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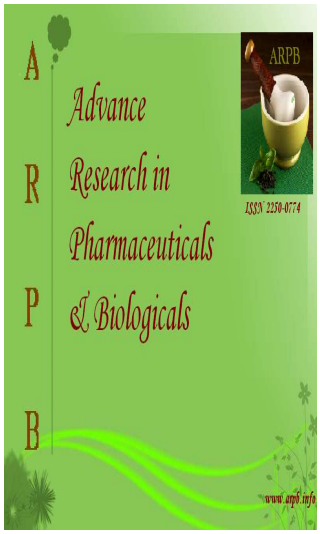

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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF ATENOLOL

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ABSTRACT:

Transdermal drug delivery systems are becoming more popular in the field of modern pharmaceutics. The present study was carried out to develop matrix type transdermal patches containing Atenolol with different ratios of HPMC (hydroxyl propyl methyl cellulose) & EC (ethyl cellulose) by solvent casting method. Propylene glycol 3% is used as plasticizer & span 80 is used as permeation enhancer. The possible drug-polymer interactions were studied by FTIR studies. Formulated transdermal patches were evaluated with regard to physicochemical characteristics, in-vitro permeation studies and stability studies. All the prepared formulations showed good physical stability. The in-vitro permeation studies were performed using Franz diffusion cell. Out of all the formulated patches HF4 & HE3 showed good permeation in 24 hrs. So these two formulations were selected as best formulations.

KEYWORDS: Atenolol, Transdermal patches, Permeation enhancer, *in-vitro* permeation study, HPMC

INTRODUCTION

Transdermal drug delivery system[1-6] (TDDS) is topically administered medicaments in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined & controlled rate. Transdermal drug delivery system has many advantages over conventional modes of drug administration, it provides a controlled rate release of medicaments, it avoids hepatic metabolism, ease of termination and long duration of action. Study has been carried out to provide an anti-hypertensive drug in Transdermal patches. The main objective is to evaluate the feasibility of controlled delivery of therapeutically effective amount of drug in matrix type drug delivery. The Transdermal drug delivery system has gained popularity over the fast decades the major penetration pathway of drug molecules through the stratum corneum of impact human skin is by diffusing through lipid envelopes of the skin cell. Atenolol[7,8] is a beta-adrenergic receptor blocking agent which has been used for the treatment of hypertension[9-11]. After oral administration, the elimination half life is 6-7 hrs. The absolute bio-availability is approximately 50% due to first pass metabolism. So an alternative route like transdermal drug delivery system is chosen to deliver the drug directly to systemic circulation.

MATERIALS AND METHODS

Atenolol (Shubh Chem Pharma, Mumbai), Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC) (Research Lab Fine Chem Industries, Mumbai), Chloroform, Methanol and Span 80 (Finar chemicals Ltd., Ahmadabad), Propylene Glycol, Glycerol, KH_2PO_4 (Sd fine chem. Ltd., Mumbai), NaOH (Thomson daker chemicals, pvt Ltd., Mumbai), Franz Diffusion Cell (Ponmani & Co, Coimbatore), Magnetic Stirrer (Remi equipments Ltd., Vasai), UV/VIS Spectrophotometer (Elico, Hyderabad), pH Meter (Hanna instruments, Italy).

Reagents preparation

Phosphate buffer[12] pH 7.4:

Place 50ml 0.2M KH_2PO_4 in 200ml volumetric flask add 39.1 ml of 0.2M NaOH and then add distilled water to make up the volume.

Preparation of Standard Curve:

Atenolol is estimated by measuring the absorbance at 275nm. The standard curve of Atenolol is prepared in phosphate buffer pH 7.4 and the standardization obeyed Beers law.

Fabrication of Transdermal Patches:

Matrix patches were casted on a glass mould by solvent casting method. Seven types of polymer patches were prepared. First three formulations were prepared by using HPMC alone having drug and polymer ratio 1:2, 1:3, 1:4 using distilled water as a solvent and one more formulation is formulated using HPMC

with permeation enhancer Span 80 (1%) having drug polymer ratio 1:4. Next two formulations were prepared by using HPMC and EC in combination having drug and polymer in the ratio 1:(2:8),1:(1:9) using methanol and chloroform as solvent (1:1) ratio and the remaining formulation is formulated with HPMC and EC by using permeation enhancer Span 80 (1%) in ratio of 1:(2:8). Propylene glycol (3%) used as a plasticizer.

