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Formulation and Evaluation of Transdermal Drug Delivery System of Atenolol

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ABSTRACT

The present study was carried out to develop the transdermal patches Containing Atenolol with different polymers of HPMC, PVPK30 and EC was added in the formulation Propylene glycol used as a plasticizer , DMSO, ethanol and eugenol is used as penetration enhancers. Solvent Casting method was used for the formulation of patches. The patches showed satisfactory folding endurance and tensile strength. And it indicated good physical stability. The drug-excipients compatibility studies were performed by Fourier Transform Infrared spectrophotometer (FTIR). The diffusion studies were performed by using modified Franz diffusion cell. *In -vitro* drug permeation test was carried for 24 hrs. F6 contain Eugenol is used as natural penetration enhancer it shows maximum drug permeation 96.45% of at the end of 24 hrs. Due to which reported that penetration enhancers had functional groups with hydrogen- bonding ability effectively improving the drug transport through skin and also improvement in the partitioning of the drug to stratum corneum. The mechanism of drug permeation was followed diffusion controlled by zero order and Higuchi matrix kinetics respectively.

Keywords: *Atenolol, Matrix type transdermal patch, HPMC, PVPK30 and EC, Solvent Casting method.*

1. INTRODUCTION

Transdermal drug delivery system (TDDS) are defined as, distinct dosage form which, when applied to the intact skin, deliver the drugs, through skin at a controlled rate to the systemic circulation. Although some drugs have inherent side effects that cannot be eliminated in any dosage form, many drugs show unwanted behavior that is specifically associated with a particular route of administration. One recent effort at eliminating some of the problems of traditional dosage form is the development of transdermal delivery system. Topical application has also been used for centuries, predominantly in the treatment of localized skin disease. Local treatment requires only that the drug permeate through the outer layer of the skin to treat the diseased state, with the hope that this occurs with little or no systemic accumulation. Certainly, each dosage form has its unique in medicine, but some attributes of the transdermal delivery system provide distinct advantages over traditional methods.[1] The transfollicular pathway in which the drug travels through cells and across them is the shortest way that most likely provides relatively large for diffusion of a molecule. The intracellular pathway avoids the cell contents,but aqueous considerably more tortuous. The transfollicular pathway involves passage or diffusion of drug molecule through the hair shaft openings, which presumably are filled with sebum.This route offers substantially lower diffusional resistance to the most of the drugs that are generally not permitted fairly through other routes.[3] However the path length is relatively long and the density of hair follicles in human skin quite low. The transdermal permeation of most neutral molecules are recognized to be primarily a process of passive diffusion across the intact stratum corneum through the transfollicular region. The transdermal drug delivery systems have been designed as an alternative route for systemic drug delivery.The systemic drug administration through skin holds several advantages such as maintains constant drug level in blood, decrease of side effects, and improvement of bioavailability by circumvention of hepatic first pass metabolism and increase patient compliance. Now a days skin considered as a safe port for drug administration, to provide continuous drug release into systemic circulation.[2] The best mixture is approximately 50% of the drug being each hydrophilic and lipophilic.

MATERIAL

Atenolol was received as a gift sample from Medrich Ltd. Banglore PVPK30, HPMC ,EC Propylene glycol, DMSO, Eugenol, Ethanol, obtained from seva fine chemical Ltd, Mumbai. All other materials and chemicals used were of either pharmaceutical or Analytical grade.

2. METHODS

Pre-formulation testing is the first step in the rationale development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when in combined with excipients. The overall objective of the pre-formulation testing is to generate information useful to the formulator in developing stable formulation. This first learning phase is known as pre-formulation.

Hence, pre-formulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies. Characterization of Atenolol.

Melting point determination

The melting point of Atenolol was determined by using melting point apparatus.

Spectroscopic studies:

FTIR spectrum interpretation

The drug-excipient interaction study was carried out by using Infrared Spectroscopy. FTIR study was carried out to check compatibility of drugs with excipient. The infrared spectrum of the pure Atenolol sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

UV spectroscopy

Preparation of calibration curve for Atenolol.

Determination of λmax

A 10mg of Atenolol was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate Buffer (pH- 7.4) to 100 ml. UV spectrum was recorded in the wavelength range 400-200 nm.

Preparation of standard solution

100 mg of Atenolol was accurately weighted and transferred to 100 ml volumetric flask containing 40 ml Phosphate buffer PH 7.4 and volume made up 100 ml with Phosphate buffer PH 7.4 From this solution, 1 ml was pipetted out and transferred to another volumetric flask and volume make up to 10 ml with phosphate buffer PH 7.4 to give 100µg/ml.

Procedure

From the above standard solution 0.2, 0.4, 0.6, 0.8, 1.0 ml was pipette out and subsequently diluted with 10 ml with Phosphate buffer PH 7.4 to give 2-12 µg/ml. The absorbances of these solutions were measured using UV spectrophotometer (Shimadzu UV-1800, Japan) at 275 nm using Phosphate buffer PH 7.4 as blank. This calibration curve was used for estimation of Atenolol in transdermal therapeutic systems in present study.

