to release the diffusion medium and hence, to cause higher release rate. Formulations A1-A4 without permeation enhancer showed less release as compared to formulations P1 – P4 with permeation enhancer.

MATHEMATICAL MODELING

In vitro release data of formulations F1 – F4 and formulations P1 – P4: Zero order kinetics

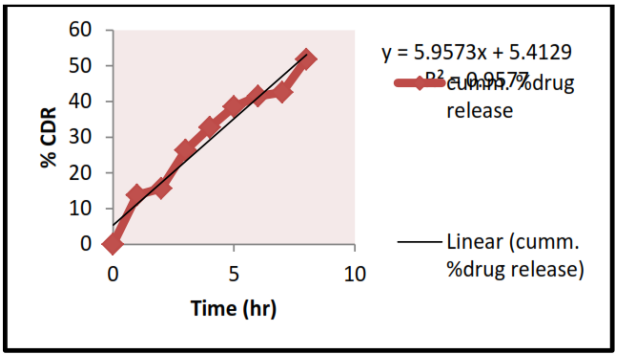

Fig. 6.13 *In vitro* release data of formulation F1: Zero order kinetic

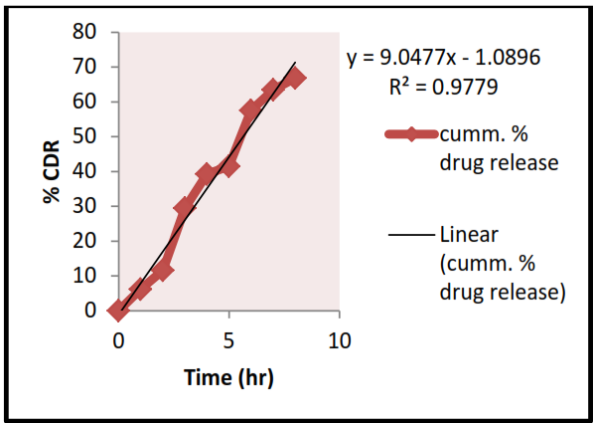

Fig.6.14 *In vitro* release data of formulation F2: Zero order kinetic

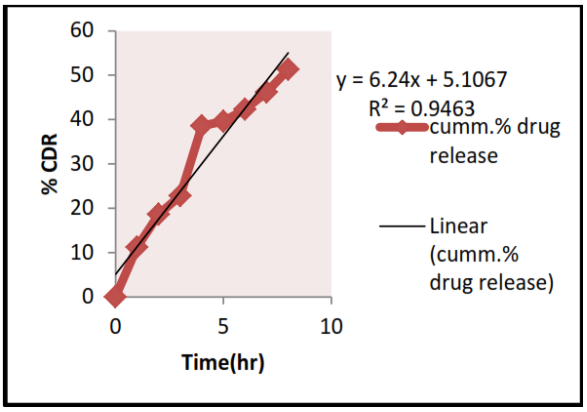

Fig.6.15 *In vitro* release data of formulation F3: Zero order kinetic

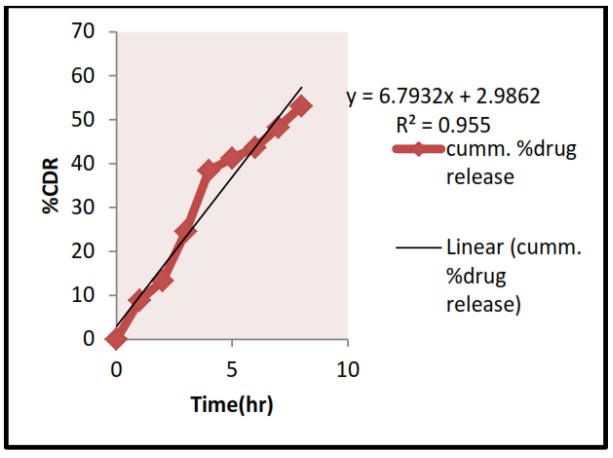

Fig.6.16 *In vitro* release data of formulation F4: Zero order kinetic

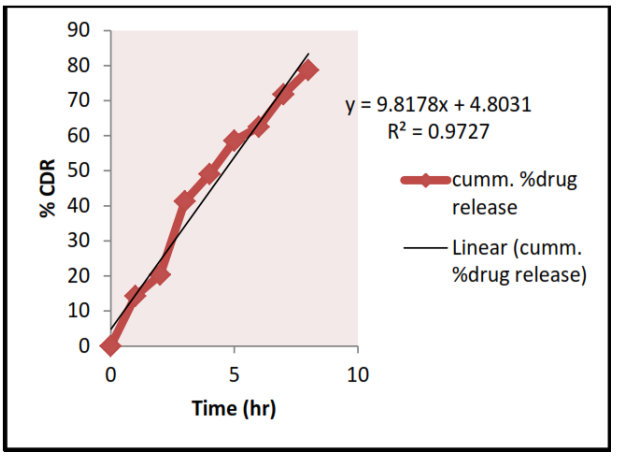