Table No: 1 Fabrication of matrix transdermal patches 3.14 sq.cm

INGREDIENTS	**HF1 (1:2)**	**HF2 (1:3)**	**HF3 (1:4)**	**HF4 (1:4)**	**HE1 (1:(2:8)**	**HE2 (1:(1:9)**	**HE3 (1:(2:8)**
Drug (Atenolol)	10mg	10mg	10mg	10mg	10mg	10mg	10mg
HPMC	20 mg	30mg	40mg	40 mg	20 mg	10 mg	20 mg
EC	---	---	---	---	80 mg	90 mg	80 mg
Span 80 (%)	---	---	---	1%	---	---	1%
Propylene glycol (%)	3%	3%	3%	3%	3%	3%	3%

Evaluation of Transdermal Patches[13- 16]

Physico-Chemical Evaluation

Thickness of the patch:

Thickness of the patch is measured by using Screw Gauge in mm.

Folding endurance:

The folding endurance measured manually for the prepared film. A strip of film is cut evenly and folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the exact value of folding endurance.

Percentage of moisture absorbed:

To check the physical stability of the film in high humidity conditions, accurately weighed films were placed in a desiccators containing saturated solution of aluminium chloride (79.5% RH) for three days. The films were re-weighed and the percentage moisture absorption was calculated using the formula.

Percentage moisture absorption =

$$\frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Percentage of moisture lost:

To check the extent of moisture loss from freshly prepared film, accurately weighed films were placed in a desiccator containing fused anhydrous Calcium chloride for 72 hrs. After 72 hrs, the films were reweighed and percentage moisture loss is calculated using the formula.

Percentage moisture loss =

$$\frac{\text{Initial weight – Final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity:

Patch is cut into pieces and put in 100 ml dissolution or diffusion medium used respectively and stirred continuously using a mechanical stirrer and the sample is withdrawn at the end of three hours and the drug content is determined spectrophotometrically at 275 nm.

Skin irritation test:

The skin irritation test was done on a healthy rabbit weighing between 2 to 3 kg. Drug loaded polymeric film of 3.14 sq cms was placed on the left dorsal surface of the rabbit. The patch was removed after 24 hours with the help of alcohol swab. The skin was examined for erythema/oedema.

***In-vitro* Diffusion Study:**

The in-vitro diffusion study is carried out by using Franz Diffusion Cell (Ponmani & Co, Coimbatore). Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14 sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A weighed amount of Transdermal patch is placed on one side of membrane. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket to maintain the temperature at 37 ± 0.5˚C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each occasion. The samples withdrawn are analyzed spectrophotometrically at 275 nm. The drug release study was performed.

Stability studies:

All the films were exposed to two selected temperatures of 37˚C and 45˚C in two different hot air ovens. Transdermal films were kept in the oven for period of 4 weeks. The films were analyzed for the drug content at the end of every week. The averages of triplicate readings were taken.

RESULTS

The calibration curve was prepared with phosphate buffer pH 7.4. The physical mixture of drug, hydroxy propyl methyl cellulose and ethyl cellulose were subjected to compatibility study using FTIR absorption spectra.

Table No: 2 Standard curve of Atenolol in phosphate buffer pH 7.4

Concentration (µg/ml)	Absorbance
0	0
10	0.071
20	0.12
30	0.174
40	0.248
50	0.315
60	0.381
70	0.45
80	0.495
90	0.53
100	0.584

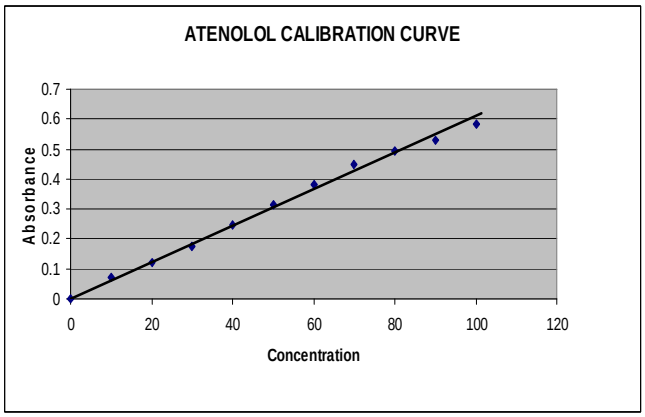


Fig.1 Slope= 0.0061 Regression= 0.9946

Compatibility Study: The drug was identified and compatibility was confirmed by FTIR spectrum from Fig no: 2, 3, and 4.