Determination of partition coefficient:

The partition coefficient of the drugs was determined using n-octanol as the oil phase and phosphate buffer pH 7.4 as the aqueous phase. The n-octanol:phosphate buffer partition coefficient serves as a parameter lipophilicity.an accurately weighed quantity of each 100mg drug was dissolved in 10 ml of the n-octanol phase and shaken at 37^0C for 24 h against 10 ml buffer in a sealed container. The two phases were separated and then they were analyzed spectro-photometerically (ShimadzuUV-1800, Japan) for respective drug contents. The partition coefficient of drug ($K_{o/w}$) was calculated using following expression;

$$\mathrm{Ko/w} = \frac{\text{Concenatration in octanol}}{\text{Concemtration in buffer}}$$

Formulation of Transdermal Patches

Formulation of Drug Incorporated Transdermal Patches

Drug loaded matrix type transdermal patches prepared by using solvent casting method .A petri plate with a total area of 50.24 cm^2 is used. Polymers are accurately weighed and dissolved in water, methanol (1:1) solution and kept aside to form clear solution. Drug was dissolved and mixed until clear solution obtained. Propylene glycol used as a plasticizers and eugenol, ethanol, and DMSO are used as a permeation enhancer. Mix the above solution and the resulted uniform solution is poured on the petri dish, which was lubricated with glycerine and dried at room temperature for 24hrs. An inverted funnel is placed over the petri plate to prevent fast evaporation of the solvent. After 24hrs, the dried Patches were removed and wrapped in aluminum foil and kept in a desiccator until used. Then the solution was poured on the Petri plate having surface

area of 50.54 cm^2. Then the patches were cut into 2x2 cm^2.

Table 1. Formulation table of Atenolol patches.

Name of ingredient	F1	F2	F3	F4	F5	F6
Drug (mg)	30	30	30	30	30	30
EC (mg)	400	-	-	400	400	400
HPMC (mg)	-	400	-	-	-	-
PVPK30 (mg)	-	-	400	-	-	-
Propylene glycol (%)	30	30	30	30	30	30
Ethanol(%)	-	-		5		
DMSO (%)	-	-	-	-	5	
Eugenol (%)	-	-	-	-	-	5

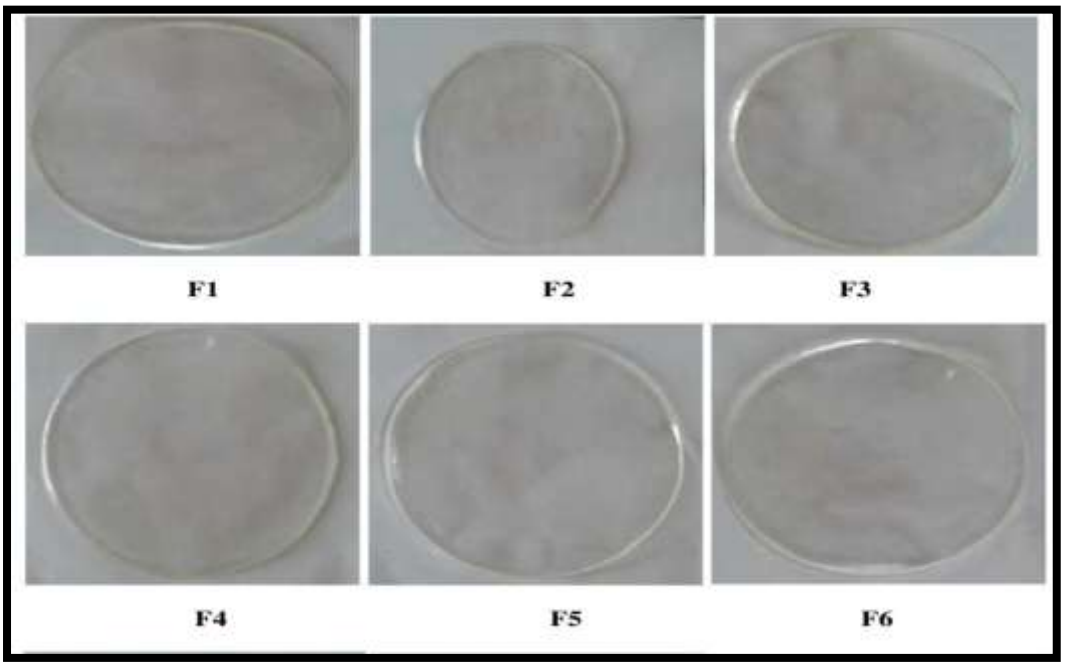

Fig: 1 Prepared transdermal patch of Atenolol.

Evaluations of transdermal patches

Thickness [5]

The thickness of patches was measured by digital vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation

Weight variation [6]

The three disks of 2x2 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation

Percentage Elongation [7-8]

The percentage elongation break is to be determined by noting the length just before the break point from the below mentioned formula.

$$\% \text{ Elongation} = \frac{L1 - L2}{L2} * 100$$

Where,

L_1- is the final length of each strip

L_2- is the initial length of each strip.

Folding endurance [9-10]

This was determined by repeatedly folding one patch at the same place till it broke. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.

