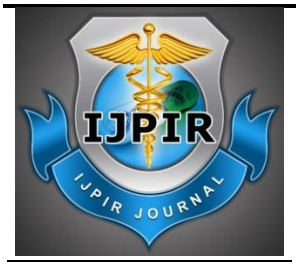
Research Article



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Formulation and evaluation of trimetazidine hydrochloride transdermal patches

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ABSTRACT

Angina is usually caused by an underlying obstruction to the coronary artery due to atherosclerosis. The most common symptom is chest pain that occurs behind the breastbone or slightly to the left of it. The pain of stable angina usually begins slowly. The current aim focuses on to fabricate Trimetazidine Hydrochloride monolithic transdermal films using various polymers like chitosan, Hydroxypropylmethylcellulose, Polyvinyl alcohol, Methyl cellulose and Ethyl cellulose. The results shows that the marketed tablet released 96.41% of drug in 40 minutes and whereas the formulation F3 released 92.10% in 24 hrs. Thus prepared transdermal formulation controls and releases the drug in a controlled manner compared to the faster release of drug by marketed product. Consequently, transdermal patches of Trimetazidine hydrochloride showed promising results under *in- vitro* conditions and thus there exist a scope for evaluation of the developed transdermal patches on suitable models.

Keywords: Trimetazidine Hydrochloride, Transdermal films, *Invitro* release and markedly product comparison.

INTRODUCTION

Angina results when there is an imbalance between the heart's oxygen demand and supply. This imbalance can result from an increase in demand without a proportional increase in supply[2]. Ischaemic heart diseases are nothing but angina

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pectoris, coronary thrombosis, myocardial infarction, arteriosclerotic heart disease, etc. Non-specific heart diseases are heart failure, cardiac dropsy, organic heart disease, myocarditis [1-8].

According to estimates, cases of cardio vascular disease (CVD) in India may increase from about 2.9 crore in 2000 to as many as 6.4 crore in 2015 and the number of deaths from CVD will also be more than double. Reports on the prevalence or incidence of ischemic heart disease (IHD) in developing countries include India are scare. By share in the burden of diseases, 31% constitutes cardiovascular diseases. Most of this increase will occur on account of coronary heart disease a mix of conditions that includes acute myocardial infarction, angina pectoris, congestive heart failure and inflammatory heart disease.

Causes

Angina is usually caused by an underlying obstruction to the coronary artery due to atherosclerosis. In some cases, it is caused by spasm that occurs naturally or as a result of ingesting cocaine. In rare cases, angina is caused by a coronary embolism or by a disease other than atherosclerosis that places demands on the heart. Most episodes of angina are brought on by physical exertion, when the heart needs more oxygen than is available from the blood nourishing the heart. Emotional stress, extreme temperatures, heavy meals, cigarette smoking, and alcohol can also cause or contribute to an episode of angina.

PHYSICOCHEMICAL PROPERTIES

Structural formula

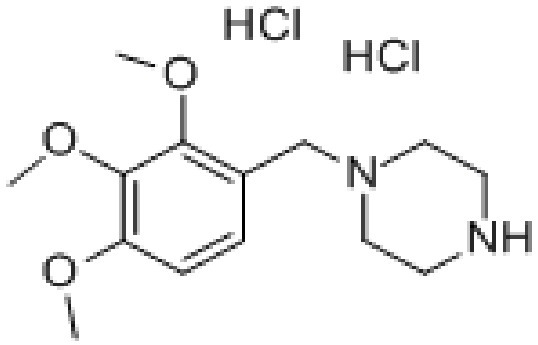

Fig. 1: Trimetazidine Hydrochloride

IUPAC Name : 1-[(2,3,4-Trimethoxybenzyl) piperazine dihydrochloride
Empirical formula : $C_{14}H_{24}Cl_2N_2O_3$
Molecular weight : 339.26 (gm/mol)
Category : Anti-anginal agent
Description : A white Crystalline Solid substance.
Solubility : Soluble in water and slightly soluble in methanol.
Melting point : 231-235 º C
Pharmacokinetic Data
Bioavailability : Approximately 80%
Protein binding : 16%
Half-life : 6 hrs
Excretion : via urine, mainly as unchanged drug.
Absorption : Rapidly absorbed.
pKa : 8.42
$P_{o/w}$: 1.04

Mechanism of action

Trimetazidine is a cellular acting anti-ischaemic agent. It has 3 main properties by which it acts as a cytoprotective agent. It inhibits the anaerobic glycolysis and fatty acid metabolism, thus allowing only aerobic glycolysis [9-20].

MATERIALS AND METHODS

Materials

All the materials used in the formulation and evaluation are procured from reliable vendors only, Trimetazidine hydrochloride, Gift sample, East west pharma Pvt. Ltd, Chennai, HPMC, Colorcon Ltd, Goa. All other excipients are from S.D Fine Chemicals, Mumbai.

