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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF ATENOLOL

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Abstract:
Transdermal drug delivery systems are becoming more popular in the field of modern pharmaceutics because it has many advantages over traditional drug delivery system and mostly used to overcome the problems associated with conventional delivery system of drugs. it is self-contained, non-invasive, painless, user- friendly and discrete dosage form. The main objective of transdermal drug delivery system is to deliver drugs into targeted organ or parts through skin at predetermined rate with minimal inter and intra patient variation. The present study was carried out to develop transdermal patches of atenolol with different ratio of HPMC (hydroxyl propyl methyl cellulose), EC (ethyl cellulose) and PVP (polyvinyl pyrrolidine) by solvent casting method. Propylene glycol 3% is used as a plasticizer and Span 80 as permeation enhancer. The identification of drug and the possible drug polymer interactions were studied by FTIR spectroscopy. Formulated transdermal patches were evaluated with regard to physicochemical characteristics (thickness, folding endurance etc.) and In-vitro permeation studies were performed using Franz diffusion cell. The data obtained from in- vitro permeation studies was treated by various conventional mathematical models (zero order, first order, Higuchi and Korsmeyer- peppa's) to determine the release mechanism from the transdermal patches formulations. Selection of a suitable release model was based on the values of R^2 (correlation coefficient), k (release constant) obtained from the curve fitting of release data. It was found that all the formulations follow the first order kinetics. The regression coefficients (R^2) for the all formulations F1 to F6 of Higuchi plot was found to be almost linear.

Keywords: *Trasdermal patches, Atenolol, Permeation enhancer, In-vitro permeation study.*

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INTRODUCTION:

Transdermal drug delivery generally refers to topical application of drug to intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin. A transdermal drug delivery device, which can be of an active or a passive design, provides an alternative route for administering medicament and allow pharmaceutical to be delivered across the skin barrier [1]. A drug is applied in a relatively high dosage to the inside of a patch, which is worm on the skin for an extended period of time. By a diffusion process, the drug is entered in the blood stream directly through the skin [2]. There is a high concentration on the patch and low concentration in the blood for a long period of time, by maintaining the constant concentration of drug in the blood flow. The best mixture is approx. 50% of the drug being each hydrophilic and lipophilic. This is because "lipid–soluble substances readily pass through the intercellular lipid bi-layer of the cell membranes whereas water-soluble drugs are able to pass limiting steps in transdermal drug delivery system. The only path of entry by Sweat ducts and hair follicles, but they are considered rather insignificants [3, 4].

Limitation of Transdermal Drug Delivery System [5]

- TDDS cannot deliver ionic drug.
- TDDS cannot achieve high drug levels in blood/plasma.
- It cannot develop for drugs having large molecular size.
- It cannot deliver drug in a pulsatile fashion.
- TDDS cannot develop if drug or formulation causes irritation to skin.
- Limitation of TDDS can be overcome to some extent by novel approaches such as iontophoresis, electrophoresis, and ultrasound.

Advantages of TDDS [6,7]

- In case of toxicity there is easy elimination of drug delivery.
- First pass metabolism of drug is avoided.
- Plasma concentration levels of drugs are reducing with decrease side effects.
- Fluctuation of plasma levels of drugs is reduced, utilization of drug candidates with short half-life and low therapeutic index.
- Delivery of a study infusion of a drug by transdermal medication over an extended period of time
- Enhancement of patient compliance and reduction of dosing frequency.
- There is an increased in the therapeutic value of many drugs via avoiding specific problems associated with the drugs like GI. Irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
- The simplified medication regimen results to improved patient compliance and reduction in inter and intra patient variability.

MATERIALS AND METHODS:

Atenolol was obtained as a gift sample from redburg Pvt. Ltd., Dehradun, India. HPMC, EC, PVP K30, Span 80, Propylene glycol, Chloroform, Methanol was purchased from Central drug house Pvt. Ltd. Delhi (IND).

Identification of Drug through Fourier Transform Infrared (FTIR)

Sample drug is identified by FTIR. FTIR spectra of sample drug are compared with the FTIR spectra of standard drug. FTIR of standard Atenolol is shown in figure 3 and FTIR spectrum of sample Atenolol is shown in figure 4

Compatibility Study of Drug with Polymers

Fourier transform infrared (Perkin Elmer, India) spectroscopy is used to study the compatibility between Atenolol and polymers used in preparation of transdermal patch. The IR spectrum was recorded using an FTIR by KBr pellet method and Nuzol method. The spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}.

Preparation of Calibration Curve of Atenolol

From the stock solution, were prepared by dissolving 50mg of each standard drug samples in 50ml volumetric flask separately and the volume was made up with phosphate buffer 7.4 to get a concentration of 1mg/ml. From this, suitable dilutions were made in phosphate buffer 7.4 to get the working standard solution of 2-12µg/ml for atenolol spectra were measured at 275nm atenolol. The absorbances of the 3 replicate analyses were carried out. Absorbance Vs Concentration were plotted to obtain the calibration graph..

Preparation of Transdermal Patch:

Transdermal patch of atenolol was prepared by solvent evaporation technique in a petridish. Six types of polymer patches were prepared. First three formulations were prepared by using HPMC, EC and PVP 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 formulations were prepared by using HPMC and EC in combination having drug and polymer by using permeation enhancer Span 80 (1%) in ratio of 1:(2:8) and using methanol and chloroform as solvent (1:1) ratio and the remaining formulation is formulated with HPMC, EC and PVP by using ratio of 1:(2:4:8). Propylene glycol (3%) used as a plasticizer.

Table 1: Composition of Transdermal Patch

S.No	Ingredient	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Drug(mg)	10	10	10	10	10	10
2	HPMC	20	-	-	40	20	20
3	EC	-	30	-	-	80	40
4	PVP	-	-	40	-	-	80
5	Span 80%	-	-	-	1%	1%	-
6	Propylene Glycol	3%	3%	3%	3%	3%	3%

Evaluation of TDDS [8-12]

Thickness of the Patch:-

The thickness of patches was measured by using a micrometer and mean value in mm is used to measure the thickness of the patch.

Folding Endurance:-

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

Percentage (%) of Moisture Absorbed:-

Checking the physical stability of the film in high humidity conditions, film that are accurately weighted were placed in a desiccators containing saturated aluminium chloride solution 79.5%RH for 3 days. The films were re-weighed and the percentage moisture absorption was calculated using the formula.

