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Formulation and Evaluation of Transdermal Patch of Captopril by Using Different Penetration Enhancer.

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ABSTRACT

OBJECTIVE: The objective of the present investigation was to formulate, evaluate and optimize transdermal patch of Captopril.

Methods: In the present investigation an attempt was made to develop transdermal patch of Captopril by using different penetration enhancer. Transdermal patch of Captopril were formulate using HPMC E15 as a film forming agent and Eudragit RS100 as a rate controlling polymer propylene glycol as plasticizer and DMSO, DMF, Oleic acid as a penetration enhancer. Transdermal patch was prepared by solvent casting method. Formulations were prepared using three independent variables namely polymer quantity , Plasticizer and penetration enhancer, whereas disintegration time and % drug release as dependent variables. The stability studies of the patch were performed for optimized batch as per ICH guideline. From the results of design batches, best batch was selected and evaluated for in vivo pharmacokinetic study in Albino rat model. The drug & excipients were characterized as per IP 2014 Drug and excipients studies using FT-IR.

Results: . Films were subjected to physicochemical characterization such as thickness, weight variation, moisture loss, moisture absorption, content uniformity, folding endurance, , in-vitro drug release. The optimized batch is passed the accelerated stability studies, no significant change in the dissolution profile. The statistically optimized formulation was characterized with FT-IR (Fourier transform-infrared spectroscopy) studies and found no chemical interactions between drug and polymer.

Conclusion: Thus the prepared transdermal patch of Captopril could be a better alternative for tablet and capsules an achieving rapid oral bioavailability in treatment of allergic rhinitis.

Keywords: Captopril, HPMC E-15, Eudragit RS 100, Dimethyl sulfoxide, dimethyl formaide, oleic acid.

I. INTRODUCTION

For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams , ointments, liquid aerosols, injectables and suppositories, as carriers. Recently, several techniques of drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and targeting the delivery of drug to a tissue. In responses to these advances, several transdermal drug delivery system have recently been developed, aiming to achieve the objective of systemic medication through topical application on the intact skin surface. The principal of transdermal drug delivery system is that they could provide sustained drug delivery (and hence constant drug concentration in plasma) over a prolonged of time. For these attributes, it is often extrapolated that sustained therapeutic activity will also be obtained with transdermal drug delivery system. [1]

Currently TDDS is one of the most promising methods for drug application. TDDS has many advantages over oral route of administration such as improves patient compliance, no pain at site of application, by passing first- pass metabolism, control drug delivery, maintaining a constant and prolonged drug level in plasma and making is possible to terminate the dose at the time of irritation[2,3].

The application of transdermal delivery to wider range of drugs is limited due to the significant barrier to penetration across the skin which is associated primarily with outermost stratum corneum layer of the epidermis[4]. Formulation on skin can be classified into two categories according to the target site of the action. One has systemic action after drug uptake from the cutaneous micro vascular network and other exhibit local effects in the skin[5].

Hypertension, a cardiovascular diseases account for a large proportion of all deaths and disability worldwide. Global burden of disease study reported that there were 5.2 million deaths from cardiovascular diseases in economically

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developed countries and 9.1 million deaths from the same causes in developing countries[6].Worldwide popularity estimate for hypertension may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension[7].

Captopril is classified as an antihypertensive. It has mean plasma half- life of 2 to 3 h, and only 40% of the orally administered drug reaches the circulation due to hepatic metabolism. The present research was directed to examine the release rate of Captopril and see the enhancer effect on the flux and enhancement ratio. This study was aimed at developing a suitable patch formulation containing Captopril for transdermal use the embedded drug should be released without any superior binding to the polymer[8,9].

The aim of the present study was to formulate, evaluate and optimize transdermal patch of Captopril by using different penetration enhancer by solvent casting method and response optimizer plot were drawn and analyzed taking dissolution and disintegration response.

II. MATERIALS AND METHOD

Materials:

Captopril Was Obtained From Whockhardt Mumbai, Hydroxypropyl Methylcellulose E 15 Labo Chemie, And Eudragit RS100 Obtained From H.D. Lab Che Aurangabad , Dimethyl Sulfoxide Obtained From Emplura Mumbai, Dimethyl Formaide Obtained From Ozone International Mumbai, Oleic Acid Obtained From Labin Mumbai, Poly Vinyl Alcohol Obtained From Himedial Labo Nasik, Dichloromethane Obtained From Emplura Acs Mumbai , Methanol Obtained From Himedia Nasik, Propylene Glycol Obtained From Meher Chemie Mumbai.

Materials used in the experimental study:

The drug, excipients and chemicals / reagents used for various experiments are enlisted as follows.

Table No. 1: List of chemicals and their sources.