Preparation of standard graph

The standard solution was prepared by dissolving 100 mg of Trimetazidine hydrochloride in phosphate buffer of pH 7.4 in 100 ml volumetric flask and the volume was made up to mark with the respective medium. The standard solution was subsequently diluted with the same media to obtain a series of dilutions containing 0, 50, 100, 150, 200, 250, 300, 350 and 400 µg/ml of drug. The absorbance of these dilutions was measured using UV spectrophotometer at 270 nm using the respective medium as a blank.

Preparation of Transdermal Patches

The transdermal patches of Trimetazidine hydrochloride were prepared by employing different polymers like Carboxymethyl chitosan, HPMC 5CPS, PVA 35cps and MC 50 cps. EC 20 cps was used for preparing rate limiting membrane by solvent casting method.

Preparation of drug reservoir

The polymeric solution was prepared by dissolving the required quantity of polymer in distilled water (3 ml) and glycerine (30% w/w of polymer) was added as plasticizer to this solution under stirring. The weighed amount of Trimetazidine hydrochloride was added to the above solution. After proper mixing the casting solution was poured in a clean glass bangle (an area of 9.61 cm^2) which was placed on the mercury surface. The patches were dried at room temperature for 24 hrs. The dried patches thus obtained were cut by cork borer into circular discs of definite size of 20 mm diameter (an area of 1.539 cm^2) containing 40 mg of drug [21-35].

Table 1: Composition of Trimetazidine hydrochloride transdermal patches using individual polymers.

Formulation code	Drug	Polymer				Drug-polymer Ratio	Plasticizer	Rate Limiting Membrane
	Trimetazidine(mg)	Carboxy methyl chitosan (mg)	HPMC 5cps (mg)	PVA 35cps (mg)	MC 50cps (mg)		Gylcerine 30% of w/w of polymer(ml)	Ethyl Cellulose (% w/v)
F1	240	240	---	---	---	1:1	0.058	2
F2	240	360	---	---	---	1:1.5	0.084	2
F3	240	480	---	---	---	1:2	0.116	2
F4	240	---	240	---	---	1:1	0.058	2
F5	240	---	360	---	---	1:1.5	0.084	2
F6	240	---	480	---	---	1:2	0.116	2
F7	240	---	---	240	---	1:1	0.058	2
F8	240	---	---	360	---	1:1.5	0.084	2

F9	240	---	---	480		1:2	0.116	2
F10	240	---	---	---	240	1:1	0.058	2
F11	240	---	---	---	360	1:1.5	0.084	2
F12	240	---	---	---	480	1:2	0.116	2
Casting Solvent		Water (3 ml)						Chloroform

Table 2: Composition of Trimetazidine hydrochloride transdermal patches using combination of polymers.

Formulation code	Drug	Polymer				Drug-polymer Ratio	Plasticizer	Rate Limiting Membrane
	Trimetazidine(mg)	Carboxy methyl chitosan (mg)	HPMC5cps (mg)	PVA 35cps (mg)	MC 50cps (mg)		Gylcerin(30% of w/w of polymer(ml)	Ethyl Cellulose (% w/v)
F13	240	240	240	---	---	1:2	0.116	2
F14	240	240	---	240	---	1:2	0.116	2
F15	240	240	---	---	240	1:2	0.116	2
F16	240	---	240	240	---	1:2	0.116	2
F17	240	---	240	---	240	1:2	0.116	2
F18	240	---	---	240	240	1:2	0.116	2
Casting Solvent		Water (3ml)						Chloroform

IN-VITRO RELEASE STUDIES

A vertically assembled Franz diffusion cell having downstream volume of 75 ml was used. The cellophane membrane was mounted on the diffusion cell and receiver compartment was filled with 75 ml phosphate buffer of pH 7.4 and the temperature was maintained at $37^0C \pm 0.5^0C$. 5 ml of sample was withdrawn every hour and replaced with 5 ml fresh buffer to maintain sink condition and their concentration was measured in UV - spectrophotometer at 270 nm. The *in-vitro* release profile of optimized formulation will be compared with that of a marketed product.

In-vitro permeation study of optimized transdermal patch across rat abdominal skin;

Preparation of the rat skin

The experiment was conducted according to the protocol approved by the institutional animal ethics committee (IAEC). The experiment was conducted according to the guidelines of CPCSEA (Committee for the purpose of control and supervision of experiment on animal). The male albino rats were sacrificed by decapitation. The fresh abdominal skin was excised from male albino rat weighing 170-190 g. The abdominal skin of excised hairless rat skin was separated along the epidermal junction. The hair of skin was removed using depilatories. The process of the removal of hair did not alter the skin properties and delivery of the drug. It was kept at water bath maintained 60^0C for exactly 50 sec. The heat

treated skin was cleared of it subcutaneous fatty substance and immediately kept in refrigerator at 10^0C. This step maintained integrity and viability of the skin [35-42].