Percentage (%) Moisture Absorbed =

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

Percentage(%) of Moisture Lost:-

In order to check the extent of moisture lose from freshly prepared film, the accurately weighed film are placed in a desiccators containing fused anhydrous calcium chloride for 72hrs, After 72hrs films were re-weighed percentage moisture is calculated using by the following formula

Percentage (%) Moisture Lost =

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

Drug Content Uniformity:-

By cutting a patch into pieces and put in dissolution of 100 ml or diffusion medium is used respectively and stirred continuously using a mechanical stirrer and after the ends of 3hrs the sample is withdrawn the drug content to be determined spectrophotometrically at 275 nm.

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

The study of *in-vitro* diffusion is carried out by using Franz Diffusion Cell. Egg membrane is used the purpose of semi-permeable membrane for diffusion. Franz diffusion cell has a receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14cm^2.

Using Franz diffusion cell *In-vitro* release studies were carried out results were shown in table 7.

Drug Release Kinetic Study

The mechanism of drug release from the transdermal patchs is analyzed by fitting the release data to following equations

Zero – Order Equation:

$$Q = k_0 t$$

Where, Q is the amount of drug released at time t

k_0 is the zero – order release rate.

First – Order Equation:

$$\text{In}\,(100 - Q) = \text{In}\,100 - k_1 t$$

Where, Q is the percent of drug release at time t

k_1 is the first – order release rate constant.

Higuchi's Equation:

$$Q = k_2 \sqrt{t}$$

Where, Q is the percent of drug release at time t

k_2 is the diffusion rate constant.

Mathematical Model for TDDS:-

The drug release mechanism and kinetics are two important characters of delivery system for the drug dissolution profile. Some kinetics models are given in Table 14.

Table 2: Mathematical Model for TDDS

Kinetic model	Mathematical relation	System that follows the model
First order	In Q_t = in Q_0+k(release proportional to amount of drug remaining)	Water soluble drug in porous matrix
Zero order	$F_t = k_0t$(release independent of drug concentration)	Transdermal system
Higuchi's square root of time euuation	$F_t = k_h^{1/2}$	Diffusion matrix formulation
Korsmeyer-peppas power law equation	$M_t/M_\infty = kt^n$	Swellable polymeric device

RESULTS AND DISCUSSION:

Calibration Curve of Atenolol:

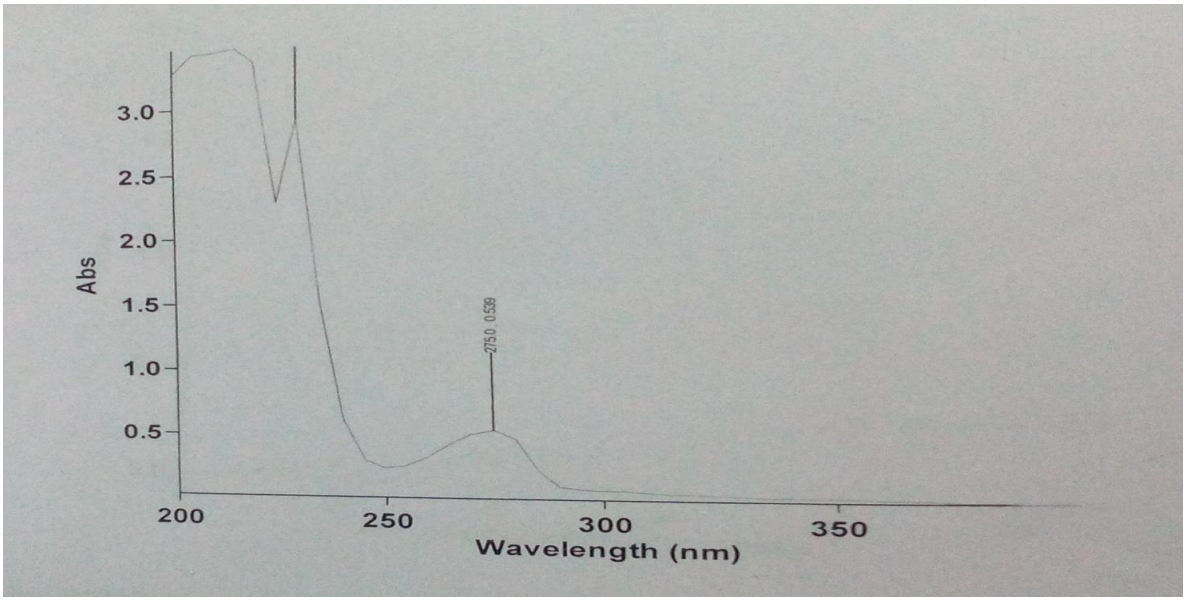

Fig 1: UV Spectrum of Atenolol

Table 3: Data for Calibration Curve of Atenolol:

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.151
3	4	0.293
4	6	0.425
5	8	0.573
6	10	0.642
7	12	0.788

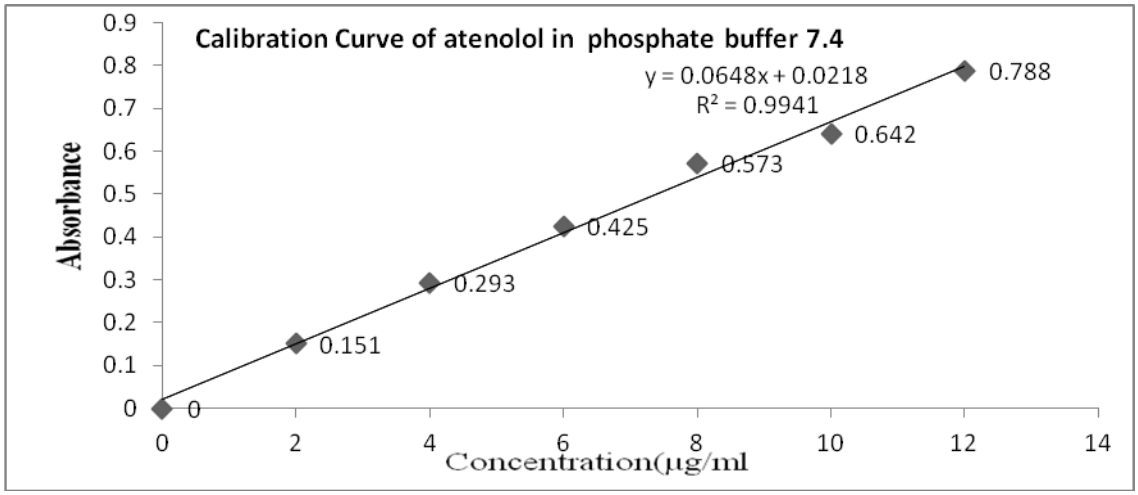

Fig 2: Calibration Curve of Atenololλ_{max}: 275 nm

Identification of Drug:

Identification of Sample Atenolol through FTIR

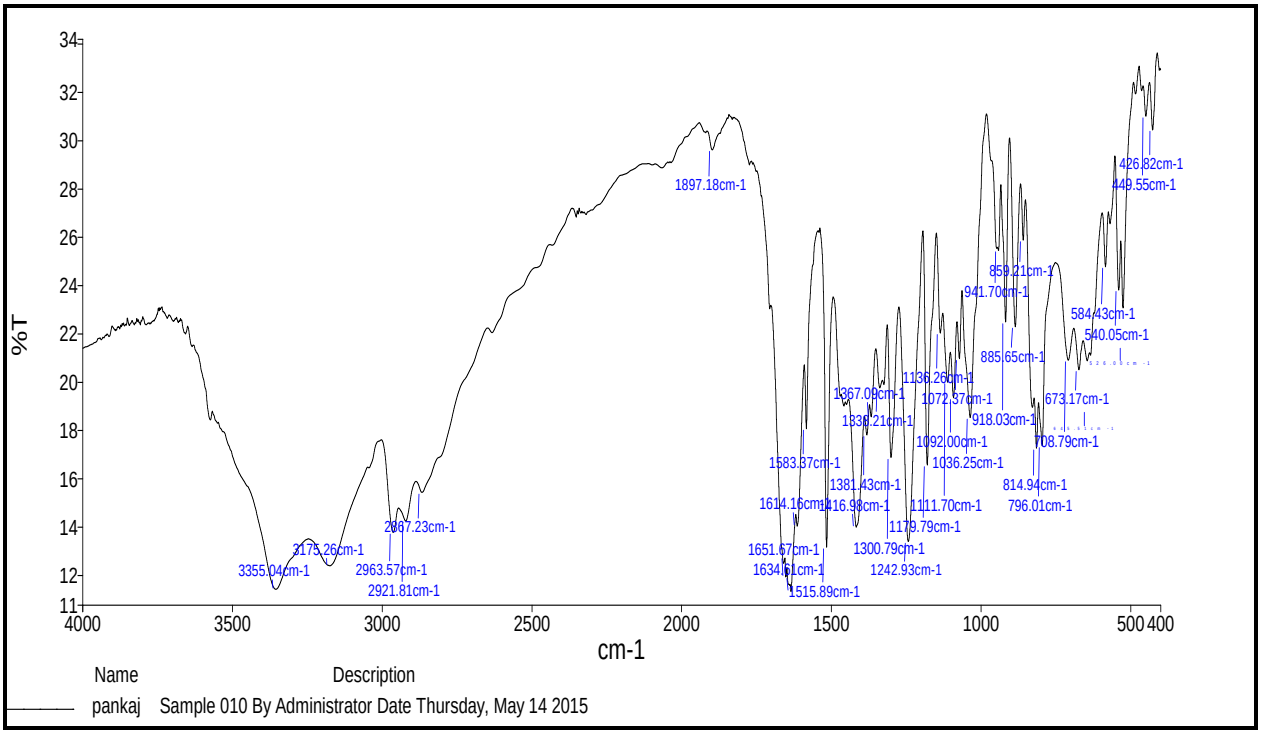

Fig 3: Identification of Sample Atenolol through FTIR

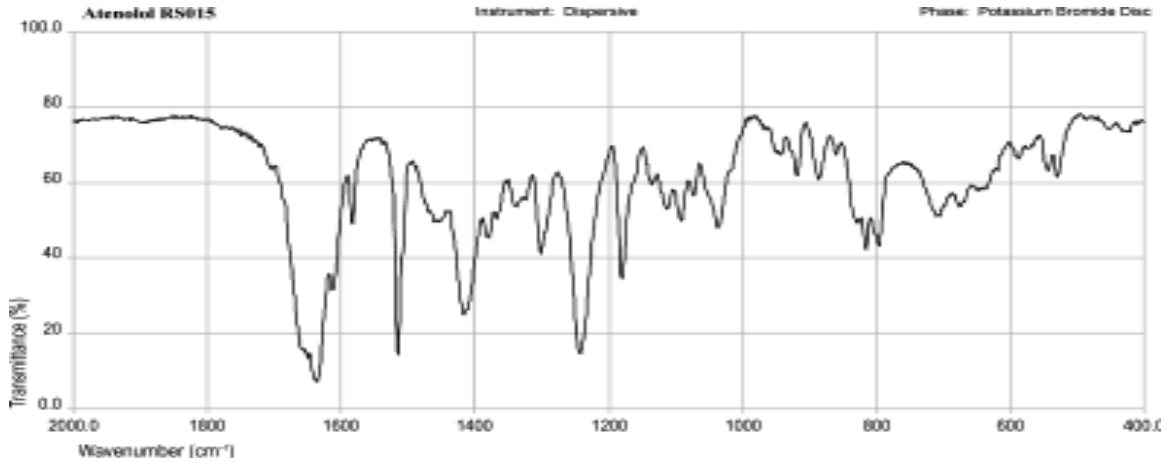

Fig 4: FTIR of Standard Spectra Atenolol (with references of BP-2009)

Table 4: Characteristics peaks of Atenolol

S.No.	Reference peaks (cm^{-1})	Obtained peaks (cm^{-1})	Functional Group	Stretching/Bending
1	1670-1630	1651.67	C=O	Stretching
2	1675-1600	1614.16	C=C(Alkenes)	Stretching
3	1550-1510	1515.89	N-H	Deformation
4	1450-1400	1416.98	C=C	Stretching
5	1480-1340	1367.09	C-H	Deformation
6	1150-1070	1072.37	C-O	Stretching
7	1300-800	814.94	C-C	Stretching
8	710-690	708.79	C-H	Deformation

Spectral Studies:

Compatibility Study of Drug with Polymers:

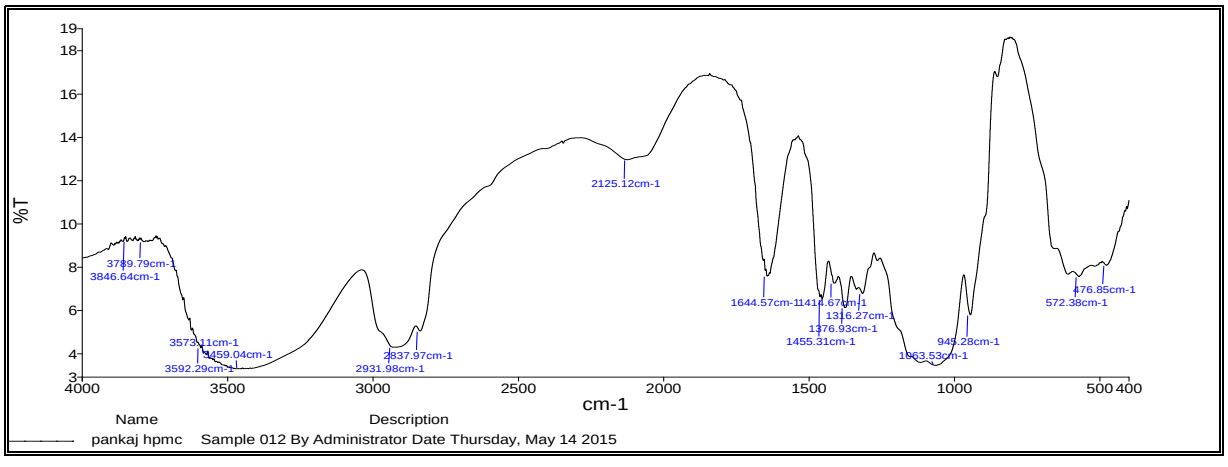

Fig 5: FTIR of HPMC

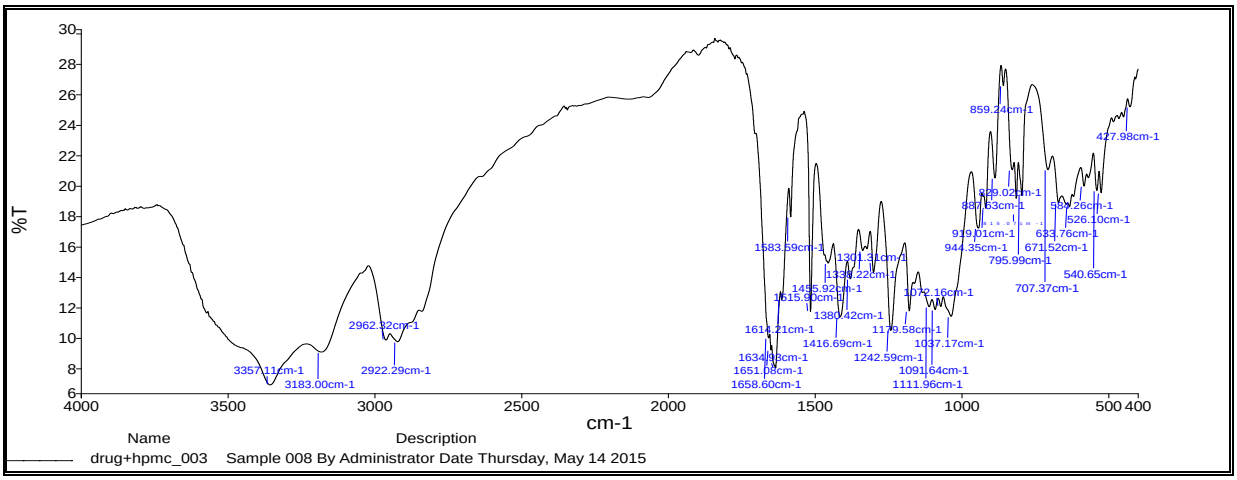

Fig 6: FTIR of Atenolol + HPMC

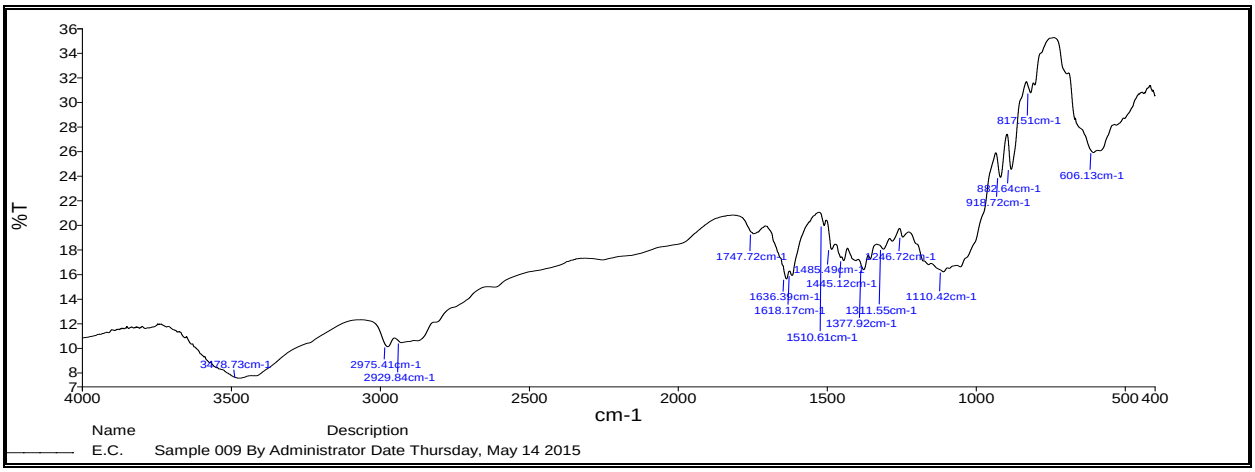

Fig 7: FTIR of Ethyl Cellulose

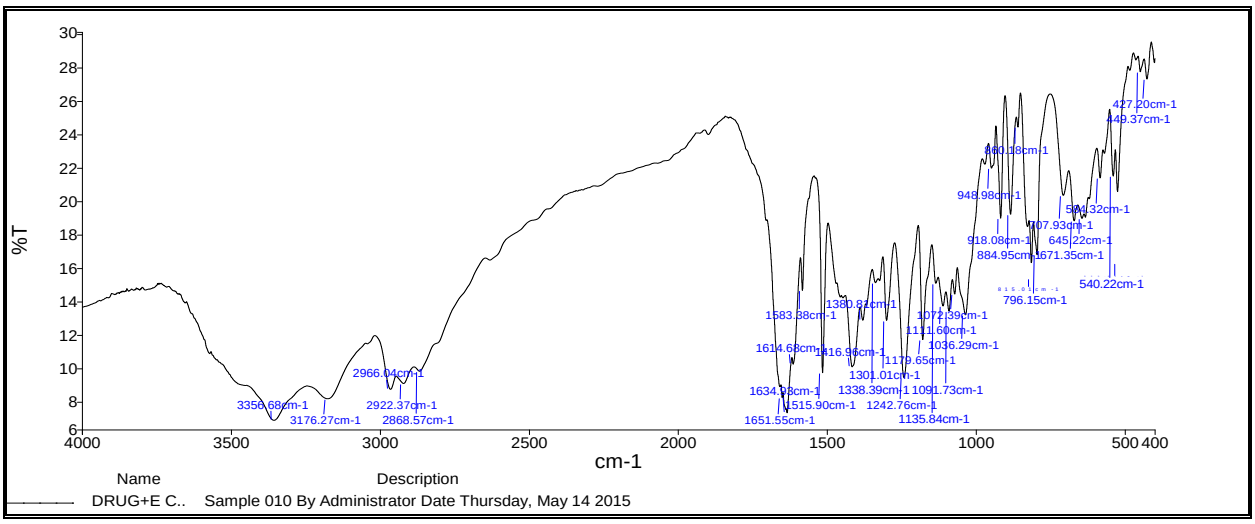

Fig 8: FTIR of Atenolol + Ethyl Cellulose

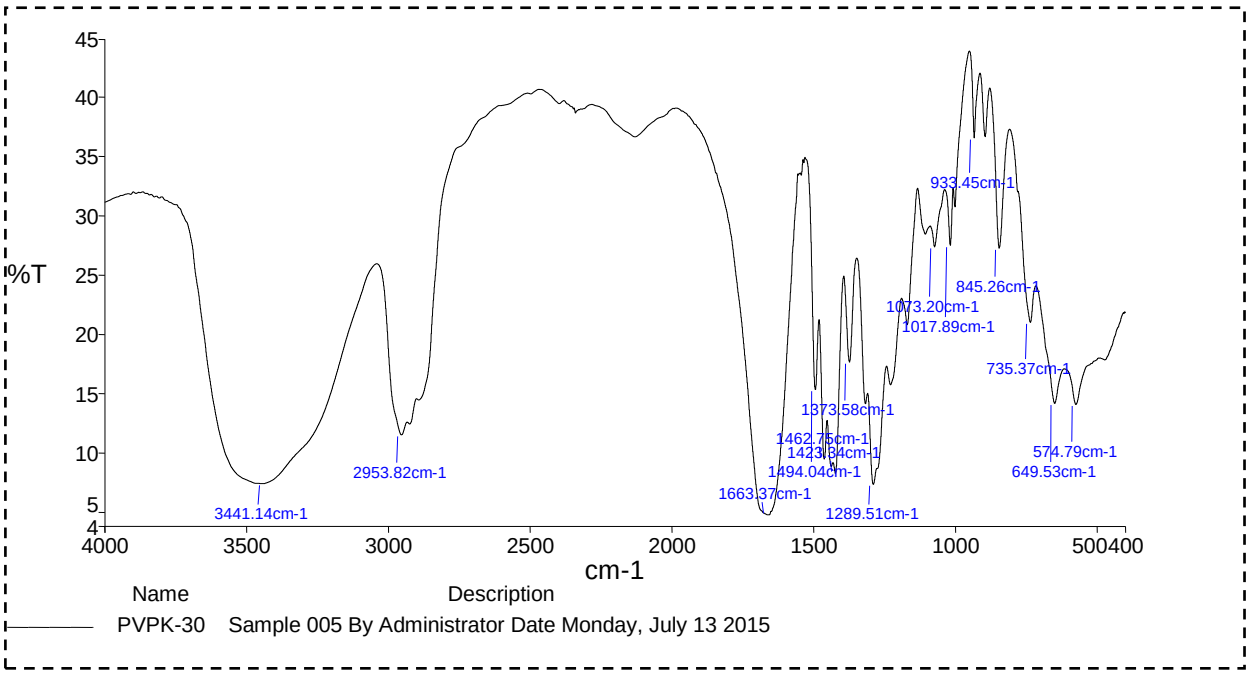

Fig 9: FTIR of PVP K30

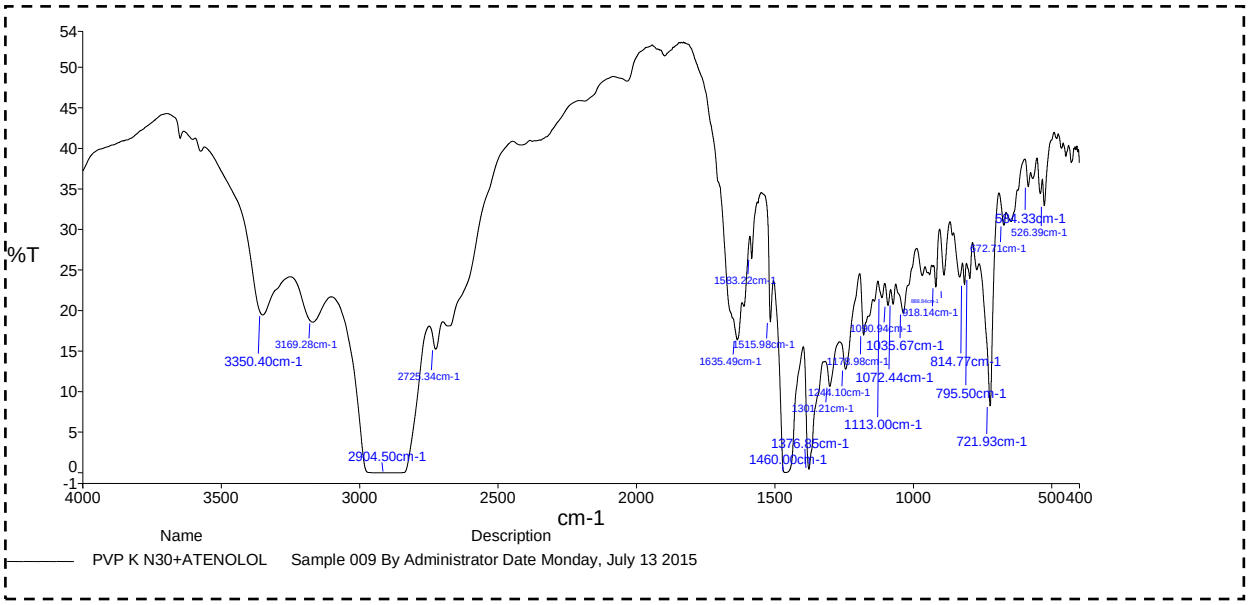

Fig 10: FTIR of Atenolol + PVP K30

Table 5: Evaluation parameters of transdermal patches of atenolol

S.No	Formulation Code	Thickness(mm)	Folding Endurance	% Moisture Absorbed	% Moisture Lost
1	**F1**	0.25±0.002	62	2.96±0.012	1.26±0.01
2	**F2**	0.26±0.004	69	2.48±0.034	1.23±0.04
3	**F3**	0.24±0.006	74	3.68±0.086	1.95±0.43
4	**F4**	0.29±0.004	88	2.74±0.054	1.35±0.02
5	**F5**	0.32±0.005	92	2.15±0.015	1.27±0.06
6	**F6**	0.34±0.002	85	5.08±0.12	3.23±0.09

Mean ± SD (n=3)

Table 6: Drug Content Uniformity

Formulation	% of Drug in 3.14 sq.cm			
	1st	**2nd**	**3rd**	**Mean**
F1	93.30	93.76	93.54	93.53
F2	91.23	91.30	91.29	91.94
F3	90.21	90.38	90.38	90.66
F4	95.16	95.08	95.24	95.49
F5	96.48	96.25	96.12	96.28
F6	94.28	94.36	94.58	94.74

***In-vitro* release study:**

Table 7: *In-Vitro* Permeation Profile of Atenolol Formulation

S.No	Time(hrs)	% Cumulative drug release					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