Sr.No	Material	Property	Source
1.	Captopril	Pure Drug	Wockhard Mumbai
2.	Poly Vinyl Alcohol	Adhesive	Himedia Labo Nashik
3.	HPMC E15	Film Former	Labo Chemie
4.	Eudragit RS 100	Rate Controlling Polymer	H.D. Lab Chme Aurangabad
5.	Dichloromethane	Solvent	Emparta Acs Mumbai
6.	Methanol	Solvent	Himedia

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	Dimethyl Sulfoxide	Penetration Enhancer	Emplura Mumbai
8.	Dimethyl Formaide	Penetration Enhancer	Ozone International Mumbai
9.	Oleic Acid	Penetration Enhancer	Labin
10.	Propylene Glycol	Plasticizer	Meher Chemie Mumbai

Equipment

Following equipment were used in the present study

Table no 2: Equipments used with their source:

Sr.No	Equipment	Model No.	Make
1.	Digital Balance	Bl-22oh	Shimadzu Japan
2.	Hot Air Oven	Or-203	Labindia
3.	Dissolution Test Apparatus	EDT – 08 L	Electrolab (Usp
4.	UV-Spectrophotometer	Uv-1800	Shimadzu Japan
5.	FTIR	Spectrum 2	PerkiElimer Spectrum
6.	pH Meter	Pico+	Labindia
7.	Magnetic Stirrer	Lms-28oe	Labtop
8.	Sonicator	3-5 L 100h	Pci Analytics

Preparation of transdermal patch by using solvent casting method:

Solvent casting method:

Transdermal patches of Captopril were prepared by solvent evaporation technique for the formulations. Solution of HPMC E15 and Eudragit RS 100 were prepared separately in dichloromethane: methanol ,mixture. The two polymeric solutions were mixed to which weighted amount of Captopril was added slowly. To the mixture, 0.25 ml of propylene glycol and penetration enhancer (DMSO, DMF, Oleic acid) were added and mixed. The drug- polymer solution was casted in aluminum mould on petridish and preserved in desiccators for until use.

Composition of formulation F1-F12.

Table No. 3:- Formulation Table Of Transdermal Patch Of Captopril By Using Different Penetration Enhancer.

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Captopril, mg	157	157	157	157	157	157	157	157	157	157	157	157
HPMC E-15(mg)	250	335	375	250	335	375	250	335	375	250	335	375
Eudragit RS 100,(mg)	250	165	125	250	165	125	250	165	125	250	165	125
Total wt of polymer(mg)	500	500	500	500	500	500	500	500	500	500	500	500
Dichloromethane ml	7	7	7	7	7	7	7	7	7	7	7	7

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Methanol ml	7	7	7	7	7	7	7	7	7	7	7	7
Propylene ml glycol ml	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
DMSO ml	-	-	-	1	1	1	-	-	-	-	-	-
DMF, ml	-	-	-	-	-	-	1	1	1	-	-	-
Oleic acid, ml	-	-	-	-	-	-	-	-	-	1	1	1

EVALUATION OF TRANSDERMAL PATCH:

Interaction Studies:-

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulations development. Interaction studies are commonly carried out in thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical character such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc., [10,11]

Thickness of the patch:[12]

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and slandered deviation for the same to ensure the thickness of the prepared patch.

Uniformity of weight:[13]

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination:[14]

It can be determined by completely dissolving a small area 4cm^2 of polymeric patch in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighted before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method.

Folding endurance:[15]

A strip of specific are is to be cut evenly and respectively folded at the same place till it broke. The number of times the patch could be folded at the same place without breaking gives the value of the folding endurance.

Percentage moisture content: [16,17]

Individually weighted patches are kept in the desiccators having fused potassium chloride at room temperature for 24 hrs. after 24 hrs the patches are to be reweighted and percentage moisture content is calculated by the formula:

$$\% \text{ Moisture absorption} = \frac{(W_f - W_i)}{W_i} \times 100$$

Where, Wi- initial weight Wf - final weight

Percentage moisture loss:- [18]

The prepared patches were to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. after 24 hrs the patches were to be reweighted and determine the percentage moisture loss from the below mentioned formula.

$$\% \text{ Moisture loss} = \frac{(W_f - W_i)}{W_i} \times 100$$

Skin irritation study: [19]

Matrices were applied to the shaved skin on the back of 4 albino rat and secured using adhesive tape. On one side of back, a control patch (without any drug) and on another side an experimental patch were secured. The animals were

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observed for any sign of eythema or oedema for a period of 7 days.

In vitro permeability studies:-[20].

The in vitro permeation studies were carried out in a modified franz diffusion cell with a receptor compartment capacity of 23ml & surface area of 3.142 cm^2. The diffusion cell consists of two compartment. One is donor compartment contains the receptor solution. The device has a water jacket for temperature control and a sampling port. The permeation study was carried out across the dialysis membrane. The receiver compartment was filled with phosphate buffer 7.4. The donor compartment was then placed in position such that the surface of the membrane just touches the receptor fluid surface. The assembly was placed on a magnetic stirrer. The solution in the receptor compartment was constantly and continuously stirred at 50 rpm. The temperature of whole assembly was maintained at 37±0.5^{0}C by circulating water from a constant temperature inside the water jacket, Water bath having water at 37^{0}C. The samples were withdrawn at different time intervals up to 24hours and replenished with an equal volume of 0.1N HCl at each withdrawal. The absorbance of withdrawn samples duly diluted was measured at 217nm using U.V Spectrophotometer.

Differential scanning calorimetric (DSC) [21].