Tensile Strength [11]

The tensile strength was determined by the apparatus designed as shown in fig 5.2.The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden plat form was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with the increment of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation. The tensile strength was calculated by using following formula.

$$\text{Tensile Strength} = \frac{\text{Breaking force}}{\text{ab}} * (1 + \Delta\frac{L}{L})$$

Where,

L - Length, b – Thickness,

a – Width, ΔL- Elongation at break

Moisture content [12]

The films were weighed and kept in desiccator containing calcium chloride at 40°C in a dryer for at least 24 hrs or more until it showed a constant weight. The percentage of moisture content was the difference between constant weight taken and the initial weight and as reported in terms of percentage by weight moisture content.

$$\text{Percentage moisture content} = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Final wt.}} * 100$$

Moisture uptake study [12]

After films, of which the size is 2x2 cm^2, were put in a desiccator with silica gel for 24 hrs and weighed, the patches were transferred to another desiccator containing saturated solution of potassium chloride solution (relative humidity 85%) after equilibrium was attained, the patches were taken out and weighed. Moisture uptake capacity was calculated according to the following equation:

$$\text{Percentage Moisture Uptake} = \frac{\text{Final wt.} - \text{Initial wt.}}{\text{Initial wt.}} * 100$$

Swelling index [12]

The patches of 2x2cm^2 was weighed and put in a Petri dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed. The degree of swelling (% S) was calculated using the formula

S (%) = Wt – Wo/Wo x 100

Where, S is percent swelling, Wt is the weight of patch at time t and

Wo is the weight of patch at time zero

Drug content [12]

The film sample of 2x2cm^2 was cut and dissolved in 100 ml volumetric flask containing phosphate buffer (pH 7.4) the flask was sonicated for 8 hrs. A blank was prepared in the same manner using drug free placebo film of same area. The solution was then filtered using a 0.45µm filter and the drug content was analyzed at 275nm by UV spectrophotometer.

Diffusion studies [12]

Diffusion Cell

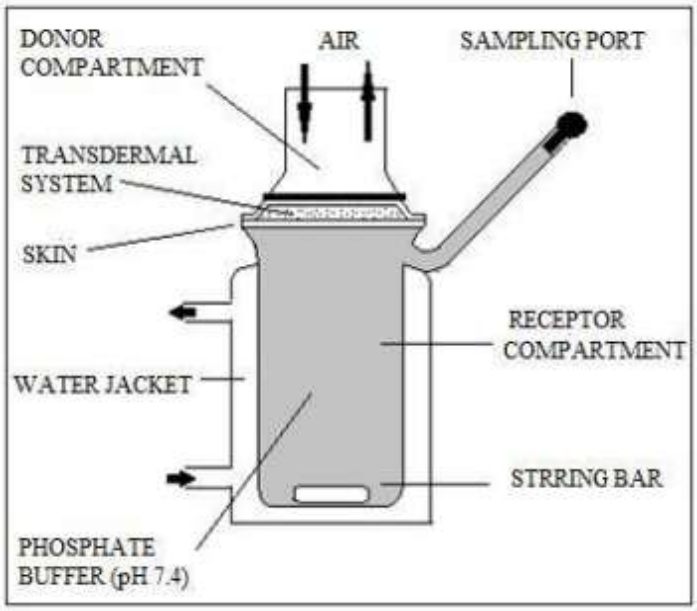

Fig 2. Diffusion cell.

Method

The glass Franz diffusion cell was used for release studies. The cellophane membrane was mounted between donor and receptor compartment. The transdermal patch was fixed on between donor and receptor compartments were clamped together and placed in a water bath maintained at 37 ± 0.5°C. The volume of receptor cell was 25 ml and the effective surface area available for permeation was 4.9062 cm^2. The receptor compartment filled with pH 7.4 phosphate buffer. The hydrodynamics of the receptor fluid was maintained by stirring the fluid at 600 rpm with star head magnet. Samples 2 ml were withdrawn at specific interval of time. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 275nm UV-spectro-photomertically.

Stability studies [12]

- The stability studies of the formulations were carried out as per ICH guidelines. The study was conducted at temperature of 40°C and 75 % RH. Transdermal systems of 2x2 cm^2 area were wrapped individually in a butter papers, packed in aluminum foils and placed in petri-dishes. These petri-dishes containing patches were stored at 40°C and 75 % RH for a period of one month. The samples were observed for physical changes like colour, flexibility, etc. The drug content was detected.

3. RESULTS

Characterization of Atenolol

Appearance and colour of drug

The sample of Atenolol was found to be white or almost white powder.

Melting Point

The melting point of the Atenolol was found to be 158^0_C.

Solublity It is soluble in ethanol, Methanol, Sparingly soluble in water ,Slightly soluble in dichloromethane, Practically insoluble in ether.

Spectroscopic studies

Determination of λmax

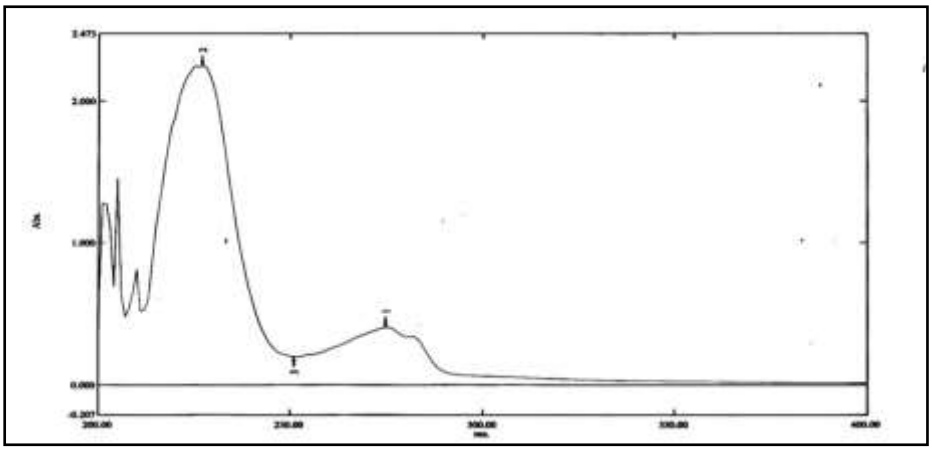

Fig. 3. UV Spectra of Atenolol in Phosphate buffer pH 7.4 at 275 nm.