Skin irritation studies

The skin irritation test was performed on twelve healthy albino rabbits weighing between 2.0 to 2.5 kg. Six rabbits each were used for testing drug reservoir and rate limiting patches. The rabbits were shaved on left and right dorsal surfaces. Aqueous solution of formalin 0.8% was used as standard irritant. Drug reservoir and rate limiting patches of 1 cm^2 were used as test patches. 0.8% of formalin was applied on the left dorsal surface of each rabbit, where as the test patches were placed on identical site, on the right dorsal surface of the rabbit. The patches were removed after a period of 24 hrs with the help of alcohol swab. The skin response was examined and was scored using Draize Evaluation of Dermal Reactions for erythema and edema for each rabbit at the end of 24 hrs. The average value was calculated which gives the Primary Dermal Irritation Index (PDII). The Draize evaluation of dermal reactions with the scores and PDII are given below:

Fourier transformer infrared spectroscopy (FTIR) study

The compatibility between drug and polymer was detected by FTIR spectra obtained on (Bruker, Canada). The pellets were prepared on KBr-press (Spectra lab, India). The spectra were recorded over the wave number range of 4000 to 500 cm^{-1}.

Differential scanning calorimeter (DSC) study

Thermograms were obtained by using a differential scanning calorimeter (Q20 V24.4, TA instrument) at a heating rate of 10^oC/min over a temperature range of 0- 400^oC. The sample was hermetically sealed in an aluminum crucible. Nitrogen gas was purged at the rate of 10 ml/min for maintaining inert atmosphere.

Stability Studies

The selected transdermal patch were wrapped with aluminum foil and stability studies were carried out according to ICH guidelines at $25^0\pm2^0$C/60%±5%, $30^0\pm2^0$C/65%±5%, 40 ± 2^oC/75±5% RH for three months in stability chamber. [43-50].

RESULTS AND DISCUSSION

Calibration Curve for the Estimation of Trimetazidine Hydrochloride

Table 3: Calibration curve for the estimation of Trimetazidine hydrochloride in pH 7.4 buffer

Sl. No	Concentration (µg/ml)	Absorbance at 270 nm*
1	0	0
2	50	0.112
3	100	0.22
4	150	0.345
5	200	0.484
6	250	0.601
7	300	0.703
8	350	0.841
9	400	0.946
Regression data	m	0.002
	c	0.007
	r	0.999

*Average of three determinants

Where, **m** = slope, **c** = intercept and **r** = correlation co-efficient

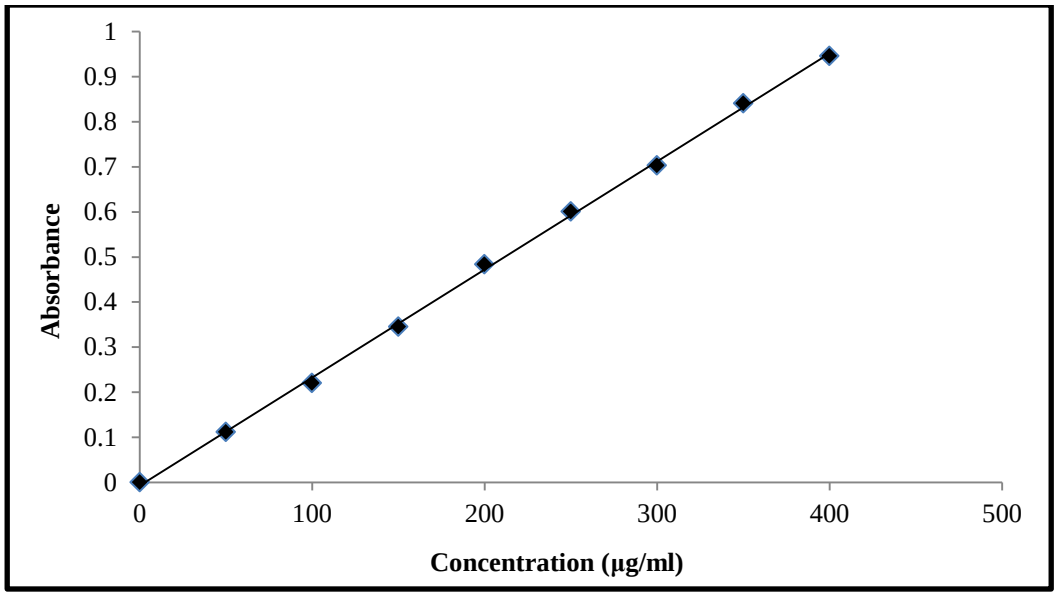

Fig. 2: Calibration curve of Trimetazidine hydrochloride in phosphate buffer of pH 7.4

Table 4: Preformulation studies of Trimetazidine hydrochloride

Studies	Identification (UV)	Melting point (^{o}C)	Solubility	Partition co-efficient	Permeability co-efficient
Results	270	235^{o}C	1.5 gm/ml	1.01	4.5
Reported [31,60,61]	269	231-235^{o}C	--	1.04	--

Physical appearance

All the patches prepared with different polymer concentration were found to be flexible, smooth, opaque, non-sticky and homogeneous in nature.