1.	0	0	0	0	0	0	0
2.	1	8.31	8.08	7.56	12.02	14.34	10.37
3.	2	17.45	14.23	13.78	21.32	22.45	19.13
4.	4	25.04	19.54	17.32	27.65	30.45	27.74
5.	6	28.19	22.38	20.18	32.61	34.87	32.83
6.	8	31.26	25.58	23.67	36.98	39.51	36.33
7.	10	36.64	28.35	27.57	43.63	46.45	40.63
8.	12	43.38	32.95	31.35	47.13	51.75	45.79

Table 8: *In- Vitro* Permeation Profile of Atenolol from Formulation F1

S.No	T	√T	logT	%Cumulative Drug Release	%Cumulative Drug Remain	log %Cumulative Drug Release	log %Cumulative Drug Remain
1	0	0	-	0	100	0	2
2	1	1	0	8.31	91.69	0.92	1.96
3	2	1.414	0.3	17.45	82.55	1.24	1.92
4	4	2	0.6	25.04	74.96	1.40	1.88
5	6	2.449	0.77	28.19	71.81	1.45	1.86
6	8	2.828	0.9	31.26	68.74	1.50	1.84
7	10	3.16	1	36.64	63.36	1.56	1.80
8	12	3.46	1.08	43.38	56.62	1.64	1.75

Table 9: *In- Vitro* Permeation Profile of Atenolol from Formulation F2

S.No	T	√T	logT	Cumulative % Drug Release	Cumulative % Drug Remain	Log Cumulative % Drug Release	Log Cumulative % Drug Remain
1	0	0	-	0	100	0	2
2	1	1	0	8.08	91.92	0.91	1.96
3	2	1.414	0.3	14.23	85.77	1.15	1.93
4	4	2	0.47	19.54	80.46	1.29	1.91
5	6	2.449	0.6	22.38	77.62	1.35	1.89
6	8	2.828	0.69	25.58	74.42	1.41	1.87
7	10	3.16	0.77	28.35	71.65	1.45	1.86
8	12	3.46	0.84	32.95	67.05	1.52	1.83

Table 10: *In- Vitro* Permeation Profile of Atenolol from Formulation F3