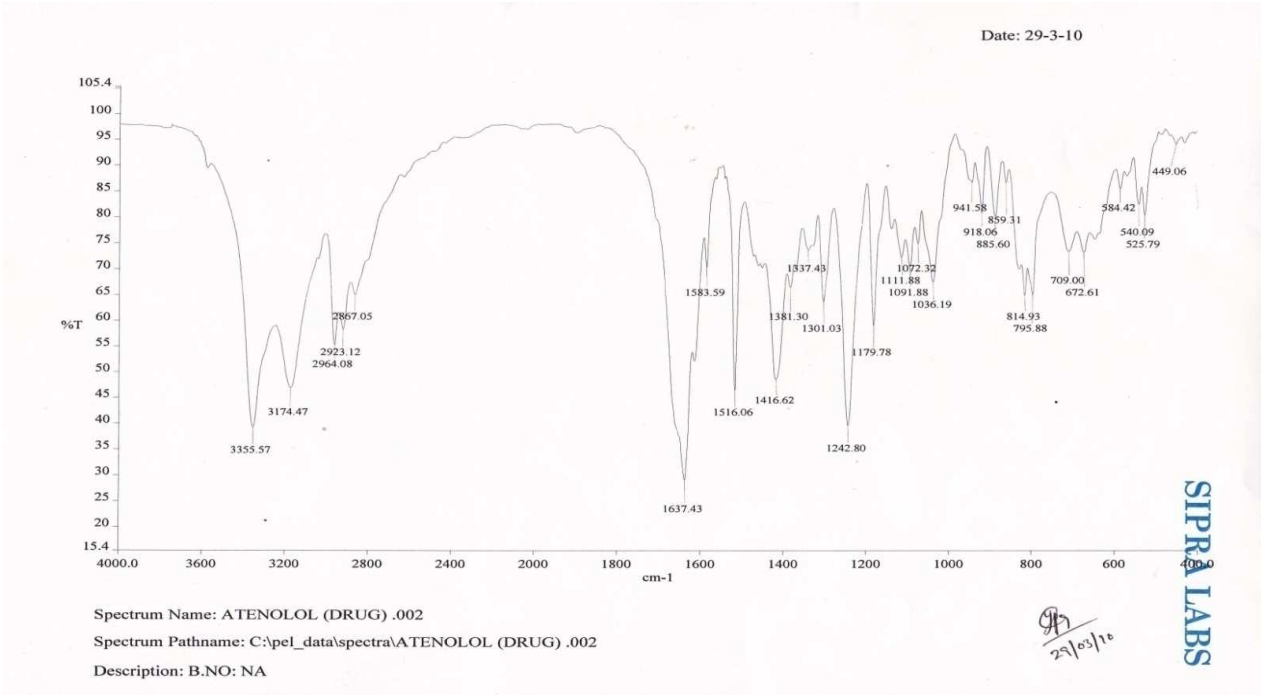


Fig.2

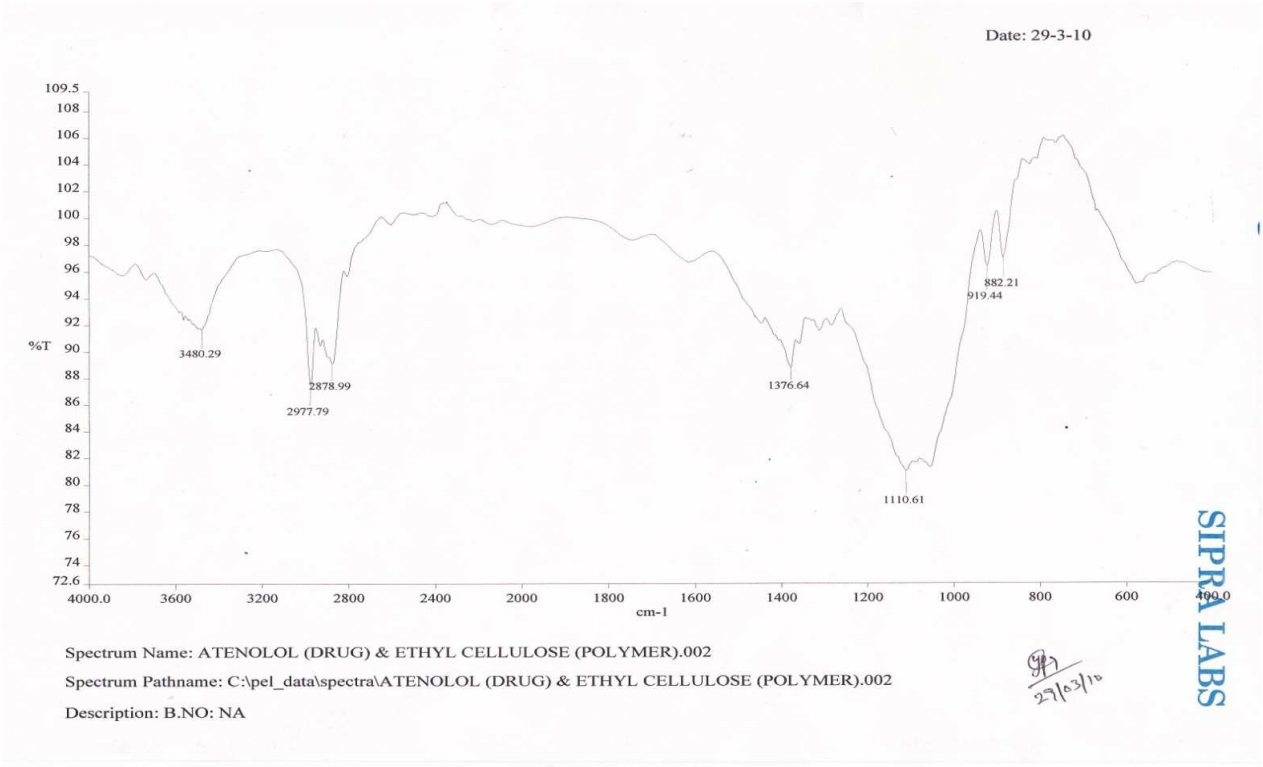


Fig.3

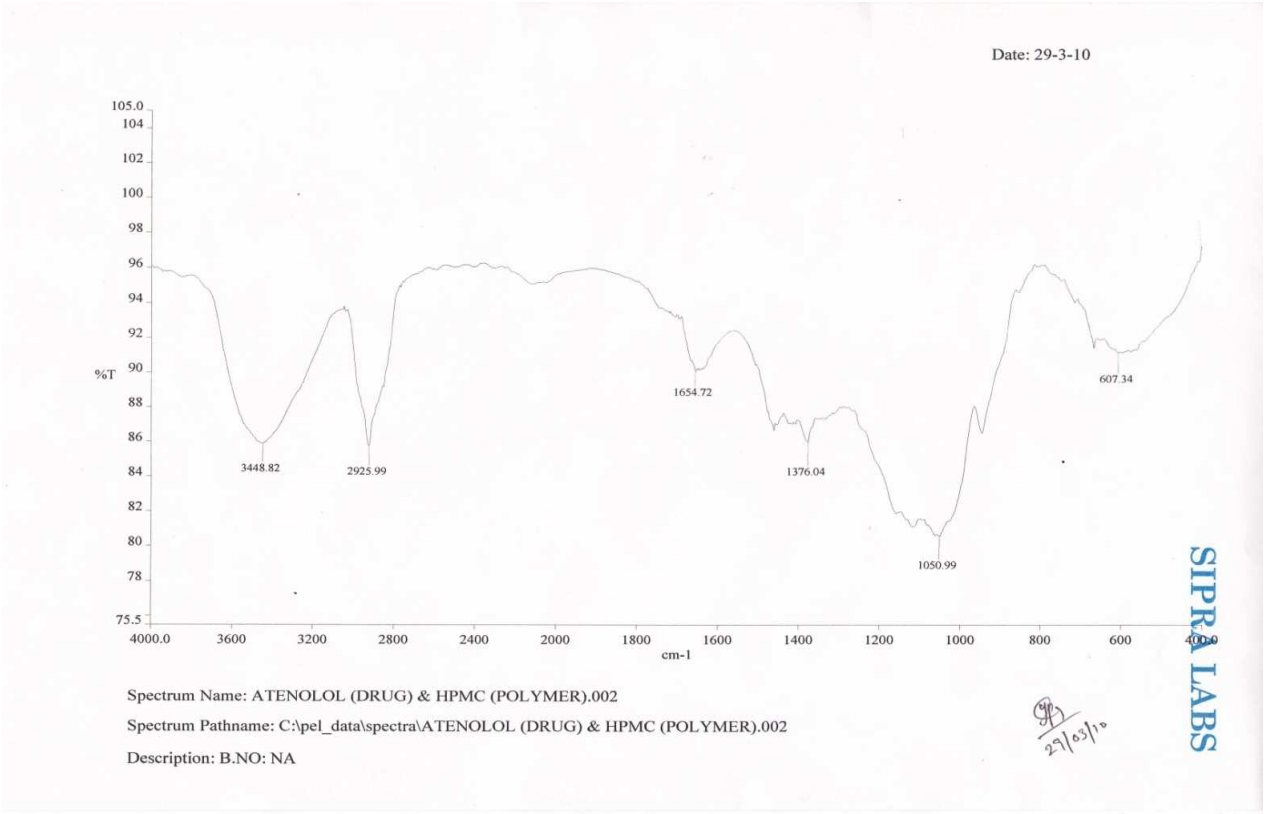


Fig No 4

Table No: 3 Physico-chemical evaluations data of Atenolol Transdermal patches

Formulation code	*Thickness (mm)	*Folding endurance	*Moisture absorbed	*Moisture lost
HF1	0.250	65	2.88	1.20
HF2	0.282	72	2.32	1.10
HF3	0.323	77	1.95	1.05
HF4	0.345	90	2.78	1.45
HE1	0.455	95	2.09	1.50
HE2	0.487	93	2.17	1.28
HE3	0.462	98	2.25	1.37

*indicates average of 3 values

Table No: 4 Drug Content Uniformity

Formulation code	% of drug in 3.14 sq.cm			
	1	2	3	Mean
HF1	95.2%	95.72%	95.56%	95.49