Table 5: Physicochemical evaluation of Trimetazidine hydrochloride transdermal patches.

Formulation code	Thickness* (mm)	Weight variation* (mg)	Folding endurance†	% Moisture Absorption*	% Moisture Loss*	Tensile strength* (Kg/mm^2)	% Drug content*
F1	0.60±0.01	81.18±0.44	140	9.87±0.12	9.60±0.18	0.130±0.01	**93.50±0.23**
F2	0.71±0.01	106.1±0.39	110	8.49±0.23	7.54±0.28	0.146±0.03	**93.05±0.75**
F3	0.78±0.02	119.2±0.35	152	8.40±0.21	8.45±0.11	0.172±0.03	**95.32±0.11**
F4	0.61±0.01	82.44±0.32	90	12.1±0.32	9.54±0.12	0.132±0.02	**92.87±0.12**
F5	0.70±0.02	105.4±0.20	67	12.3±0.21	8.66±0.23	0.152±0.01	**92.60±0.13**
F6	0.82±0.01	121.3±0.32	60	13.0±0.23	8.75±0.21	0.170±0.02	**93.75±0.20**
F7	0.62±0.01	81.44±0.22	97	8.49±0.23	8.49±0.23	0.135±0.01	**91.20±0.33**
F8	0.68±0.02	100.4±0.12	80	8.40±0.21	8.40±0.21	0.150±0.02	**93.25±.21**
F9	0.74±0.01	120.3±0.38	76	9.67±0.11	9.47±0.13	0.163±0.01	**93.75±36**

*Average of three determinations± SD, †n =3.

Table 6: Physicochemical evaluation of Trimetazidine hydrochloride transdermal patches.

Formulation code	Thickness* (mm)	Weight variation* (mg)	Folding endurance†	% Moisture absorption*	% Moisture loss*	Tensile strength* (Kg/mm^2)	% Drug content*
F10	0.62±0.01	**80.50±0.32**	110	9.64±0.23	9.87±0.18	**0.121±0.05**	94.60±0.11
F11	0.70±0.02	104.4±0.20	115	9.49±0.26	8.44±0.24	0.132±0.06	93.60±0.26
F12	0.77±0.01	122.3±0.23	106	9.40±0.23	8.90±0.28	0.148±0.03	92.75±0.20
F13	0.72±0.01	120.2±0.42	112	9.87±0.17	9.87±0.12	0.165±0.01	93.20±0.23
F14	0.73±0.01	121.1±0.33	120	9.20±0.54	8.49±0.27	0.171±0.02	93.75±0.20
F15	0.73±0.01	120.7±0.41	101	9.30±0.41	8.40±0.29	0.158±0.02	94.20±0.21
F16	0.76±0.01	119.3±0.34	85	8.23±0.32	**9.87±0.12**	0.161±0.01	93.1±0.34
F17	0.76±0.02	121.4±0.39	96	9.12±0.23	8.49±0.26	0.161±0.02	93.6±0.22
F18	0.78±0.01	**121.6±0.32**	88	9.22±0.22	8.40±0.24	0.152±0.02	94.2±0.43

*Average of three determinations ±SD, †n =3.

Table 7: *In-vitro* drug release profile of Trimetazidine hydrochloride transdermal patch F1.

S. no	Time (hrs)	Absorbance	Concentration	Dilution factor	Amount in 5 ml aliquots	Amount in 75 ml	Cumulative loss accumulated	Cumulative drug released	% Cumulative drug released
1.	0	0	0	0	0	0	0	0	0
2.	1	0.256	128	1	0.64	9.6	0	9.6	24
3.	2	0.289	144.5	1	0.72	10.83	1.36	12.2	30.5
4.	3	0.357	178.5	1	0.89	13.38	2.25	15.64	39.10
5.	4	0.498	249	1	1.24	18.67	3.5	22.17	55.43
6.	6	0.576	288	1	1.44	21.6	4.94	26.54	66.35
7.	8	0.673	336.5	1	1.68	25.23	6.62	31.86	79.65
8.	10	0.7	350	1	1.77	26.62	8.39	35.02	87.55
9.	12	0.711	355	1	1.75	26.25	10.14	36.39	90.99

*Average of three determinations.

Table 8: *In-vitro* drug release profile of Trimetazidine hydrochloride transdermal patches.