Standard Calibration curve of Atenolol.

Table 2. Calibration curve data for Atenolol in Phosphate buffer pH 7.4

Sr. No.	Concentration (µg/ml)	Absorbance at 275 nm
1	0	0
2	2	0.155
3	4	0.275
4	6	0.405
5	8	0.535
6	10	0.655
7	12	0.789

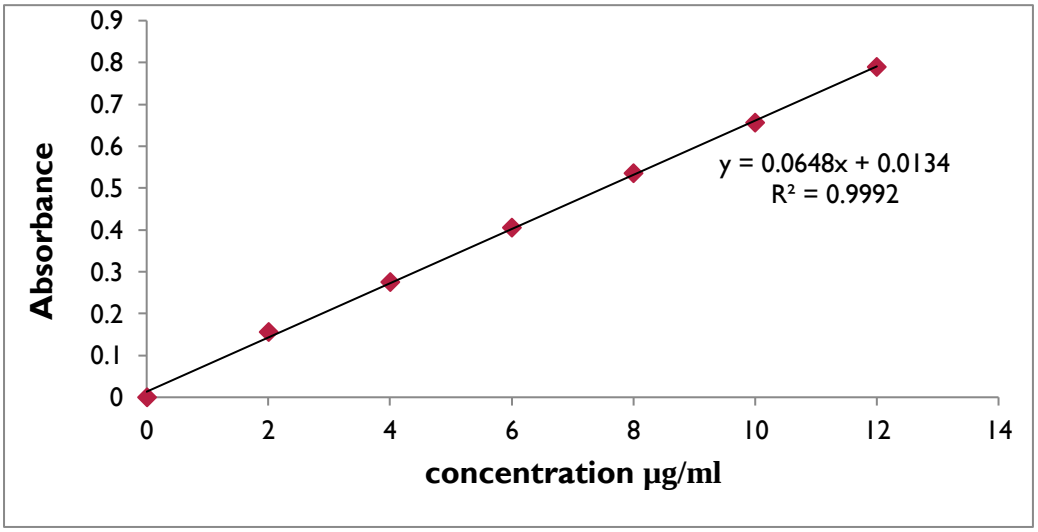

Fig -4. Standard graph of Atenolol in Phosphate buffer pH 7.4

Compatibility Studies

FT-IR Spectroscopy for pure drug: -

The FT-IR spectrum of Atenolol presented in Figure 6.3 and FTIR peaks of Atenolol are given in Table 6.2

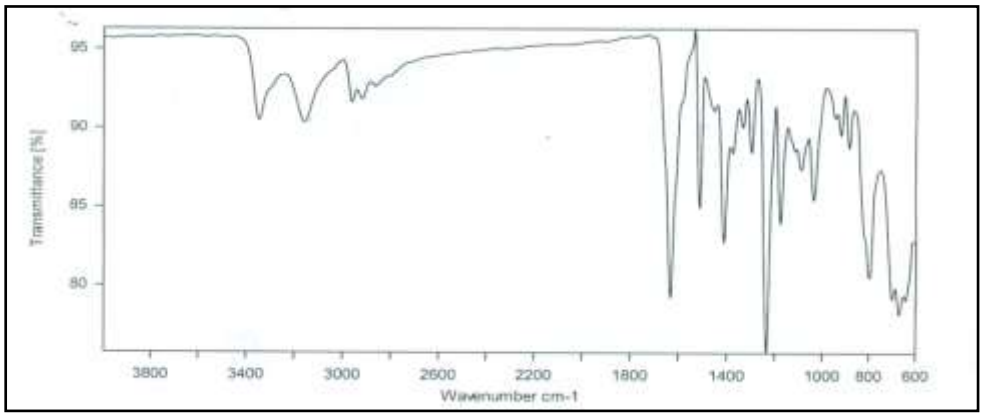

Fig 5. FTIR Spectra of Pure Atenolol.

The FT-IR spectrum of Atenolol shown in Figure 6.3, revealed the presence of distinctive peak at 1631 cm^{-1} due to C=O stretching , at 1510 cm^{-1} owing to –N-H deformation, at 1234 cm^{-1}owing to –C-O, at 750 cm^{-1}due to aromatic substitution and at 1443 cm^{-1} due to –C-H deformation respectively.

Table 3. Interpretation of FTIR spectra.