HF2	96.13%	95.40%	96.09%	95.87
HF3	97.45%	96.10%	96.35%	96.63
HF4	98.20%	97.05%	97.30%	97.52
HE1	97.36%	98.15%	97.08%	97.53
HE2	96.18%	95.20%	95.87%	97.75
HE3	98.45%	98.12%	98.06%	98.21

Skin irritation Test: Skin irritation test on rabbit showed no sign of skin reaction and erythema hence the fabricated Transdermal patch was suitable for further studies.

Table No: 5 *In-Vitro* diffusion studies of various formulations

CUMULATIVE % DRUG DIFFUSION								
S.NO	**TIME**	**HF1**	**HF2**	**HF3**	**HF4**	**HE1**	**HE2**	**HE3**
1	0	0	0	0	0	0	0	0
2	0.25	0.98	2.95	4.91	3.934	1.96	1.96	2.95
3	0.5	1.98	3.98	8.93	8.918	3.96	2.98	7.918
4	0.75	3	5.03	14.98	11.032	6.98	5	13.95
5	1	4.03	9.049	19.16	17.114	9.06	7.04	19.098
6	2	6.06	12.14	25.37	21.327	12.16	9.13	23.344
7	4	10.09	16.27	30.7	27.573	14.32	13.21	28.639
8	6	15.18	25.39	36.11	33.918	18.49	16.37	35
9	8	18.37	28.75	39.63	39.377	21.73	19.59	40.475
10	10	22.6	33.14	42.22	43.934	27.98	23.83	47.016
11	12	26.9	37.6	45.83	50.524	33.34	27.16	52.672
12	14	29.29	40.16	48.5	58.196	38.78	29.55	58.409
13	16	31.72	42.75	51.21	63.032	44.31	32.96	63.245
14	18	35.16	46.36	53.95	67.934	49.91	35.44	69.131
15	20	37.67	49.03	56.72	73.885	54.62	39.91	74.114
16	22	40.21	51.73	60.5	76.967	59.39	44.45	79.163
17	24	44.75	55.45	64.34	81.065	65.21	50.04	85.262