The DSC thermo gram was recorded using differential scanning calorimeter (TA-60 WS thermal analyszer, schimadzu japan). Approximately 2-5 mg of drug sample was heated in an aluminium (Al- crucibles, 40 AL) from 300 c t0 3000 c at a heating rate of 100 c / min under a stream of nitrogen a flow rate of 50 ml/min.

RESULT AND DISCUSSION

Preparation of the working standard solution:

Working standard solutions ranging in concentration from 5 to 30 mcg/ ml were prepared by appropriately diluting the standard solution with phosphate buffer pH 7.4. the absorbance of each working standard solution was measured at 217 nm using a shimadzu UV spectrophotometer using phosphate buffer of pH 7.4 as a blank. Data for each and every experiment was obtained in triplicates and statistically analyzed. The calibration curve for Captopril in phosphate buffer pH 7.4.

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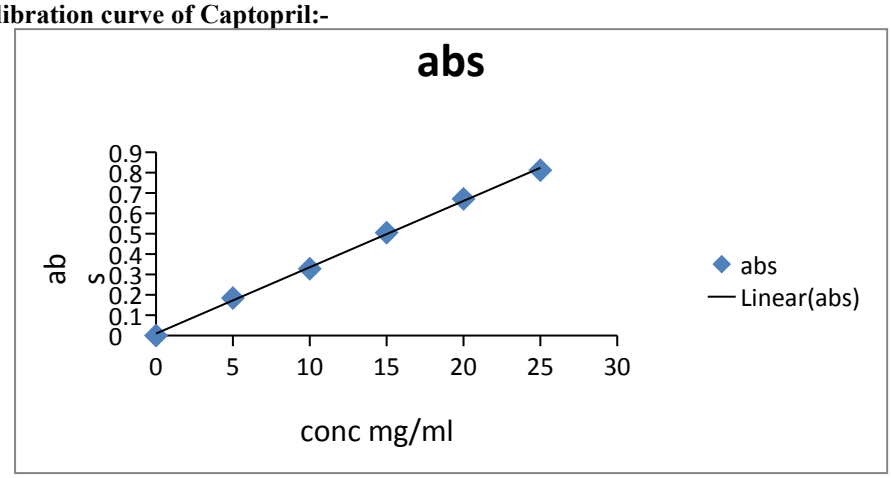
Table no 4. Conc. & abs. Obtained for calibration curve of Captopril in phosphate buffer pH 7.4.

Sr.No.	Concentration µg/ml	Absorbance
0	0	0
1	5	0.114
2	10	0.203
3	15	0.311
4	20	0.401
5	25	0.489
6	30	0.594

Standard Calibration curve of Captopril:-



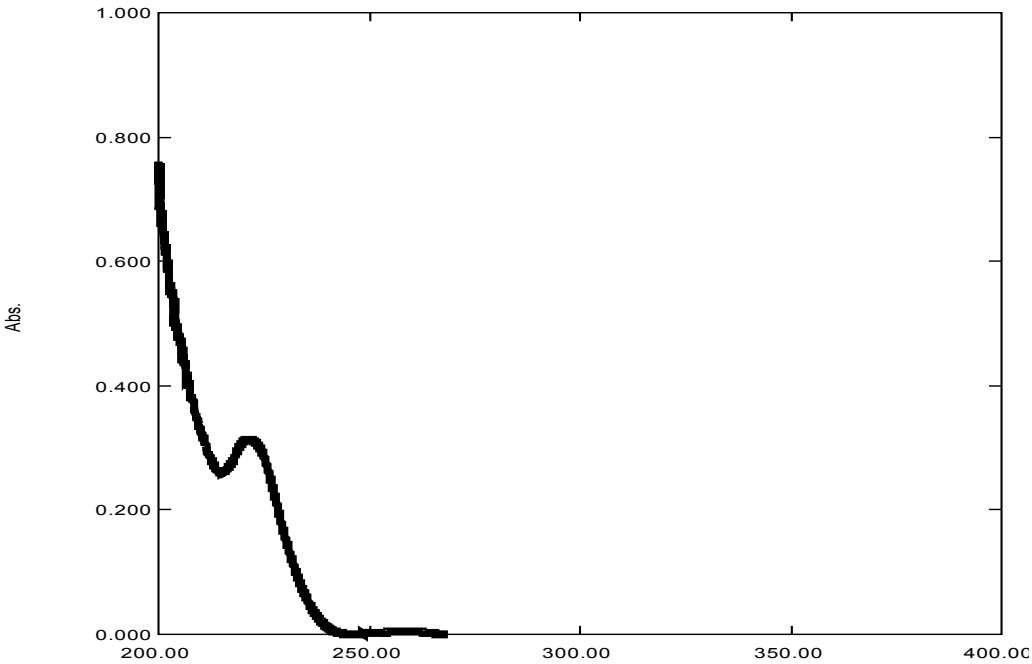


Fig No. 01: UV Spectra Of Captopril

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FTIR study

The FTIR of drug and physical mixture of formulation ingredients of optimized batch were measured using fourier Transformer infrared spectrophotometer. The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade. This mixture was then scanned over a wave number range of 4000 to 400 cm^{-1}