Sr .No	Functional Group	Standard Value	Obtained Value
1	Ketone group	1680-1630 cm^{-1}	1631 cm^{-1}
2	Amide group	1550-1510 cm^{-1}	1510 cm^{-1}
3	Ether	1300-1000 cm^{-1}	1234 cm^{-1}
4	C-H	1450-1375 cm^{-1}	1443 cm^{1}
5	Aromatic substitution	750 cm^{-1}	750 cm^{-1}

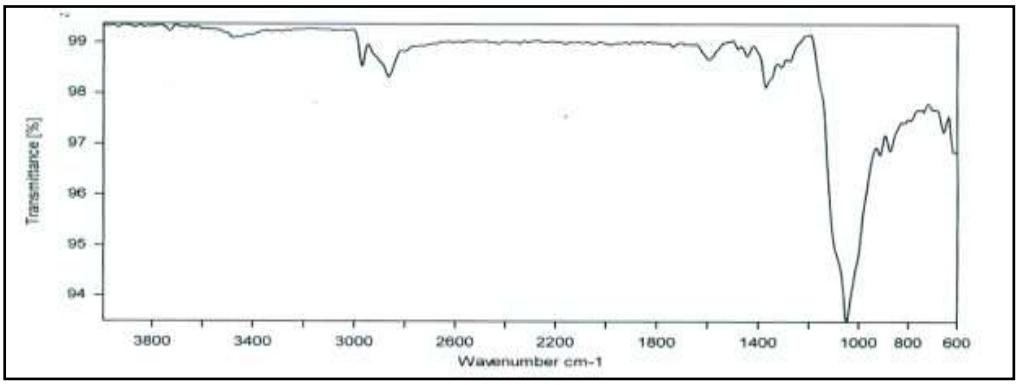

Fig 6. FTIR Spectra of EC.

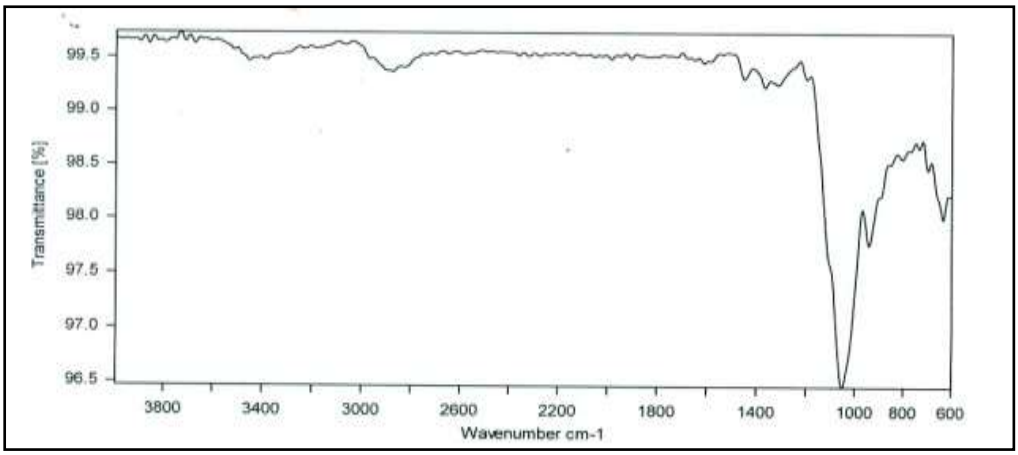

Fig 7. FTIR Spectra of HPMC

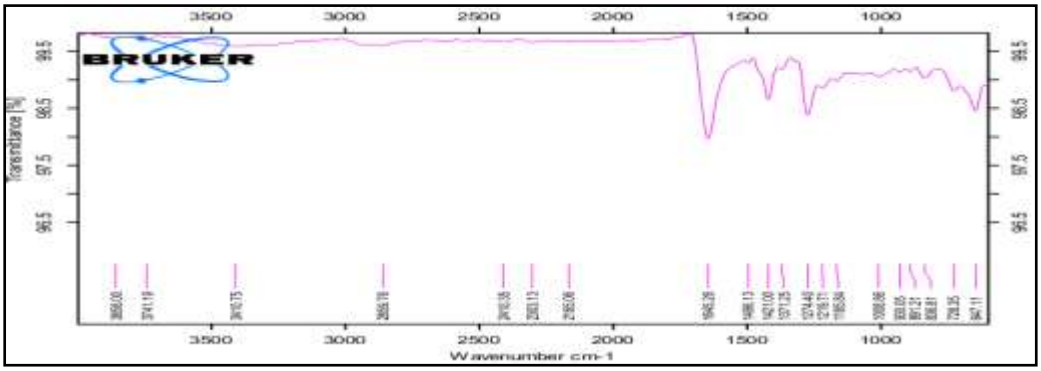

Fig 8. FTIR Spectra of PVPK30.

Drug-Polymers Interaction Study

The FT-IR spectrum of drug and polymers revealed that major frequencies of functional groups of pure drug remain intact in physical mixture; hence, there was no major interaction between the drug and polymers used in the study.

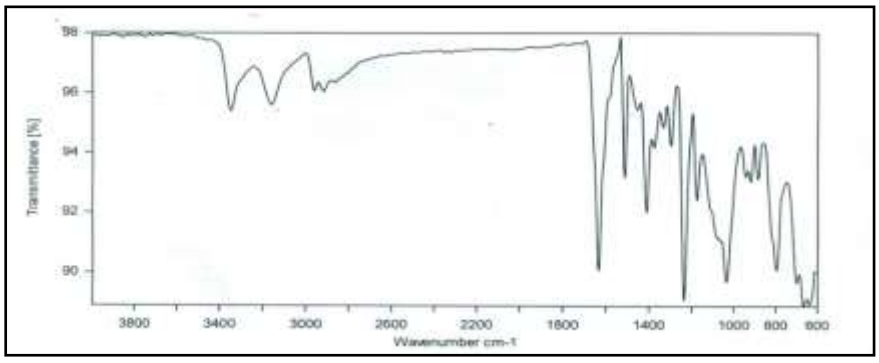

Fig 9. FTIR Spectra of Atenolol +HPMC.