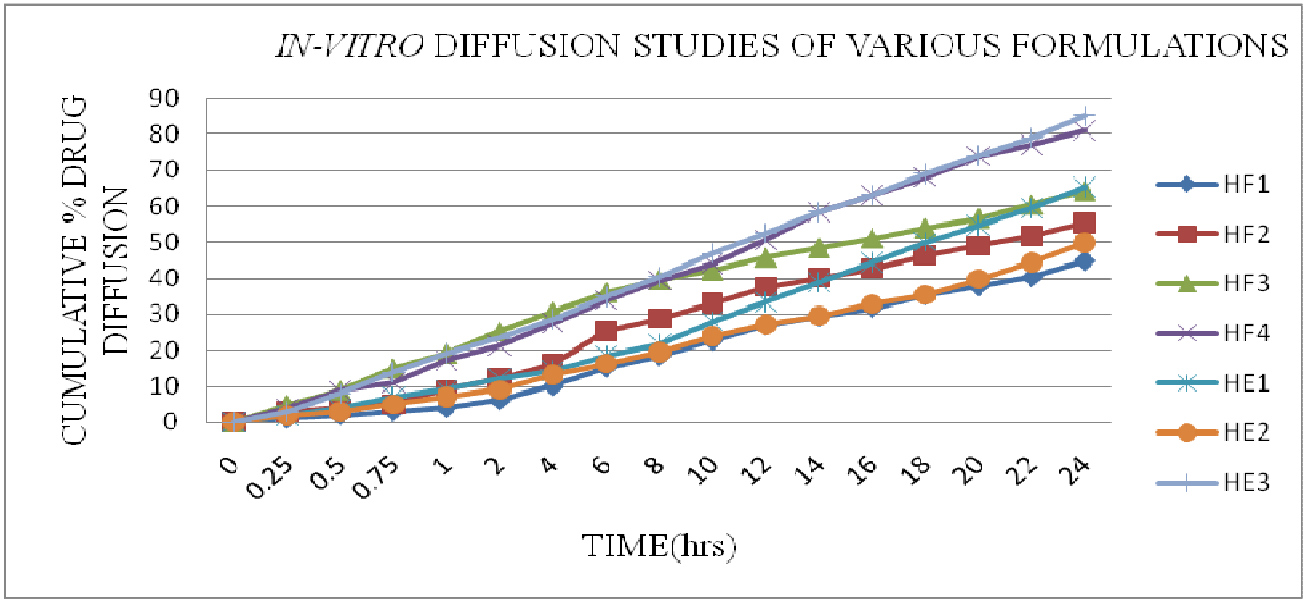


Fig.No 5

Cumulative % and Kinetic Values obtained from different formulations

Result given in Table No 6.

Table No: 6 Cumulative % and Kinetic Values obtained from different formulations

Formulation	% of Drug Penetrated after 24hrs from patch	Zero order plot	First order plot	Higuchi plot	Korsemeyer plot	
		Regression	Regression	Regression	Slope	Regression
HF4	81.065	0.987	0.907	0.989	Y=0.694X+0.959	0.748
HE3	85.262	0.896	0.616	0.987	Y=0.714X+0.954	0.747