Fig. 6.17 *In vitro* release data of formulation P1: Zero order kinetic

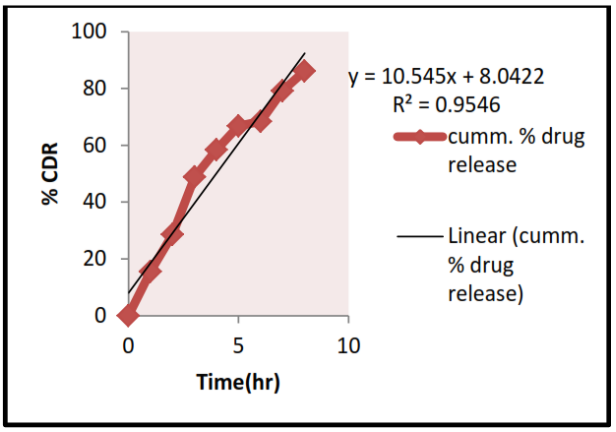

Fig.6.18 *In vitro* release data of formulation P2: Zero order kinetic

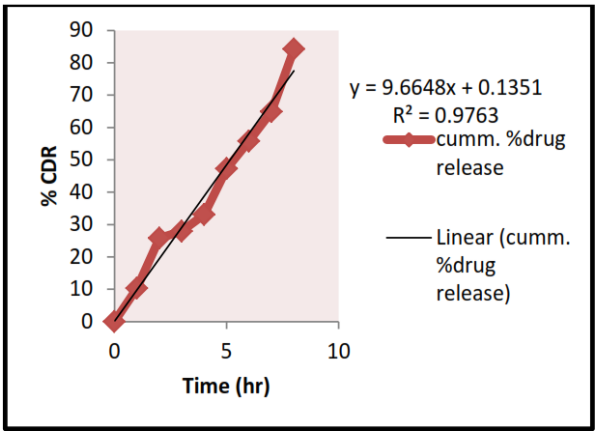

Fig.6.19 *In vitro* release data of formulation P3: Zero order kinetic

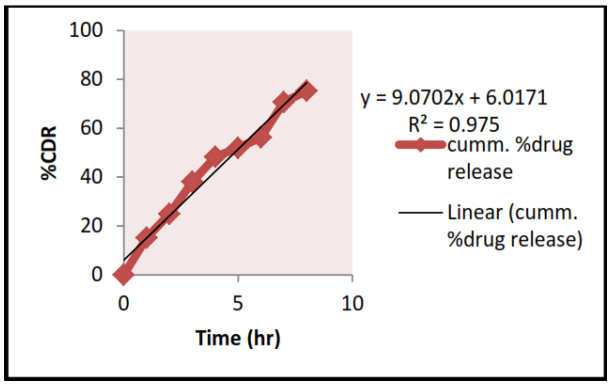

Fig.6.20 *In vitro* release data of formulation P4: Zero order kinetic

6.3.2 In vitro release data of formulations F1 – F4 and formulations P1 – P4: First order kinetic

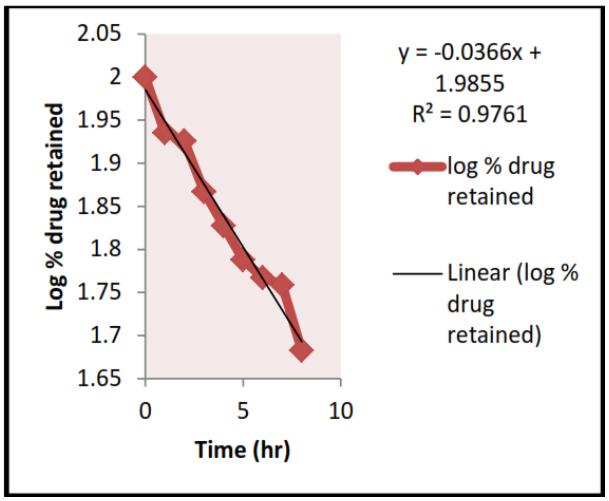

Fig.6.21 *In vitro* release data of formulation F1: First order kinetic

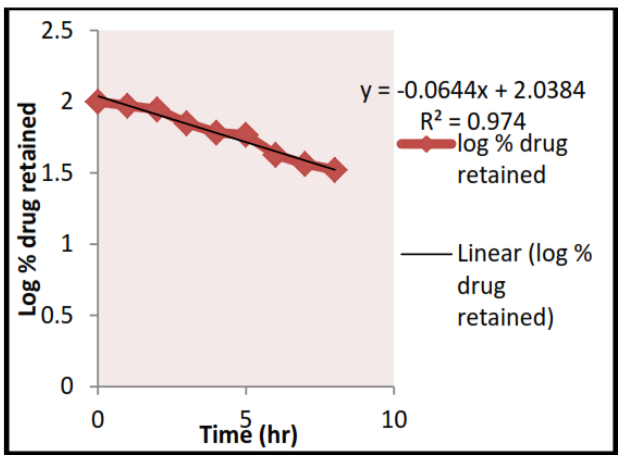

Fig. 6.22 *In vitro* release data of formulation F2: First order kinetic

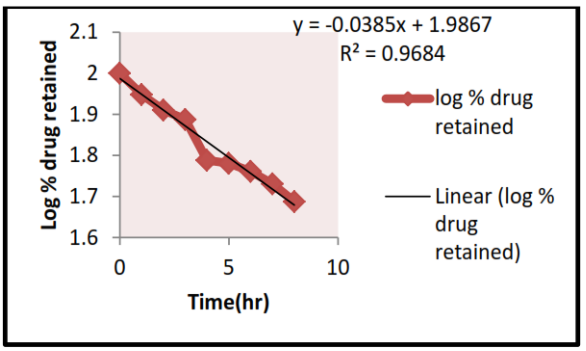