1. FTIR spectra of Captopril.

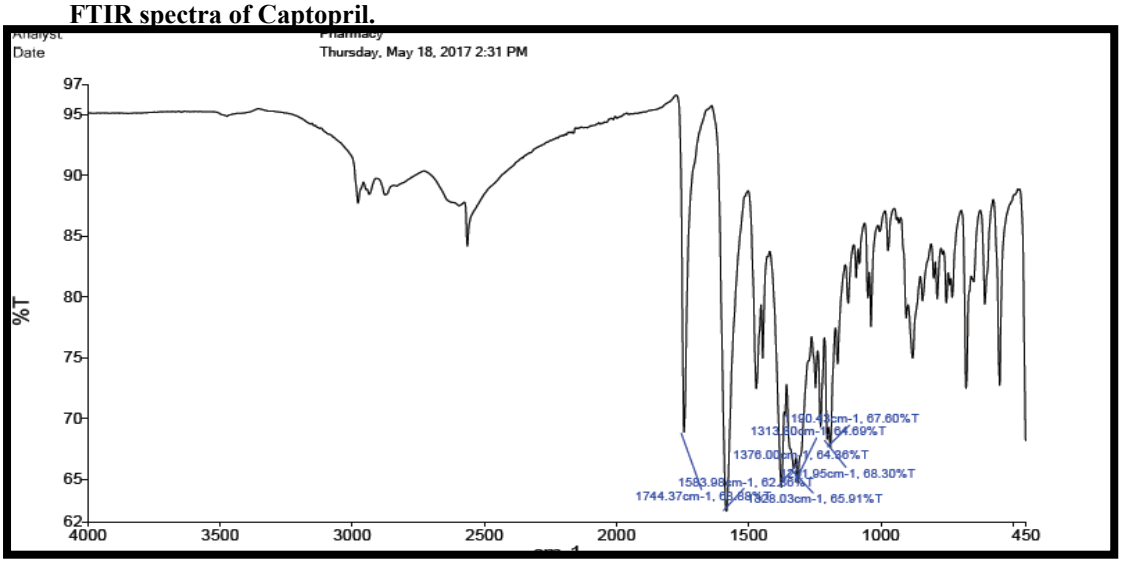

Figure. No 2: FTIR spectra of Captopril

2. FTIR spectra of Captopril + HPMC E15 +Eudragit RS100

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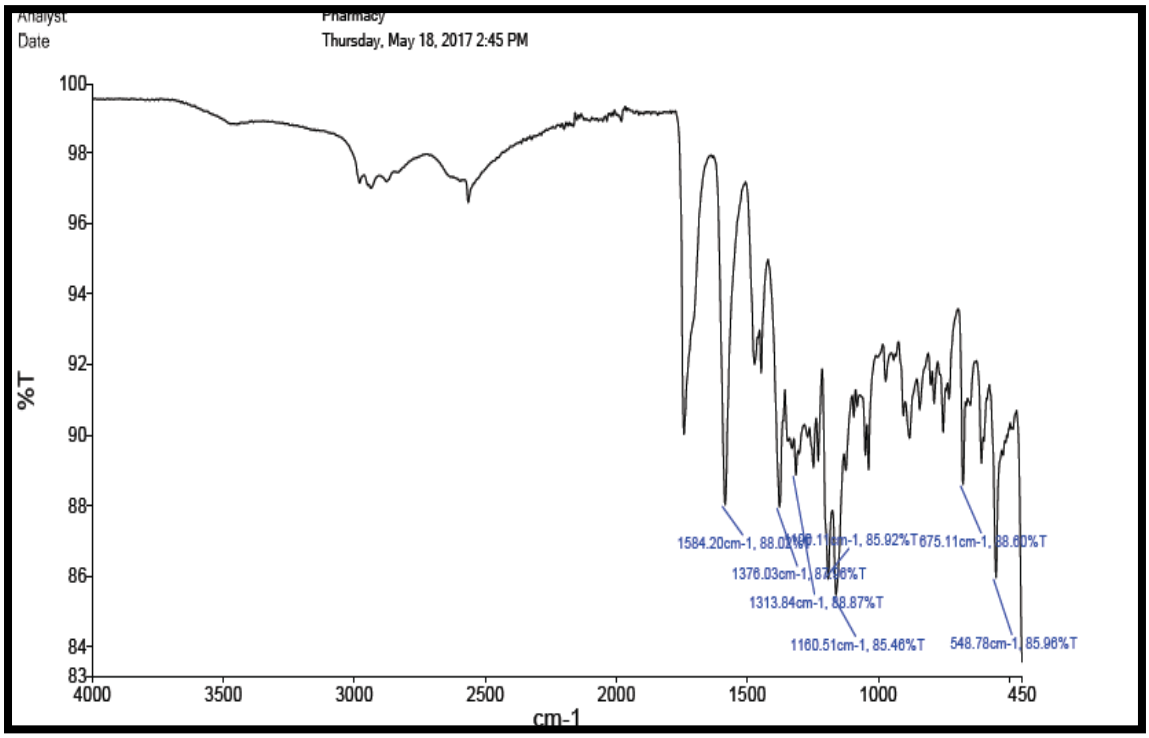

Figure. No 3: FTIR spectra of Captopril +HPMC E15 +Eudragit RS100

DSC study

The DSC thermograms of pure drug and optimized final formulation were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 100C/min over a temperature range of 400C to 3000C.