Time (hrs)	Cumulative percentage of drug released*								
	F1 (CH) 1:1	F2 (CH) 1:1.5	F3 (CH) 1:2	F4 (H) 1:1	F5 (H) 1:1.5	F6 (H) 1:2	F7 (PVA) 1:1	F8 (PVA) 1:1.5	F9 (PVA) 1:2
0	0	0	0	0	0	0	0	0	0
1	24	20.7	20.4	18.0	18.9	17.0	20.0	22.7	21.6
2	30.5	26.6	31.3	32.3	30.4	30.3	31.5	23.5	24.7
3	39.1	35.1	35.7	39.3	39.7	36.5	41.2	29.0	32.7
4	55.4	39.3	41.2	46.3	48.7	41.5	47.6	35.1	40.4
6	66.3	48.5	48.9	57.9	62.4	45.7	55.0	41.5	46.2
8	79.6	62.2	55.7	65.0	70.4	51.2	66.9	49.3	52.7
10	87.5	72.6	61.6	71.1	77.8	61.7	79.1	59.0	63.3
12	90.9	82.4	70.5	89.7	83.7	68.9	90.6	76.8	74.2

16	--	89.9	77.4	--	89.4	77.0	--	89.1	80.2
20	--	--	84.2	--	--	84.3	--	--	85.8
24	--	--	**92.1**	--	--	90.9	--	--	90.8

*Average of three determinations. CH= Carboxymethyl chitosan, H= Hydroxypropylmethylcellulose

Table 9: *In-vitro* release profile of Trimetazidine hydrochloride transdermal patches.

Time (hrs)	**Cumulative percentage of drug released***								
	F10 (MC) 1:1	**F11 (MC) 1:1.5**	**F12 (MC) 1:2**	**F13 (CH+H)**	**F14 (CH+PVA)**	**F15 (CH+MC)**	**F16 (H+PVA)**	**F17 (H+MC)**	**F18 PVA+MC)**
0	0	0	0	0	0	0	0	0	0
1	18.5	18.9	19.6	18.3	17.1	16.1	18.8	20.4	19.7
2	28.3	24.4	22.4	28.4	29.5	30.1	23.5	31.3	25.6
3	32.4	31.4	29.7	32.4	34.0	36.5	29.1	35.7	30.6
4	41.3	44.7	36.7	37.5	39.2	42.6	35.3	41.2	39.07
6	54.4	53.7	42.0	44.4	48.9	49.8	41.9	48.9	45.6
8	65.5	60.6	47.9	50.6	53.8	55.2	47.8	55.7	52.4
10	75.9	72.9	62.4	60.3	58.9	61.3	56.2	61.6	63.0
12	90.0	79.0	73.1	67.6	66.8	67.4	62.1	70.5	72.6
16	--	88.6	81.4	74.6	74.1	75.5	70.2	77.4	78.5
20	--	--	86.7	83.3	83.7	84.3	79.7	84.2	84.5
24	--	--	91.4	91.2	89.5	90.0	89.3	90.2	90.1

*Average of three determinations. CH= Carboxymethyl chitosan, H= Hydroxypropylmethylcellulose