Fig.6.23 *In vitro* release data of formulation F3: First order kinetic

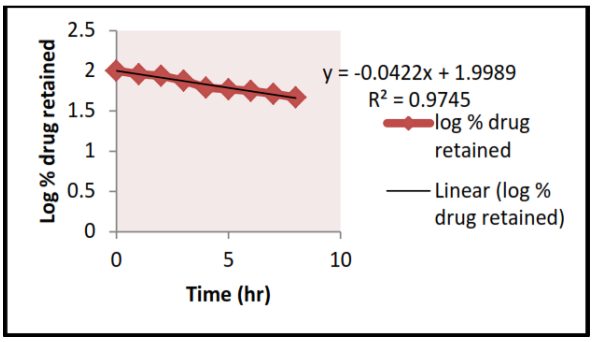

Fig. 6.24 *In vitro* release data of formulation F4: First order kinetic

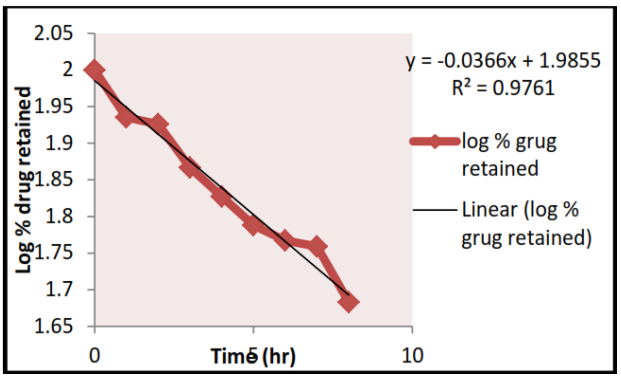

Fig.6.25 *In vitro* release data of formulation P1: First order kinetic

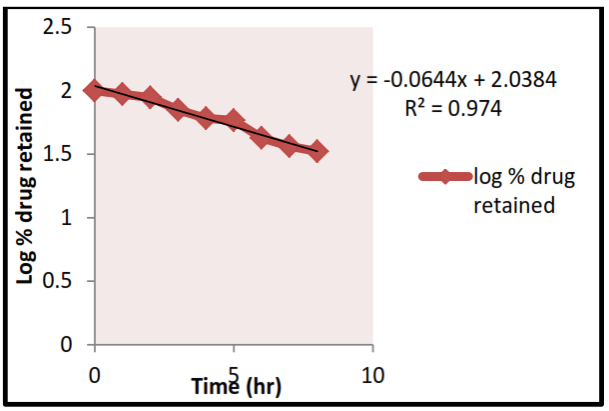

Fig.6.26 *In vitro* release data of formulation P2: First order kinetic

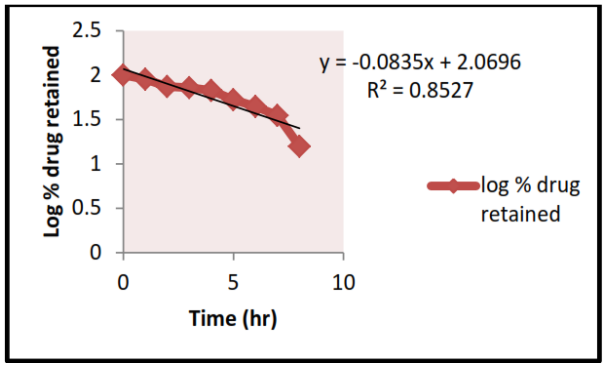

Fig.6.27 *In vitro* release data of formulation P3: First order kinetic

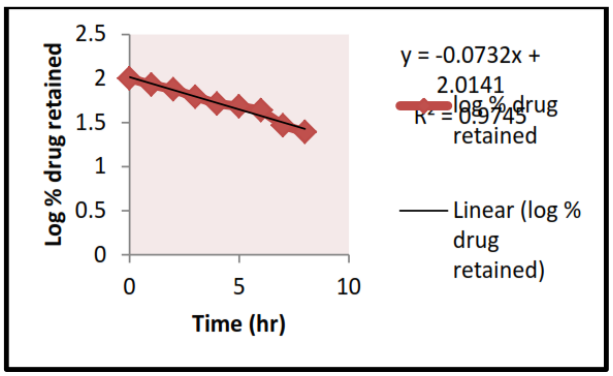

Fig.6.28 *In vitro* release data of formulation P4: First order kinetic

6.3.3 In vitro release data of formulations F1 – F4 and formulations P1 – P4: Higuchi model

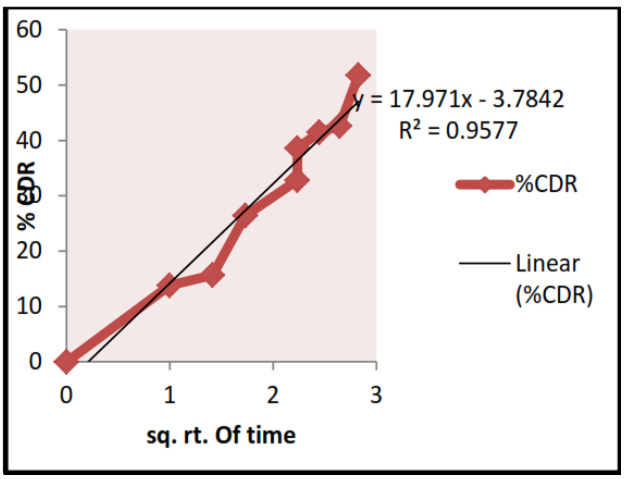