1. Captopril

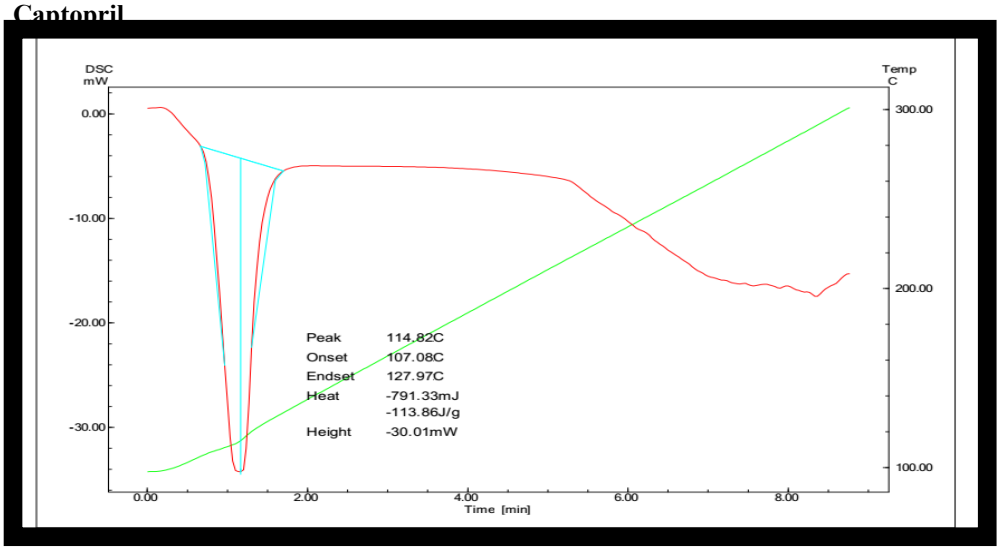

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Figure. No 4:DSC thermogram of Captopril

2. Captopril + polymer

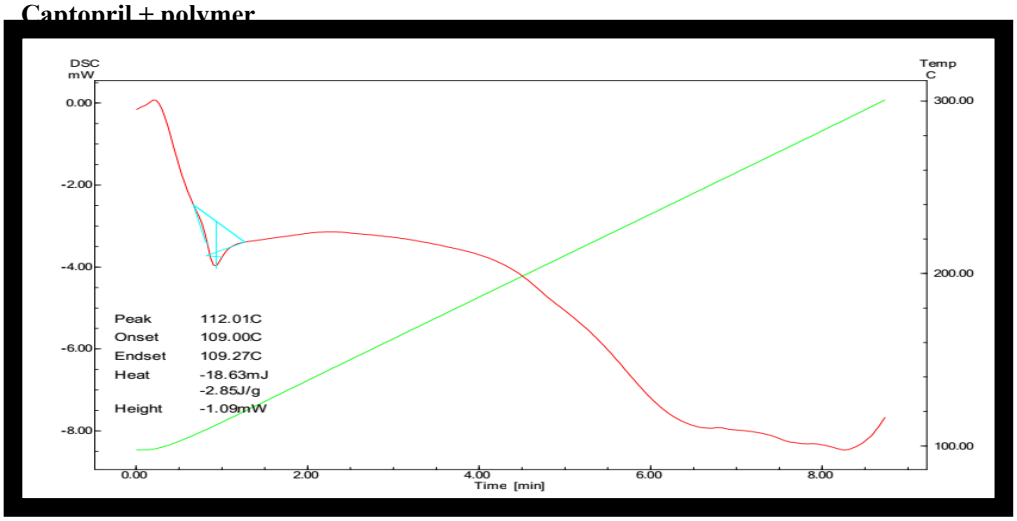

Figure. No. 5: DSC the thermogram of Captopril + polymer

In-vitro dissolution studies:

In present work, an attempt has been made to increase the % drug release of Captopril with changes in concentration of polymers & plasticizers by solvent casting method

Table no.5: In-vitro dissolution study of Captopril. [F1-F4].

Time (hr.)	% drug release			
	F1	F2	F3	F4
1	7.36	6.45	7.50	6.94
2	15.34	12.70	13.92	17.92
3	23.48	19.76	21.77	29.36
4	31.08	26.78	28.62	40.86
5	37.60	35.43	35.58	52.42
6	44.83	44.01	42.83	64.86
7	51.93	52.15	49.35	75.75
8	58.48	60.30	55.60	87.50