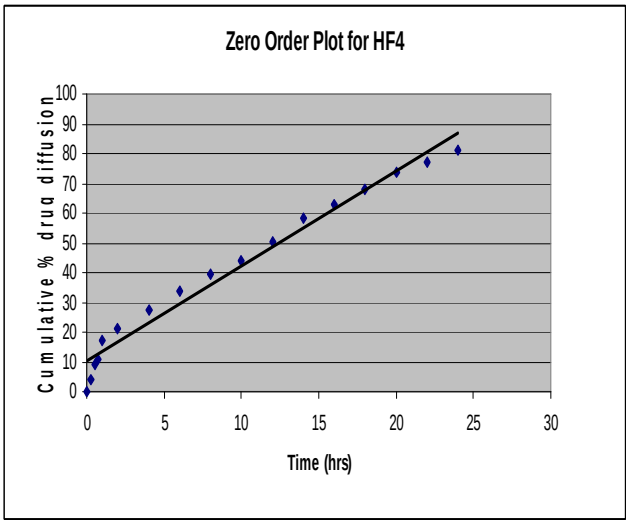


Fig.No.6

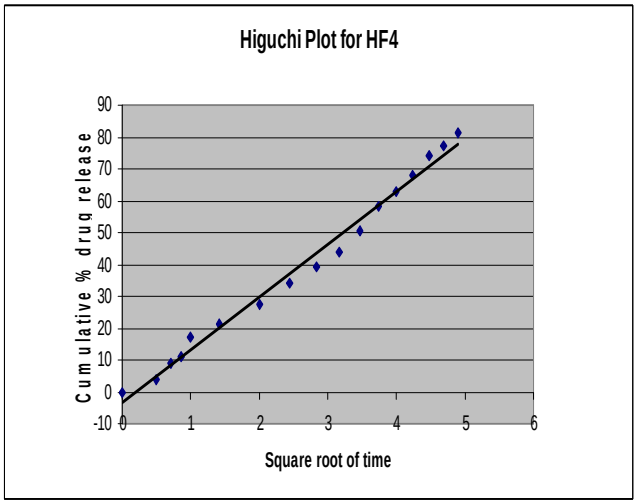
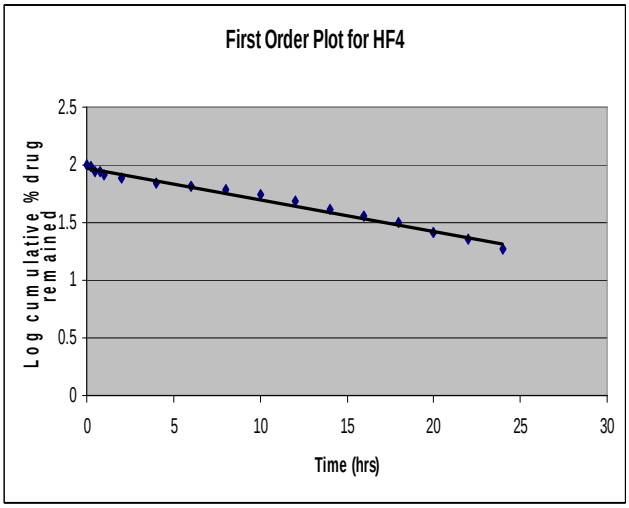


Fig.No.8



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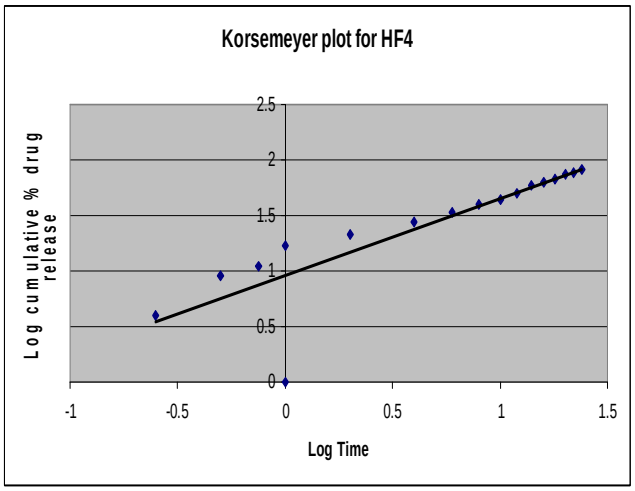

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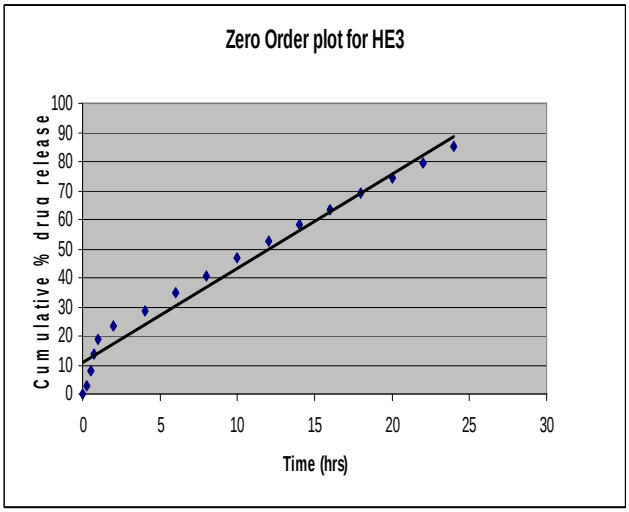
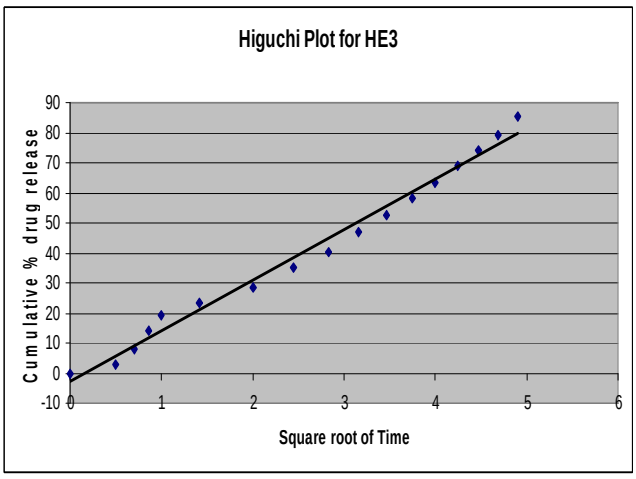