Fig.6.29 *In vitro* release data of formulation F1: Higuchi mode

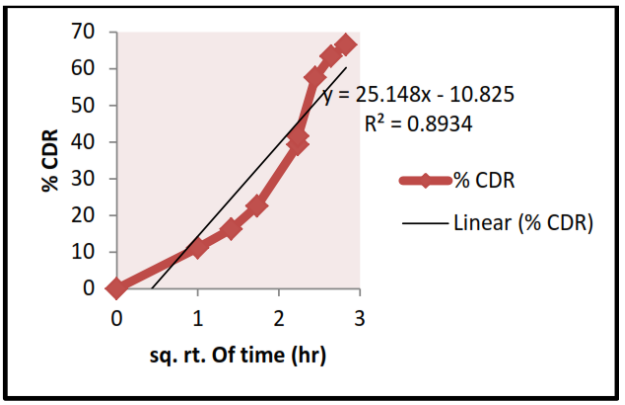

Fig.6.30 *In vitro* release data of formulation F2: Higuchi model

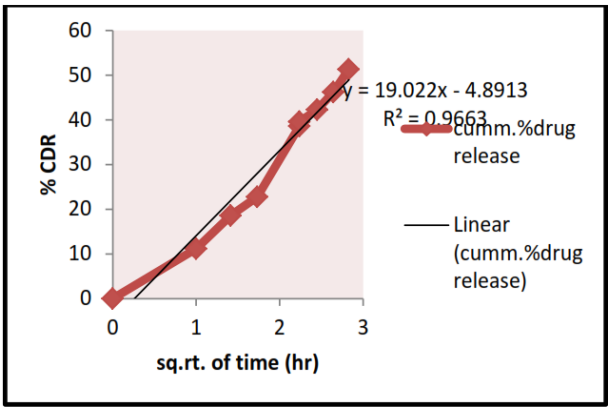

Fig.6.31 *In vitro* release data of formulation F3: Higuchi model

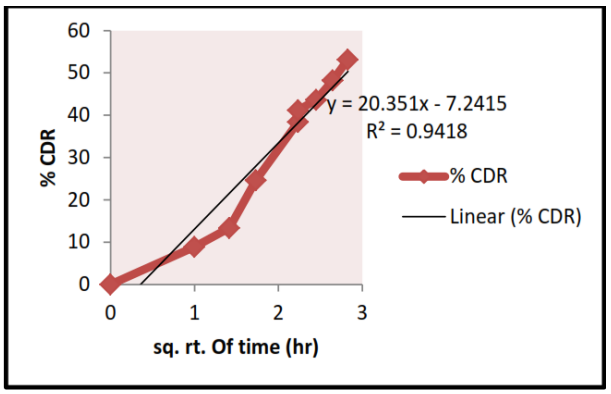

Fig.6.32 *In vitro* release data of formulation F4: Higuchi model

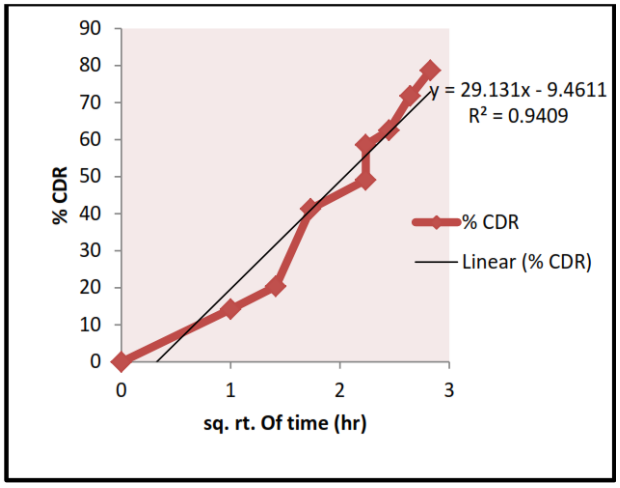

Fig.6.33 *In vitro* release data of formulation P1: Higuchi model

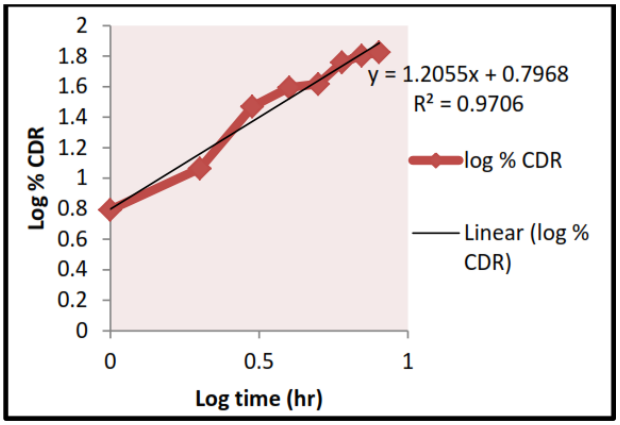

Fig. 6.34 *In vitro* release data of formulation P2: Higuchi model

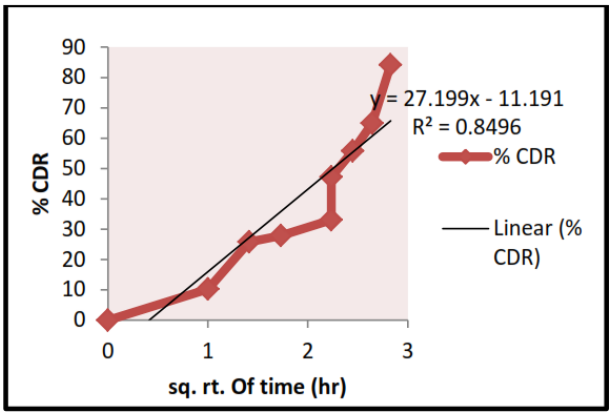

Fig. 6.35 *In vitro* release data of formulation P3: Higuchi model

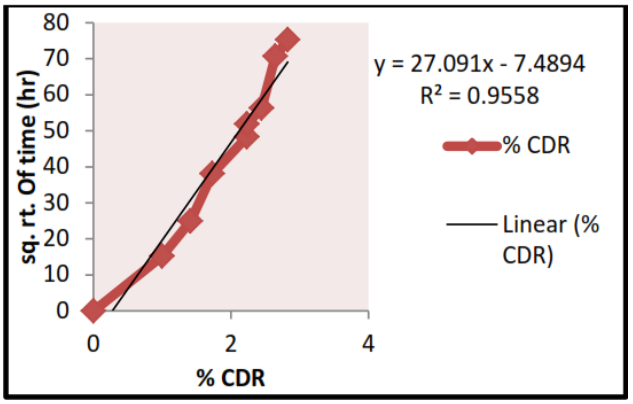

Fig. 6.36 *In vitro* release data of formulation P4: Higuchi model