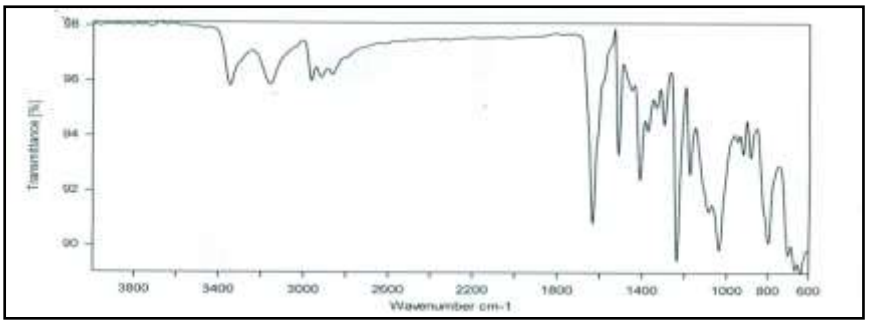

Fig 10. FTIR Spectra of Atenolol + EC

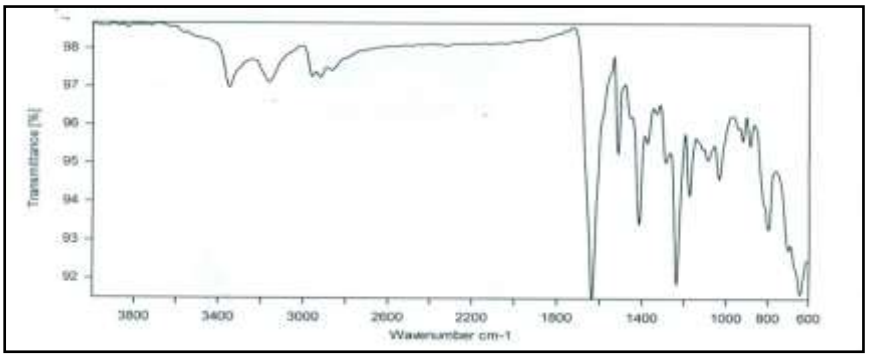

Fig 11. FTIR Spectra of Atenolol + PVP30.

The overlay of IR spectrum of drug and mixture of drug with polymer is shown in figure 6.8, 6.9 and 6.10 respectively which shows that peaks observed in spectrum of pure drug were also observed in spectrum of mixture of drug with polymer. No significant changes in peak pattern in the IR spectra of pure Drug and mixture of drug with polymer indicates that there is no interaction between pure drug and polymer**.**

Evaluation of Transdermal patches

Physicochemical Evaluation

Table 4. Physicochemical evaluation data of Atenolol Transdermal patches.

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content	Folding endurance	Tensile strength Kg/mm^2
F_1	0.36±0.01	0.234±0.01	93.92±3.32	135.7±12.04	3.45±0.81
F_2	0.34±0.02	0.218±0.005	92.59±3.14	132.6±21.0	3.84±1.80
F_3	0.38±0.004	0.222±0.021	91.51±2.17	134±18.20	2.40±0.70
F_4	0.37±0.008	0.228±0.011	94.65±2.42	130±24.33	4.45±2.18
F_5	0.35±0.09	0.225±0.017	93.36±2.02	131±22.03	3.41±0.86
F_6	0.37±0.003	0.228±0.014	94.71±1.42	132±10.41	3.91±1.84

Table 5. Physicochemical evaluation data of Atenolol Transdermal patches.

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F_1	24.43±2.51	1.85±0.35	4.87±3.13	24.17±1.38
F_2	23.80±2.12	2.6±0.77	3.6±3.7	25.75±0.72

F_3	25.75±2.61	3.1±1.29	5.3±1.22	25.50±2.12
F_4	26.25±4.12	3.2±1.82	4.7±0.85	23.41±0.74
F_5	28.04±4.71	3.23±2.78	5.7±1.45	22.82±1.25
F_6	25.26±4.19	2.7±0.98	4.76±1.06	24.18±1.37

Table 6. *In-vitro* Drug Permeation of Atenolol from F6 through cellophane membrane.

Time in (hrs)	Square root of time (hrs)	Log time (hrs)	F6		
			% Drug Permeated	Log % Drug Permeated	Log % Drug Retained
2	1.41	0.30	8.84	0.92	1.96
4	2.00	0.60	15.55	1.19	1.92
6	2.45	0.78	28.78	1.45	1.85
8	2.83	0.90	39.72	1.59	1.78
10	3.16	1.00	49.07	1.69	1.70
12	3.46	1.08	62.60	1.79	1.57
16	4.00	1.20	72.25	1.85	1.44
20	4.47	1.30	83.19	1.92	1.22
24	4.90	1.38	96.45	1.98	0.55

Table 7. *In-vitro* Drug Permeation of Atenolol Data Batches F1-F6.