S.No	T	√T	logT	Cumulative % Drug Release	Cumulative % Drug Remain	Log Cumulative % Drug Release	Log Cumulative % Drug Remain
1	0	0	-	0	100	0	2
2	1	1	0	7.56	92.44	0.88	1.97
3	2	1.414	0.3	13.78	86.22	1.14	1.94
4	4	2	0.47	17.32	82.68	1.24	1.92
5	6	2.449	0.6	20.18	79.82	1.31	1.90
6	8	2.828	0.69	23.67	76.33	1.37	1.88
7	10	3.16	0.77	27.57	72.43	1.44	1.86
8	12	3.46	0.84	31.35	68.65	1.50	1.84

Table 11: *In- Vitro* Permeation Profile of Atenolol from Formulation F4

S.No	T	√T	logT	Cumulative % Drug Release	Cumulative % Drug Remain	log Cumulative % Drug Release	log Cumulative % Drug Remain
1	0	0	-	0	100	0	2
2	1	1	0	12.02	87.98	1.08	1.94
3	2	1.414	0.3	21.32	78.68	1.33	1.90
4	4	2	0.6	27.65	72.35	1.44	1.86
5	6	2.449	0.77	32.61	67.39	1.51	1.83
6	8	2.828	0.9	36.98	63.02	1.57	1.80
7	10	3.16	1	43.63	56.37	1.64	1.75
8	12	3.46	1.08	47.13	52.87	1.67	1.72

Table 12: *In- Vitro* Permeation Profile of Atenolol from Formulation F5

S.No	T	√T	logT	Cumulative % Drug Release	Cumulative % Drug Remain	log Cumulative % Drug Release	log Cumulative % Drug Remain
1	0	0	-	0	100	0	2
2	1	1	0	14.34	85.66	1.16	1.93
3	2	1.414	0.3	22.45	77.55	1.35	1.89
4	4	2	0.6	30.45	69.55	1.48	1.84
5	6	2.449	0.77	34.87	65.13	1.54	1.81
6	8	2.828	0.9	39.51	60.49	1.60	1.78
7	10	3.16	1	46.45	53.55	1.67	1.73
8	12	3.46	1.08	51.75	48.25	1.71	1.68