6.3.4 In vitro release data of formulations F1 – F4 and formulations P1 – P4: Korsmeyer Peppas model

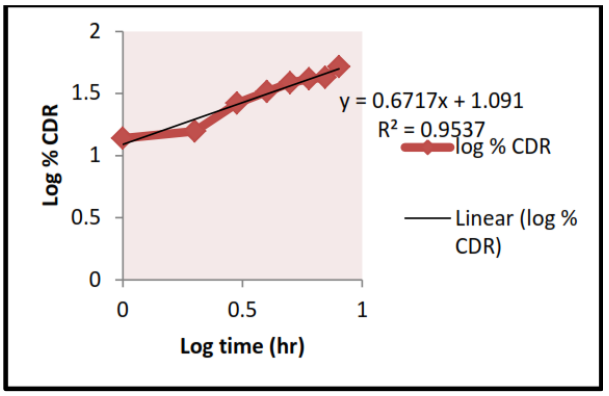

Fig.6.37 *In vitro* release data of formulation F1: Korsmeyer peppas model

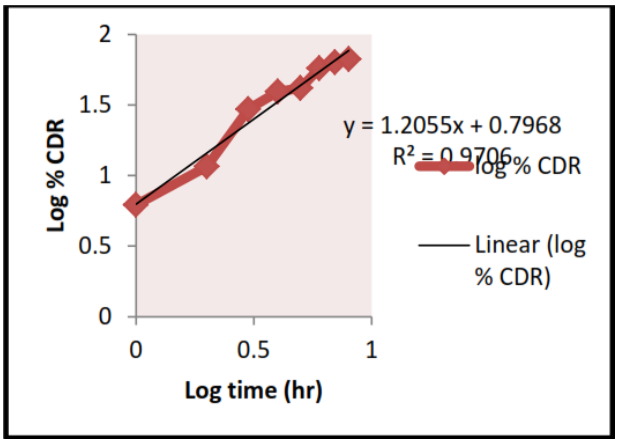

Fig.6.38 *In vitro* release data of formulation F2: Korsmeyer peppas mode

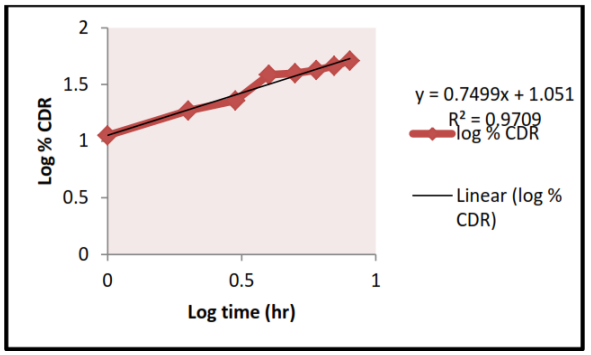

Fig.6.39 *In vitro* release data of formulation F3: Korsmeyer peppas model

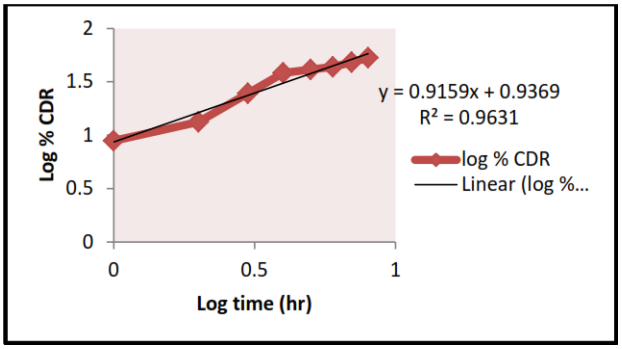

Fig.6.40 *In vitro* release data of formulation F4: Korsmeyer peppas model

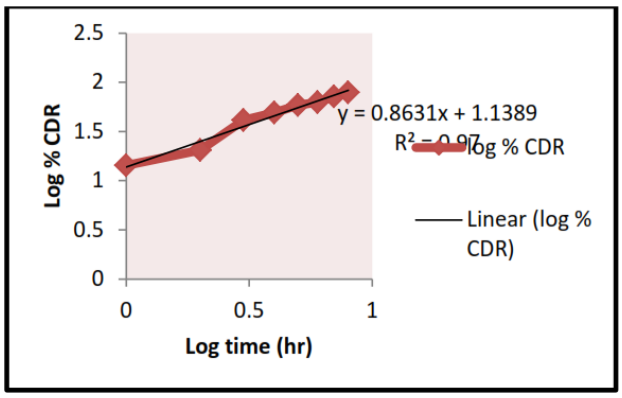

Fig.6.41 *In vitro* release data of formulation P1: Korsmeyer peppas model

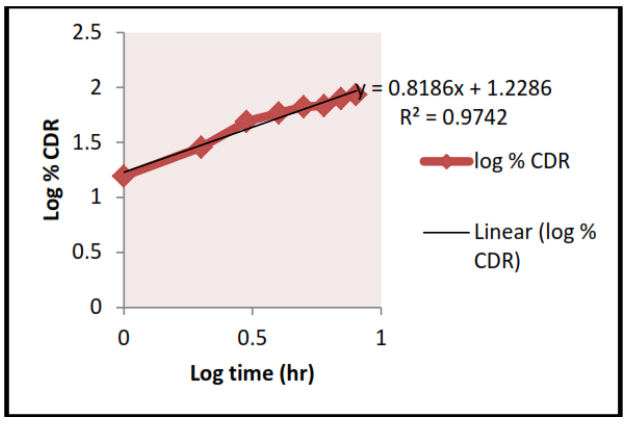

Fig.6.42 *In vitro* release data of formulation P2: Korsmeyer peppas model