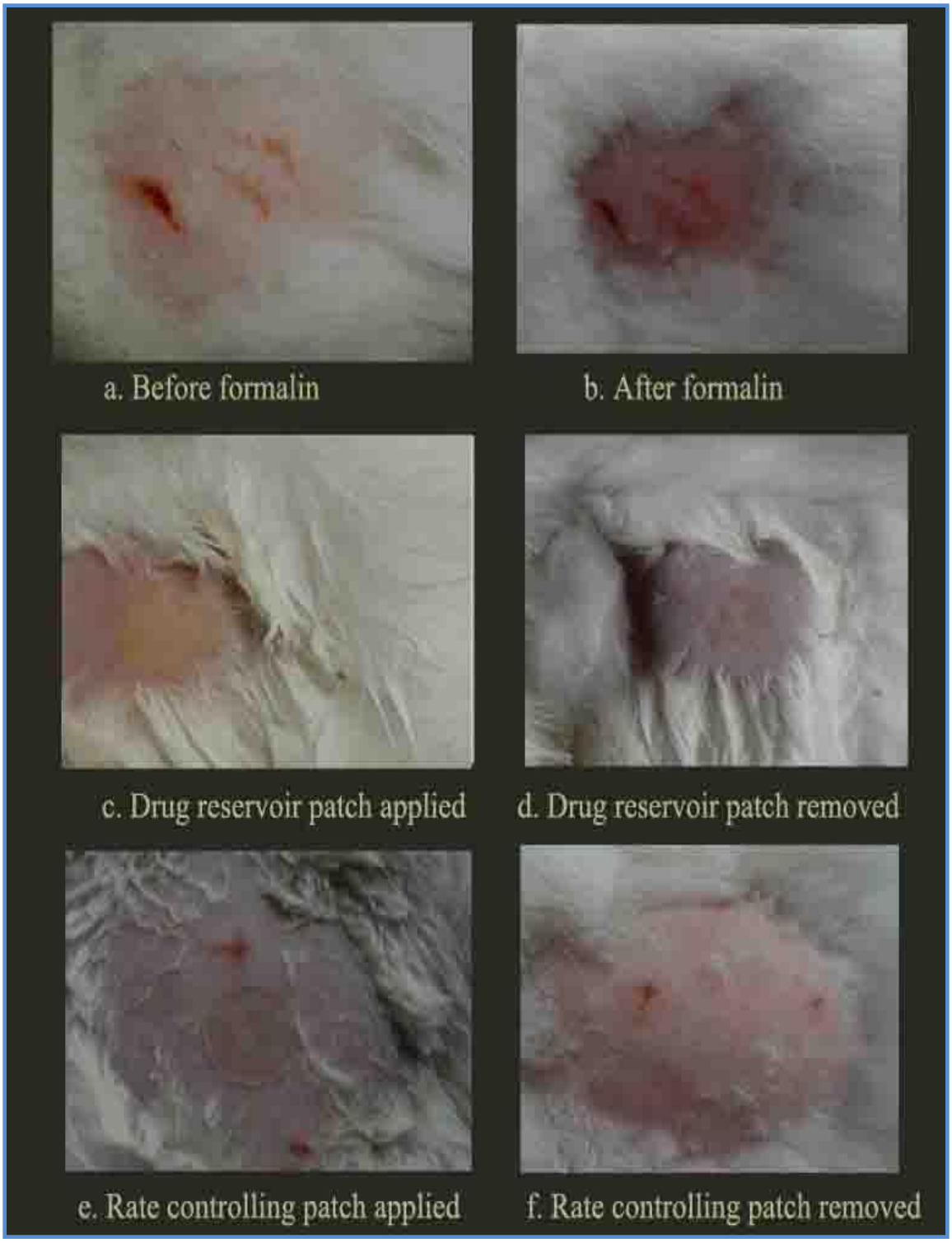

Fig. 3: Photograph of skin irritation studies on rabbit skin.

Draize Evaluation of Dermal Reactions

Skin Reactions	**Score**
Erythema Formation (Most severely affected area graded):	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema Formation (Most severely affected area graded):	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (Edges of area well defined by definite raising)	2
Moderate edema (Raising approximately 1 millimeter)	3
Severe edema (Raised more than 1 mm and extending beyond the area of exposure)	4

The resulting Primary Dermal Irritation Index (PDII) was classified as follows:

PDII	**Classification**
<0.5	Non-irritating
0.5 – 2.0	Slightly irritating
2.1 – 5.0	Moderately irritating
>5.0	Severely irritating

Table 10: PDII values obtained from the observation of the rabbit skin, are given below:

Subject	**Erythema**		**Edema**	
	Intial*	**Final***	**Intial***	**Final***
Formalin 0.8%	0	**2**	0	0
Drug reservoir patch	0	0	0	0
Rate limiting patch	0	0	0	0