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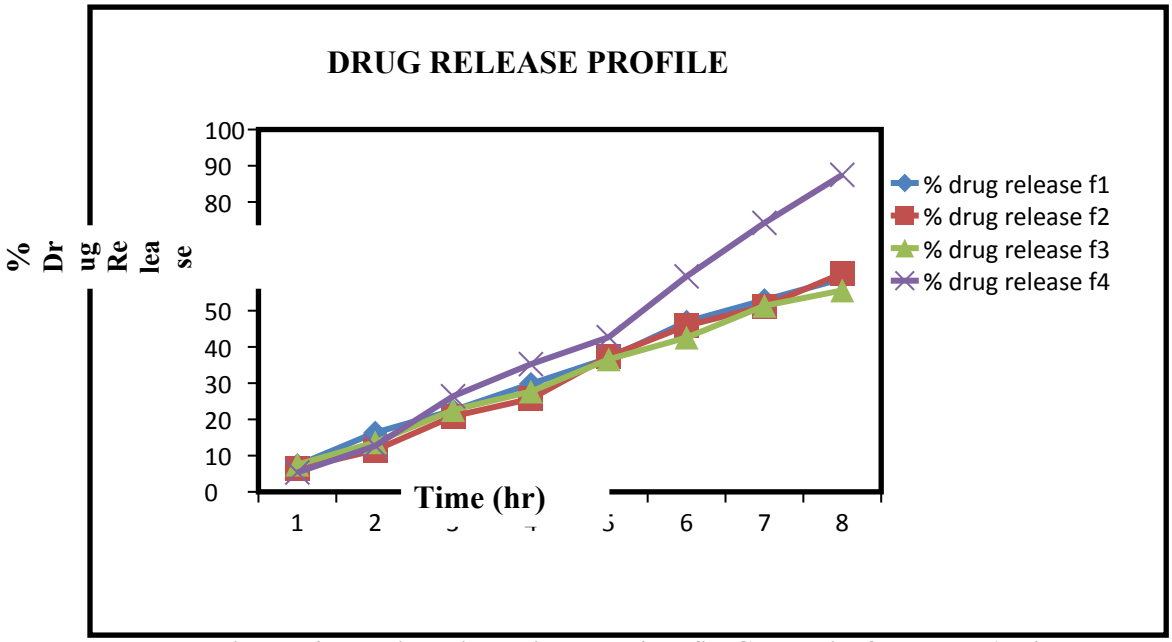

Fig. no. 6 : In- vitro dissolution study/ profile Captopril of batches F1-F4

Table no.6: In-vitro dissolution study of Captopril. [F5-F8].

Time (hr.)	% drug release			
	F5	F6	F7	F8
1	6.54	6.32	9.85	7.41
2	16.97	15.36	22.64	18.36
3	27.69	24.88	34.29	29.59
4	38.29	34.30	46.57	40.68
5	48.77	43.61	58.62	52.04
6	59.12	52.82	70.18	62.49
7	69.35	62.30	82.52	73.59
8	79.47	71.68	94.69	86.18

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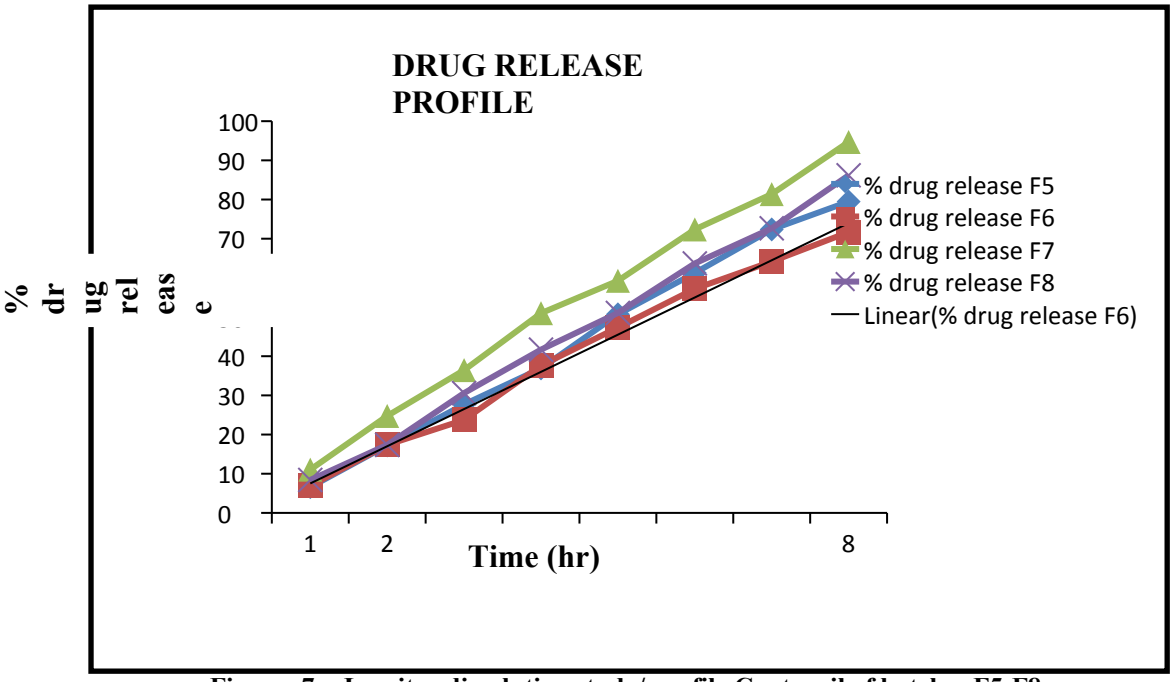

Fig. no. 7 : In- vitro dissolution study/ profile Captopril of batches F5-F8.