Fig.No.10

Fig.No.11



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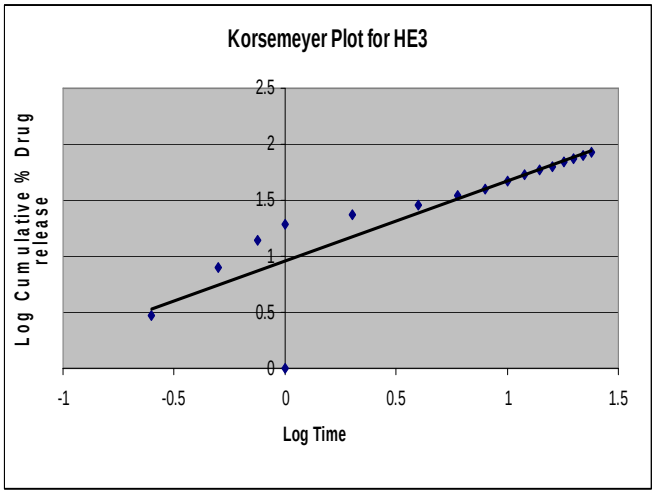

Fig.No.13

Stability Study:

The patches were observed for the changes in colour, appearance, flexibility and drug content at a regular interval of one week for one month. All the films were stable at 37°c and 45°c with respect to their physical parameters and drug content.

DISCUSSION

The calibration curve of pure Atenolol (fig no.1) was plotted with phosphate buffer pH 7.4. The compatibility between Drug and polymer was studied by using FTIR absorption spectra showing in fig no. 2, 3, and 4.

The preliminary study conducted on compatibility between Atenolol with HPMC and EC revealed that there is no interaction between the drug and polymer as from FTIR spectra.

The polymers are the backbone for Transdermal delivery. The widely used polymers for the fabrication of Transdermal patches are Cross-linked polyethylene glycol (PEG) networks, Acrylic-acid matrices, Ethyl

cellulose (EC), Polyvinylpyrrolidine (PVP), Hydroxy Propyl Methyl Cellulose (HPMC), Organogels, Ethyl vinyl acetate (EVA) co-polymers, and Chitosan etc. Among these polymers, HPMC was selected for preparation of Patches. Since, HPMC is used as rate controlling polymer for sustained release and also it acts as stabilizing agent. Hence, it is commonly employed in formulation of patch.

The physico-chemical characteristics such as thickness of the patch, folding endurance, percentage of moisture absorbed, percentage of moisture lost, and drug content analysis were found to be within the acceptable limits. The patches were found to be stable to withstand the stress.

***In vitro* Diffusion studies of Transdermal patches:**

The *In vitro* skin diffusion study showed that drug permeation through the semi permeable membrane from HF1, HF2, HF3, HF4, HE1, HE2, HE3 was 44.75%, 55.45%, 64.34%, 81.06%, 65.21%, 50.04%, 85.26% respectively in 24 hrs.

Among these formulations HF4 and HE3 showed good permeations in 24hrs. So these HF4 and HE3 were selected as best formulations.

All the patches showed Zero order release with diffusion, as the possible mechanisms of drug release. This study suggesting that the patches can meet the sustained release characteristics.

CONCLUSION

Transdermal patch showed good controlled release properties. The results of the present study demonstrated that Atenolol can be considered for Transdermal patch containing HPMC & EC as polymers & Span 80 as permeation enhancer for controlled release of the drug over a period of 24 hrs for the management of hypertension. The Transdermal drug delivery system holds a promising future in effective Transdermal delivery of bioactive agents and opportunities for clinicians to experiment with various drugs to study their systemic and local effects.

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