*Average of 6 readings

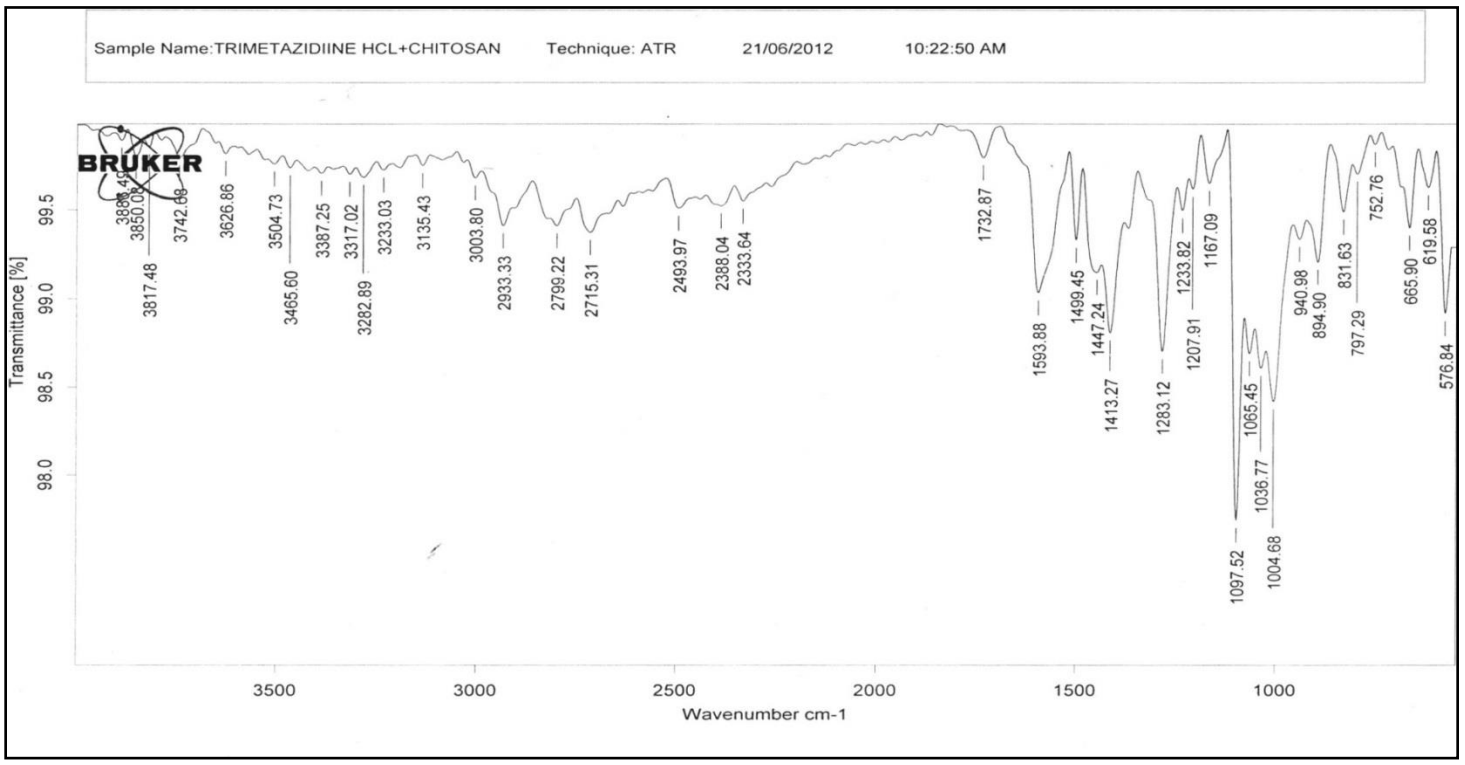

Fig. 4: FTIR spectra of Trimetazidine hydrochloride transdermal patch F3 (TMZ+CH).

Table 11: Stability study of Trimetazidine hydrochloride optimized transdermal patch F3 after a period of three months.

Temperature and relative humidity	Physical appearance	Weight variation* (mg)		Drug content* (mg)		$T_{50\%}$ (hrs)		$T_{90\%}$ (hrs)	
	After	Before	After	Before	After	Before	After	Before	After
$25^0\pm2^0$C/60%±5%	No change	119.2±0.35	119.1±0.30	95.32±0.11	95.22±0.20	6.13	6.12	23.46	23.44
$30^0\pm2^0$C/65%±5%	No change	119.2±0.35	117.2±0.21	95.32±0.11	94.10±0.14	6.13	6.11	23.46	23.47
$40^0\pm2^0$C/75%±5%	No change	119.2±0.35	112.2±0.21	95.32±0.11	93.44±0.31	6.13	6.11	23.46	23.96

*Average of three determinations ± SD.

Table 12: *In-vitro* release profile of Trimetazidine hydrochloride optimized transdermal patch F3 after stability studies for 3 months.

Time (hrs)	Fresh F3	F3* at $25^0\pm2^0$C/60%±5%RH	F3* at $30^0\pm2^0$C/65%±5%	F3* at $40^0\pm2^0$C/75%±5%
0	0	0	0	0
1	20.43	20.43	20.53	20.34
2	31.36	31.36	32.46	32.35
3	35.73	35.73	35.41	35.39
4	41.26	42.668	42.81	42.80
6	48.91	49.00	49.06	49.04

8	55.70	55.79	54.65	54.63
10	61.65	61.74	61.62	60.60
12	70.5	70.58	70.562	69.38
16	77.40	77.49	77.46	77.41
20	84.23	84.31	84.29	83.65
24	92.15	92.09	92.01	90.14

*Average of three determinations.