Table no.7: In-vitro dissolution study of Captopril. [F9-F10].

Time (hr.)	% drug release			
	F9	F10	F11	F12
1	6.13	8.20	7.35	6.54
2	17.10	20.09	18.32	17.91
3	27.73	32.45	30.17	28.95
4	38.41	44.47	42.08	40.04
5	49.15	57.36	53.66	51.20
6	59.95	69.13	66.10	62.42
7	70.81	82.14	77.80	73.29
8	81.73	96.02	90.79	85.03

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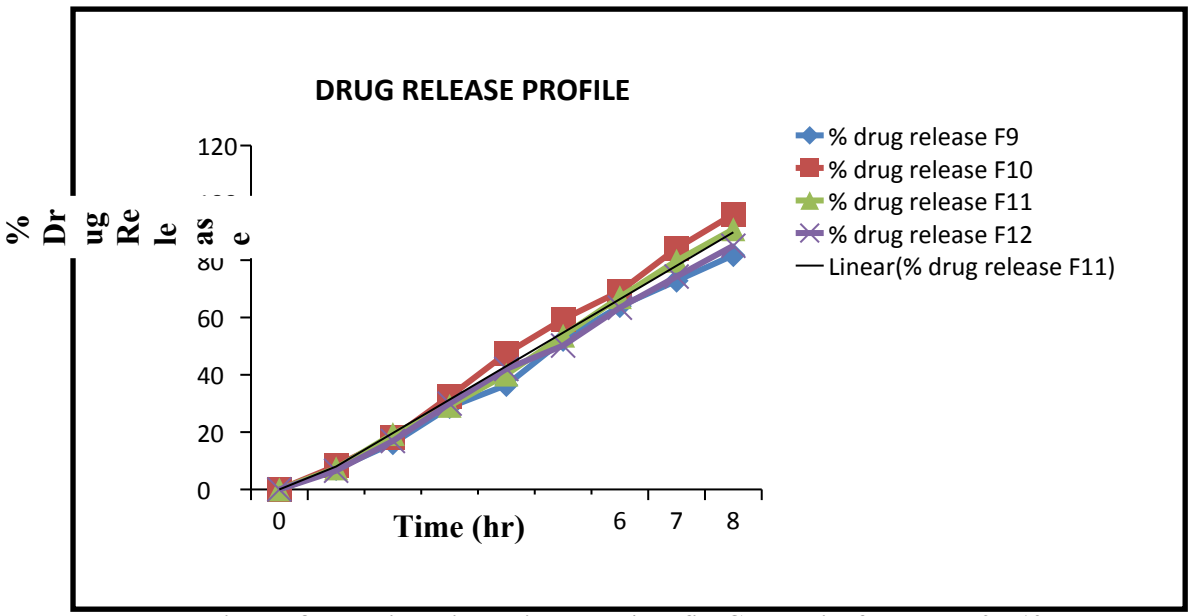

Fig. no. 8 : In- vitro dissolution study/ profile Captopril of batches F9-F12.

Table No.8: Permeability coefficients, flux of Captopril with different enhancers

SR.NO	ENHANCER	PERMEABILITY COEFFICIENT (cm/hr)	FLUX (µg/cm2/hr)
1	Pure drug	48.52	81.63
2	DMSO	72.95	178.61
3	DMF	80.18	204.00
4	Oleic Acid	94.78	216.80

Table No.9: Evaluation parameter of Transdermal patch

Batch code	Weight uniformity (g/cm2)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content uptake	Moisture Content loss
F1	0.040±0.0030	0.1733±0.005	97±1.24	95.36%	3.6031.56	4.7611.649
F2	0.0416±0.0015	0.21±0.01	108±1.63	97.89%	3.9671.37	5.0432.625
F3	0.040±0.0057	0.20±0.0057	104±3.74	102.69%	4.1661.44	4.3421.595
F4	0.039±0.001	0.19±0.0037	117±2.44	98.01%	4.2731.48	4.4771.598
F5	0.01308±0.001	0.18±0.0057	119±3.74	96.98%	5.2622.63	3.6511.644
F6	0.038±0.0016	0.18±0.0057	103±4.18	97.27%	6.1401.51	4.6001.644
F7	0.037±0.0015	0.17±0.0057	102±3.29	98.74%	5.4052.70	4.7351.695

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F8	0.0378±0.0015	0.17±0.0057	118±2.49	95.97%	5.4052.70	5.7713.023
F9	0.0383±0.0015	0.18±0.0057	109±2.94	96.32%	5.2622.63	5.6092.934
F10	0.0353±0.0015	0.16±0.0577	115±3.39	99.12%	5.7142.85	4.1031.853
F11	0.0356±0.0015	0.16±0.0057	106±1.24	97.41%	6.6661.64	5.0201.800
F12	0.0373±0.0015	0.17±0.01	110±2.16	96.45%	2.7022.70	3.7561.695

Skin Irritation Studies:

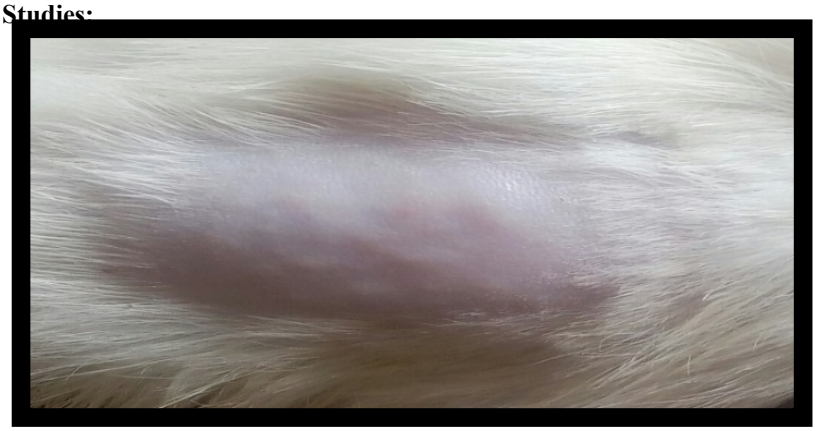

Fig.No.9: Rat skin after shaving

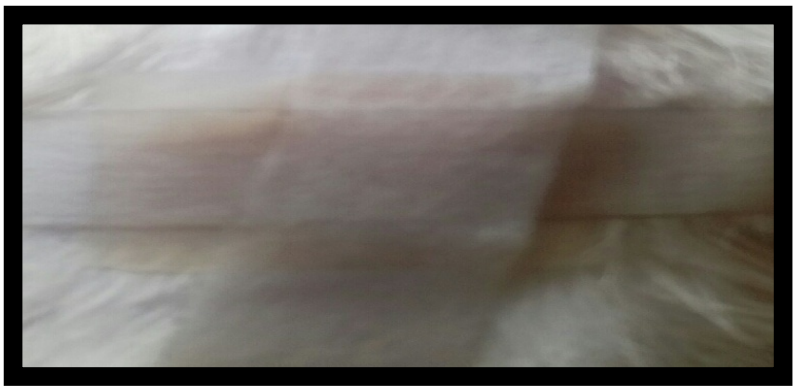

Fig.No.10: Rat skin after application of patch

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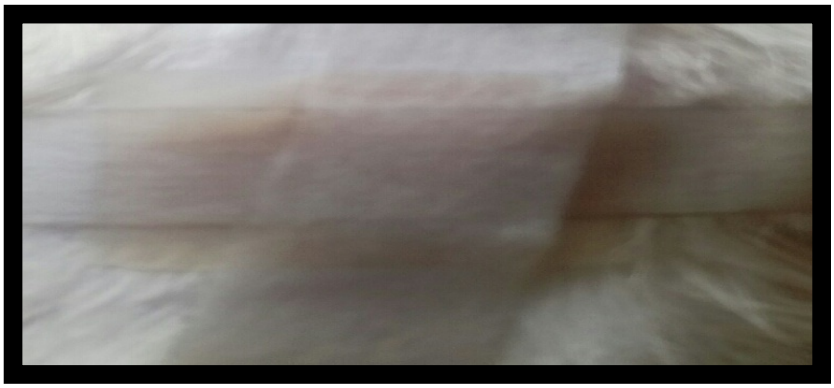

Fig.No.11: Rat skin after application of patch

There is no Erythma or Edema Found on Rat Skin.

Stability study

The stability study conducts by ICH guideline. It showed No significance change in properties of the optimized formulation & the drug release. Short term stability studies were performed in a Stability chamber over a period of 3 weeks (21 days) on the promising transdermal patch formulation F10.Sufficient number of films formulation were packed in stability container and kept in a Stability chamber at Temperature 450c & RH 75%. Samples were taken on 21st day for drug content estimation; also the thickness, weight, folding endurance and in-vitro disintegration studies were performed to determine the drug release profile.

Table no.10: accelerated stability study

Batch code	Weight uniformity (g/cm2)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content uptake	Moisture Content loss
F10 before stability	0.0353±0.0015	0.16±0.0577	115±3.39	99.12%	5.712.85	4.101.85
F10 After stability	0.035±0.0030	0.1533±0.005	97±1.24	97.36%	3.6031.56	4.7611.64

Table no.11: accelerated stability study % drug release

Sr.no.	Time (hr.)	Cum. % drug released ± S.D. 1st day	Cum. % drug released ± S.D. 21 st day
1	00	00	00
2	1	8.20	7.99

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3	2	20.09	19.68
4	3	32.45	31.52
5	4	44.47	44.12
6	5	57.36	56.71
7	6	69.13	68.96
8	7	82.14	81.98
9	8	96.02	95.35

III.

IV. CONCLUSION:-

Transdermal antihypertensive drug patch of Captopril were successfully formulated using solvent casting method. The process variables that could affect the film qualities were systematically investigated. Additionally, application of experimental design resulted into selection of significant factors that could affect the disintegration, dissolution and ultimate bioavailability of drug from film formulation. A film containing HPMC E15 (film forming polymer) and Eudragit RS100 (rate controlling polymer) at specific amount is desirable for prolong the drug release and specific amount of penetration enhancer with them help to diffusion of Captopril. The results of this study indicate that Captopril containing transdermal patch is a promising approach therapy to maximum bioavailability and prolong release of the drug.

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