Table 13: *In- Vitro* Permeation Profile of Atenolol from Formulation F6

S.No	T	√T	logT	Cumulative % Drug Release	Cumulative % Drug Remain	log Cumulative % Drug Release	log Cumulative % Drug Remain
1	0	0	-	0	100	0	2
2	1	1	0	10.37	89.63	1.02	1.95
3	2	1.414	0.3	19.13	80.87	1.28	1.91
4	4	2	0.6	27.74	72.26	1.44	1.86
5	6	2.449	0.77	32.83	67.17	1.52	1.83
6	8	2.828	0.9	36.33	63.67	1.56	1.80
7	10	3.16	1	40.63	59.37	1.61	1.77
8	12	3.46	1.08	45.79	54.21	1.66	1.73

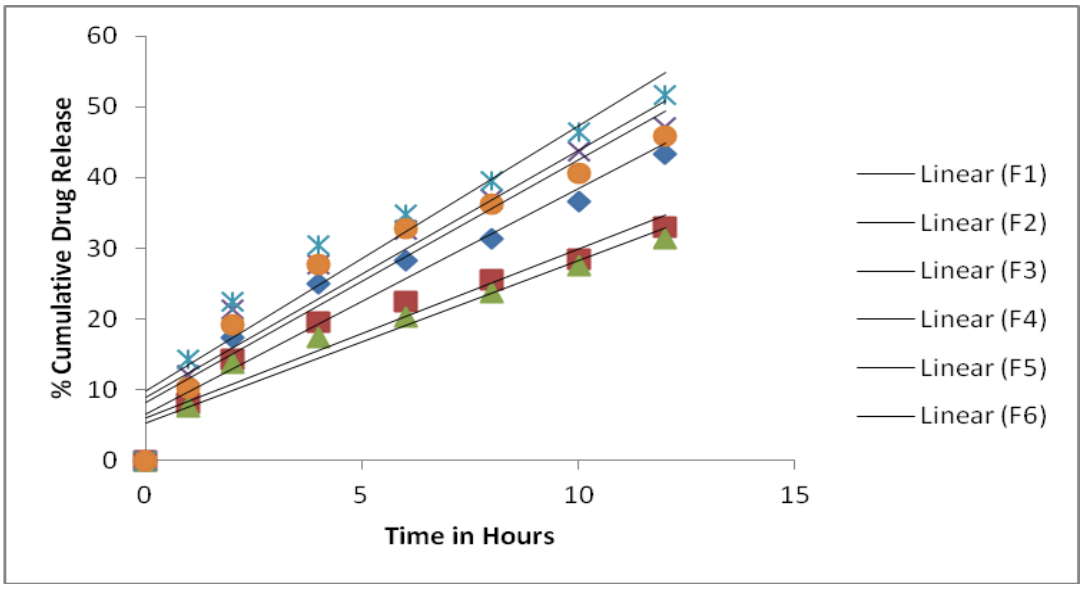

Fig 11: Zero Order Release Plot of Atenolol Transdermal Patches

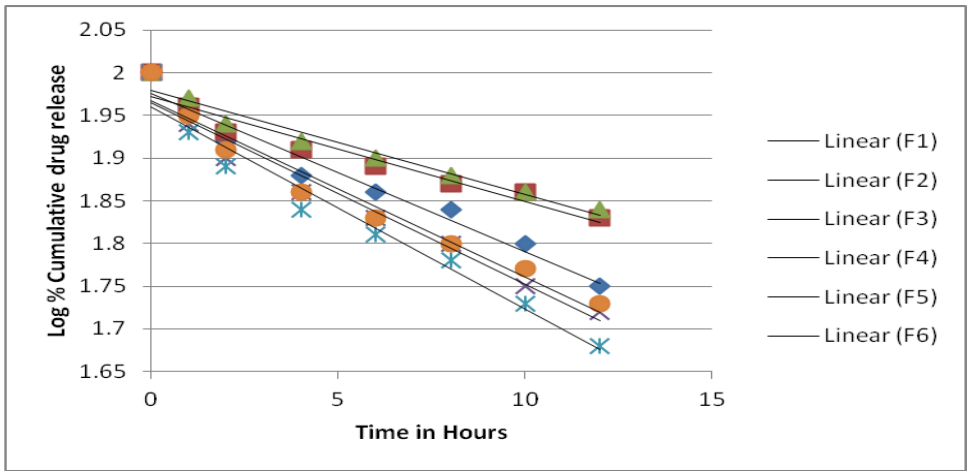

Fig 12: First Order Release Plot of Atenolol Transdermal Patches

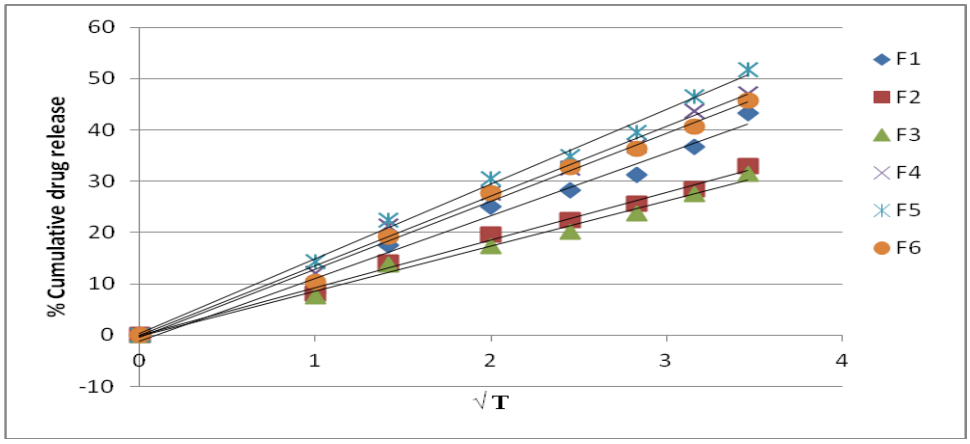

Fig 13: Higuchi Plot of Atenolol Transdermal Patches

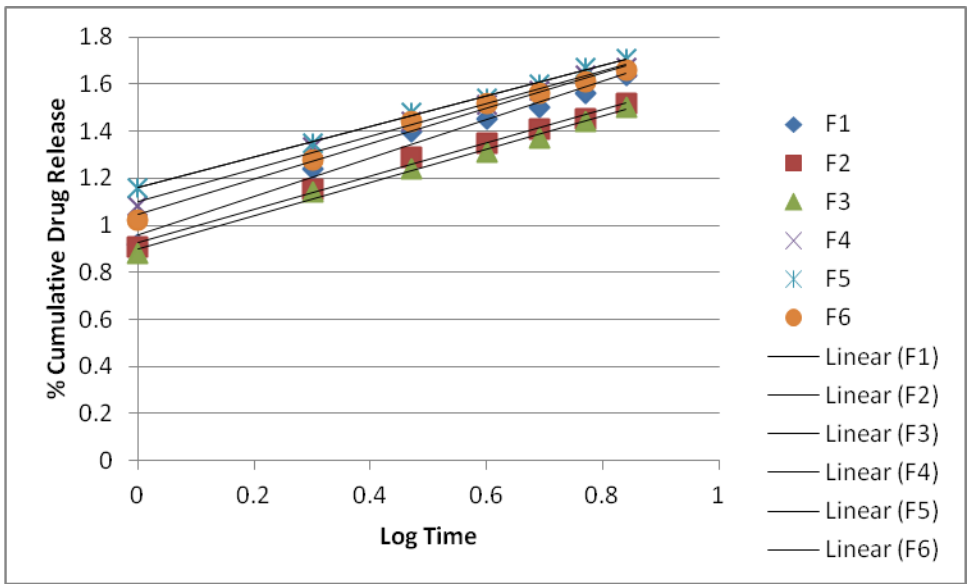

Fig 14: Korsmeyer Peppa's Plot of Atenolol Transdermal Patches

Mathematical Modeling:

Table 14: Model Fitting Release Profile of Formulation F1 to F6

Formulation code	Regression coefficient (R^2)			Korsmeyer-Peppas	
	Zero order	First order	Higuchi model	R^2	n
F1	0.924	0.964	0.983	0.959	0.601
F2	0.912	0.932	0.993	0.981	0.523
F3	0.927	0.958	0.990	0.975	0.525
F4	0.914	0.963	0.966	0.979	0.515
F5	0.916	0.961	0.995	0.992	0.487
F6	0.911	0.961	0.993	0.978	0.561

The calibration curve of pure Atenolol was plotted phosphate buffer 7.4 to get a concentration of 1mg/ml. From this, suitable dilutions were made in phosphate buffer 7.4 to get the working standard solution of 2-12µg/ml for atenolol spectra were measured at 275nm atenolol. The absorbances of the 3 replicate analyses were carried out. Absorbance Vs Concentration were plotted to obtain the calibration graph, calibration graph shown in figure 2 and table 1. The compatibility between Drug and polymer was studied by using FTIR absorption spectra showing in figures 3-10. The preliminary study conducted on compatibility between Atenolol with HPMC EC and PVPK 30 revealed that there is no interaction between the drug and polymer as from FTIR spectra. The polymers are the backbone for Transdermal delivery. Span 80 (1%) having drug polymer ratio 1:4. Next formulations were prepared by using HPMC and EC in combination having drug and polymer by using permeation enhancer Span 80 (1%) in ratio of 1:(2:8) and using methanol and chloroform as solvent (1:1) ratio and the remaining formulation is formulated with HPMC, EC and PVP by using ratio of 1:(2:4:8). Propylene glycol (3%) used as a plasticizer.

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 study of *in-vitro* diffusion is carried out by using Franz Diffusion Cell. Egg membrane is used the purpose of semi-permeable membrane for diffusion. Franz diffusion cell has a receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14cm^2. Using Franz diffusion cell *In-vitro* release studies were carried out. F1, F2, F3, F4, F5 and F6 was 43.38%, 32.95%, 31.35%, 47.13%, 51.75%, 45.79%, respectively in 12 hrs.