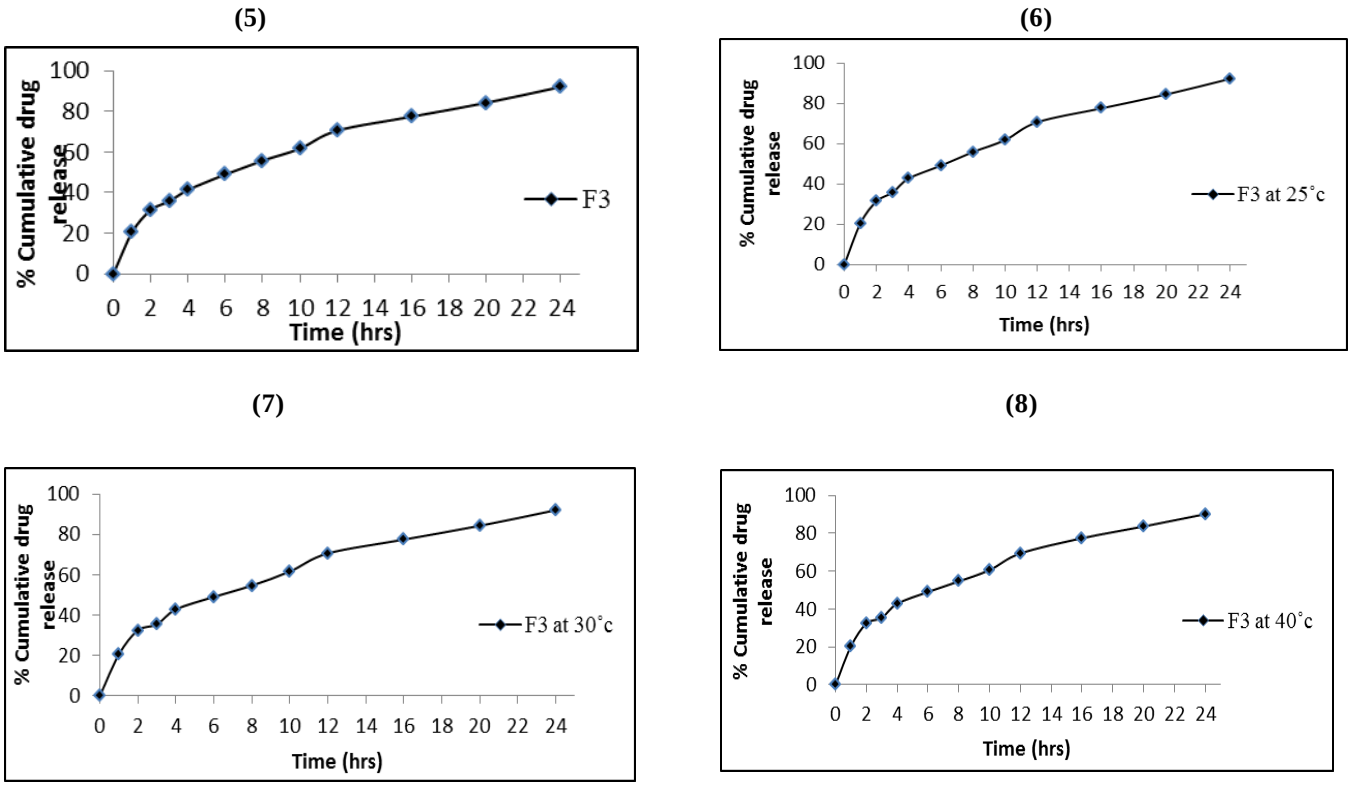

Fig. 5, 6, 7, 8: *In-vitro* release of Trimetazidine hydrochloride optimized transdermal patch F3 after stability studies for three months.

In- vitro release study

The *in-vitro* release study was done by using vertically assembled Franz diffusion cell having a downstream volume of 75 ml. Cellophane membrane was mounted in between donor and receptor compartment. The receptor compartment was filled with 75 ml of phosphate buffer pH 7.4 and temperature was maintained at 37± 1ºC. The transdermal patches prepared by using different drug reservoir polymers like carboxymethylchitosan HPMC, PVA and MC (in different drug: polymer ratio i.e., 1:1, 1:1.5 and 1:2) and EC (2% w/v) were analyzed for *in-vitro* release studies. The formulations F1, F4, F7 and F10 (drug: polymer ratio 1:1) containing carboxymethylchitosan, HPMC, PVA and MC as polymers released 90.9, 89.7, 90.6 and 90.0% of drug respectively, for a period of 12 hrs (Table 9 & 10. Fig. 10, 11, 12 & 13). Similarly formulations F2, F5, F8 and F11 (drug: polymer ratio 1:1.5) containing carboxymethylchitosan, HPMC, PVA and MC as polymers released 89.9, 89.4, 89.1 and 88.6% of drug respectively, for a period of 20 hrs.

FTIR Study

As described earlier IR spectra of drug and its formulation is one of the techniques used for characterization of formulations. It is mainly based on the values of characteristics absorption bands for different functional groups and various bonds present in drug molecule. Hence it may be concluded that there is no interaction of the drug with the polymers used for the study.

Stability studies

The stability studies were carried out for the optimized formulation (F3) at 25±2^{0}C/60±5%RH, 30±2^{0}C/65±5%RH and 40±2^{o}C/75±5% RH as per ICH guidelines for a period of three months. These samples were analyzed every four weeks. The optimized transdermal patches were evaluated for their appearance, weight variation, drug content and drug release study shows the values of physicochemical parameters before and after stability studies. No significant changes in the appearance, weight of the transdermal patches was observed during the stability study. The drug content of F3 after stability studies was found to be 95.22, 94.10 and 93.44% respectively at different temperatures and relative humidity.

CONCLUSION

From this current research it has been observed that, the Formulation F3 (Carboxymethyl chitosan as drug reservoir polymer, EC as rate limiting membrane and glycerin as plasticizer) released highest percentage of drug i.e., 92.1% of drug in 24 hrs compared to other formulations in *in-vitro* release studies and was considered as optimized formulation. Formulation F3 gives prolonged release of drug as compared to the marketed film coated tablet, TRIVEDON-20. Selected transdermal patches were found to be stable with respect to appearance, weight variation, drug content and *in-vitro* release profiles during the stability study period. Therefore, transdermal patches of Trimetazidine hydrochloride showed promising results under *in- vitro* conditions and thus there exist a scope for evaluation.

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