Time (hrs)	F1	F2	F3	F4	F5	F6
2	8.85	7.53	8.58	8.43	5.87	8.84
4	16.64	14.03	14.47	14.42	11.70	15.55
6	28.56	27.26	27.31	27.20	33.95	28.78
8	35.18	36.47	32.65	33.99	35.26	39.72
10	50.10	48.85	46.19	47.46	46.45	49.07
12	58.75	60.39	57.40	58.69	60.05	62.60
16	71.58	72.38	67.03	68.46	69.64	72.25
20	73.02	83.43	76.92	79.27	80.58	83.19
24	84.76	90.00	79.29	92.57	93.85	96.45

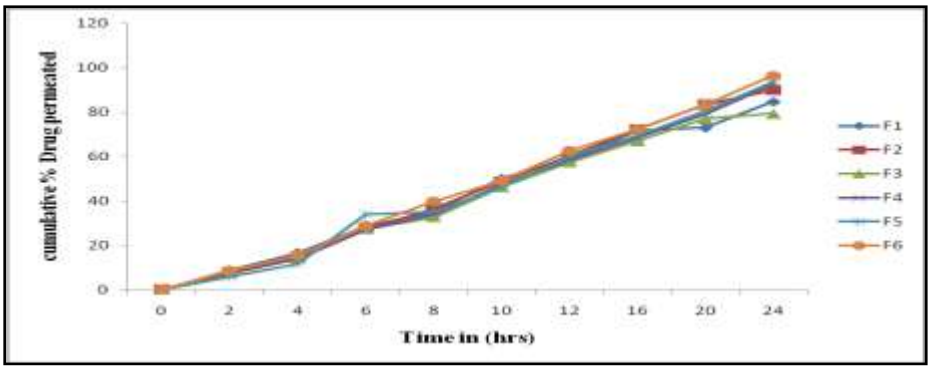

Fig. 12. Comparative *In-vitro* Permeation Profile of Atenolol According to Zero Order Kinetics Formulations F_1-F6.

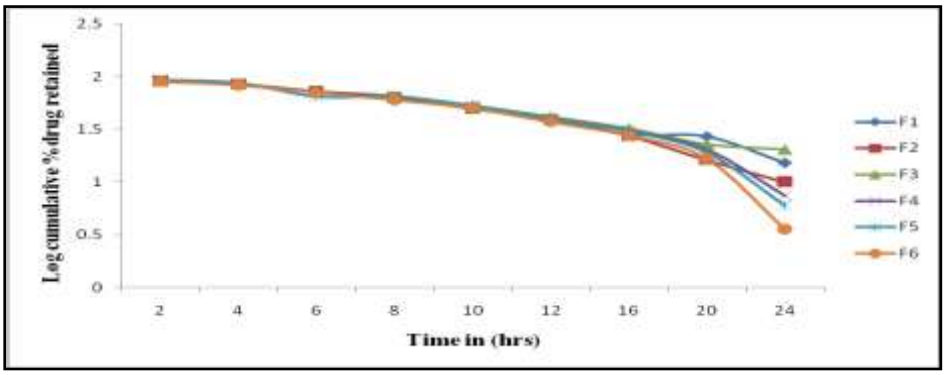

Fig. 13 Comparative *In-vitro* Permeation Profile of Atenolol According to First Order release Kinetics Formulations F_1-F_6.

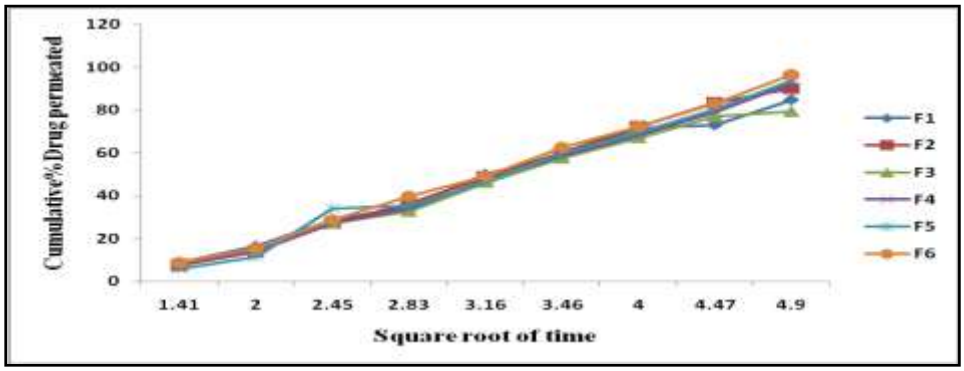

Fig. 14. Comparative *In-vitro* Permeation Profile of Atenolol According to Higuchi Matrix Kinetics for Formulations F_1- F_6

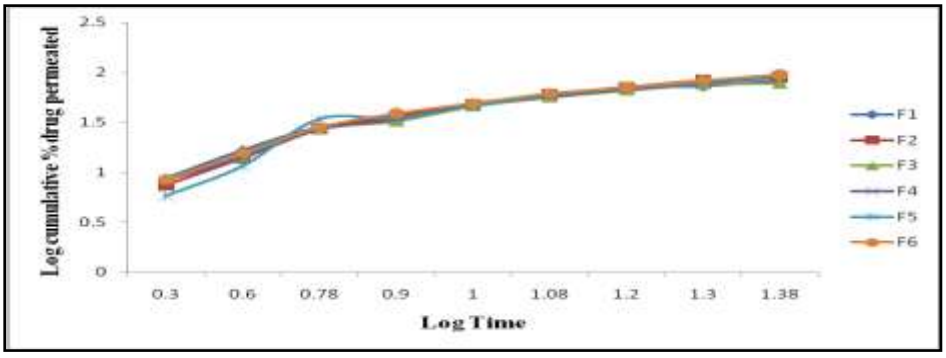

Fig. 15. Comparative *In-vitro* Permeation Profile of Atenolol According to Korsmeyer-Peppas Kinetics for Formulations F_1- F_6.