CONCLUSION:

Atenolol is a multiple-action cardiovascular drug that is used for the treatment of hypertension now approved in many countries. Administration of atenolol by oral route caused various disadvantages and has some limitations, so the transdermal drug delivery approach is used to deliver these agents, which maintain relatively consistent plasma level for long term therapy and overcome various disadvantages associated with oral administration. TDDS have great potential being able to use for both hydrophobic and hydrophilic active substances.

Transdermal patch of atenolol contain HPMC, EC and PVP as polymers, PG as plasticizer and Span 80 as permeation enhancer for control release of the drug over an extended period of 12 hrs. Greater understanding of the different polymers and different mechanism of biological interactions are required to optimize this drug delivery system.

REFERENCES:

1. Aulton, M.E., 2002. The science of dosage form design. London. Churchill Livingstone. Issue 3, pg. 449-553.

2. Ansel, H.C., 1985. Introduction to pharmaceutical dosage form. Philadelphia. Pg. 25-70.
3. Lachman L, and Liberman, H.A., 1990. A text book of theory and practice of industrial pharmacy, Varghese publication house. Issue 3, pg. 88-94.
4. Ro BI, Dawson TL. The role of sebaceous gland activity and scalp micro¯oral metabolism in the etiology of seborrheic dermatitis and dandru€. J Investigative Dermatol SP. 2005; 10(3): 194.
5. Singh MC, Naik AS and Sawant SD. Transdermal Drug Delivery Systems with major emphasis on Transdermal patches : A Review. Journal of Pharmacy Research 2010; 3(10): 2537-2543.
6. Dawson, T.L., 2005. The role of sebaceous gland activity and scalp microsomal metabolism in the etiology of seborrheic dermatitis and dandruff. J Investigative Dermatol SP. Vol.10, Issue 3, pg. 194-197.
7. James, William; Berger, Timothy; Elston, Dirk (2005) Andrews' Diseases of the Skin: Clinical Dermatology (10th ed.). Saunders. Pg 2-3.
8. Y.W. Chein. Novel drug delivery systems, Marcel Dekker, New York, ed. II, revised and expanded, pp. 301-380.
9. Raghuraman S, Velrajan R, Ravi B, Jeyabalan D, Sankar V, Benito J. Design and evaluation of Propranolol hydrochloride buccal films, Indian J Pharma Sci. 2002; 64(1): 32-36.
10. Draize JH, Woodward G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J PharmacolExpTher. 1944; 82: 377-390.
11. Mutalik S, Udupa N. Formulation development, in vitro and in vivo evaluation of membrane controlled transdermal systems of Glibenclamide. J Pharm Pharmaceut Sci. 2005; 8(1): 26-38.
12. Chandrashekar NS, Shobharani RH. Design, fabrication and calibration of modified diffusion cell for transdermal diffusion studies. Int J Pharm Excip. 2005; 3: 105.