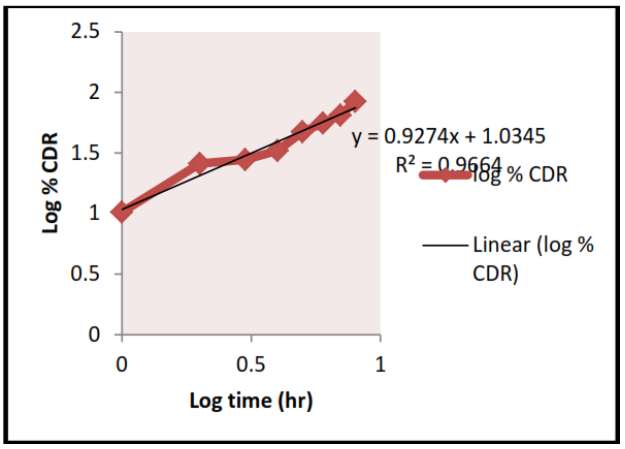

Fig6.43 *In vitro* release data of formulation P3: Korsmeyer peppas model

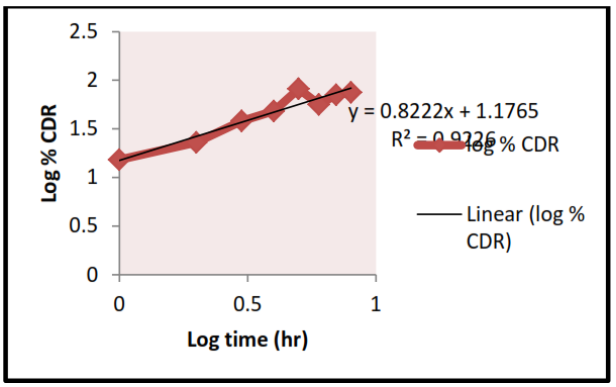

Fig.6.44 *In vitro* release data of formulation P4: Korsmeyer peppas model

Table: 6.47 R^2 value of model fitting of Fluconazole

FORMULATION CODE	ZERO ORDER	FIRST ORDER	HIGUCHI MODEL	PEPPAS KINETICS
F1	0.957	0.976	0.957	0.953
F2	0.977	0.974	0.893	0.970
F3	0.946	0.968	0.966	0.704
F4	0.955	0.974	0.941	0.963
P1	0.972	0.976	0.940	0.970
P2	0.954	0.978	0.961	0.974
P3	0.976	0.852	0.849	0.966
P4	0.975	0.974	0.955	0.922

The diffusion kinetics of the drug fluconazole was analyzed by graphical method for zero order (Figure 6.10-6.17), First order (Figure 6.18-6.25), Higuchi model (Figure 6.26-6.33) and Peppas kinetics model (Figure 6.34-6.41). After fitting data to these models, value of regression coefficients from all the models were obtained and the value which was closer to 1 was selected as the best fit model for the drug release. The regression value for the formulation P2 (ERS100 and HPMC in the ratio of 2:8) have showed optimum release i.e. R^2 = 0.978. It showed the first order kinetic.

6.4 Stability Study:

The patches were observed for the changes in color, appearance, flexibility at a regular interval of days for a week and the drug content observed after one week.

Table: 6.48 Stability study data for Fluconazole patches

Formulation code	Drug content at room temp.	Drug content at accelerated conditions	
		37°C	45°C
F1	83.15	82.65	81.6
F2	93.85	92.81	92.6
F3	91.57	90.2	89.5
F4	87.89	86.72	86.3
P1	95.08	95	94.6
P2	97.89	97.68	96.82
P3	94.03	93.65	92.83
P4	96.66	95.81	94.86

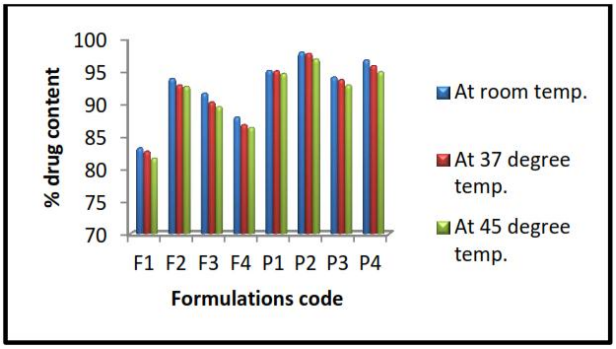

Fig.6.45 Graphical representation of stability data of Fluconazole transdermal patches

All the patches were stable at 37°C and 45°C with respect to their physical parameters and drug content.

CONCLUSION:

The formulation showed maximum *in-vitro* drug release (86.1%) having excellent permeability through skin. Formulated Transdermal patches fitted to mathematical kinetic models. From the result of data fitted to various models it was found that the optimized formulation P2 (ERS100: HPMC) by solvent evaporation method had ratio (2: 8) showed first order of drug release i.e. the formulation P2 showed diffusion controlled mechanism.

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