Table 8. Kinetic values for drug release from transdermal therapeutic system.

Sr. No	Zero Order	First Order	Higuchi	Korsmeyer-Peppas		Best Fit Model
	(r^2)	(r^2)	(r^2)	(r^2)	(n)	
F_1	0.990	0.949	0.990	0.902	0.93	Zero order
F_2	0.996	0.856	0.996	0.906	1.05	Higuchi matrix
F_3	0.989	0.968	0.989	0.911	0.95	Zero order
F_4	0.995	0.862	0.995	0.926	1.04	Higuchi matrix
F_5	0.988	0.843	0.988	0.859	1.13	Zero order
F_6	0.997	0.805	0.997	0.914	1.01	Zero order

Stability Study

Present study was carried out to check the permeation and physical appearance of optimized batch F6 was selected as an optimum batch and the stability study was carried out at accelerated conditions of 40^0C and 75% RH at an interval of one month.

Table 9. Stability Study of batch F6: -

Sr. no	Evaluation Parameter	At o day	After 30 days
1	Thickness (mm)	0.38 ± 0.086	0.36 ± 0.065
2	Weight variation	0.227±0.013	0.225 ± 0.011
3	% Drug Content	94.71 ± 1.41	93.68 ± 1.25
4	Folding endurance	132 ± 10.41	130 ± 12.14
5	Tensile Strength Kg/mm^2	3.91 ± 1.84	3.43 ± 1.64
6	% Elongation	25.26 ± 4.19	24.41 ± 4.3
7	% Moisture content	2.7 ± 0.98	2.5 ± 0.94
8	% Moisture uptake	4.76 ± 1.06	4.89 ± 3.03
9	Swelling index	24.18 ± 1.37	23.46 ± 0.97

Table 10. Drug permeation study:

Time in (hrs)	Cumulative % Drug permeated (At 0 day)	Cumulative % Drug Permeated (After 30 days)
2	8.84	7.53
4	15.55	14.47
6	28.78	27.31
8	39.72	35.18
10	49.07	48.85

12	62.60	60.39
16	72.25	71.58
20	83.19	82.18
24	96.45	95.38

4. DISCUSSION

For the development of every dosage form, pre-formulation trial is an important step. This is more so in case of transdermal drug delivery systems, in which the drug has to pass through the multi-layered lipid sheet as well as aqueous environment of the viable tissue. The goals of the pre-formulation studies are to establish

1. The necessary physicochemical parameters of the drug substances
2. Its kinetics rate profile and
3. Its compatibility with common additives

Pre-formulation Study

Spectroscopic studies

Determination of λ max

A solution of 10µg/ml of Atenolol was scanned in the range of 200 to 400nm. The drug exhibited a λmax 275nm in phosphate buffer pH 7.4 and had good reproducibility. The spectrum obtained is shown in the figure 3. The peak showed in the figure is much similar to the reported peak.

Calibration curve of Atenolol

(Table 2.) shows the calibration curve data of Atenolol in phosphate buffer pH 7.4 at 275nm. (Figure 3.) shows the standard calibration curve with a regression value of 0.999, slope of 0.064 and intercept of 0.013 in phosphate buffer pH 7.4 The curve was found to be linear in the concentration range of 2–12µg/ml. On the basis of obtained results (see table 2. and figure 3.); it was concluded that Atenolol obeys Beer- Lambert's law in the range of 2- 12 µg/ml.

Solubility

The solubility of the drug in a given vehicle determines the active concentration at which the drug could be presented on to the surface of skin. Hence, a good solubility in a chosen vehicle ensures the movement of the drug through delivery systems. The Atenolol is soluble in ethanol, slightly soluble in dichloromethane, and sparingly soluble water, practically insoluble in ether.

Partition Coefficient

The drug without sufficient lipophilicity encounters difficulty in crossing the lipid bilayer. However, when the lipophilicity becomes too prominent, the drug may form a reservoir within these layers. Hence, a balance of hydrophilicity and lipophilicity is desirable in the structure of drug and octanol-phosphate buffer(PH7.4)partition coefficient is thought be good indicator. We found a partition coefficient value of 0.051 for Atenolol.

Melting Point

There is a linear correlation between log flux and reciprocal of melting points indicating that the lower the melting point, the better the penetration. The melting point of Atenolol was found to be 158°C.

Compatibility studies

The combinations were compared with the spectra of pure drug and individual polymer.

The principle peak obtained for the combinations were almost similar to that of the drug.

The FTIR spectra of drug, PVPK30, EC and HPMC, drug-PVPK30, drug-EC and drug–HPMC did not shown any changes. The possibility of interaction was ruled out as there was no major shift in the absorption bands of drug and the formulation.

5. FTIR

FTIR spectrum for Atenolol indicated characteristics peaks belonging to measure functional groups such as principle peaks at wave number at 1631 cm^{-1} due to C=O stretching , at 1510 cm^{-1} owing to –N-H stretching, at 1234 cm^{-1} owing to –C-O, at 750 cm^{-1}due to aromatic substitution and at 1443 cm^{-1} due to –C-H deformation respectively.

Formulations of Transdermal Patches: -

Six formulations of Atenolol transdermal Patches compose with different polymers PVP K30, Ethyl cellulose, HPMC and Propylene glycol as a plasticizer also DMSO and Eugenol and Ethanol is used as penrtration enhancer. Where prepared by solvent Casting techniques using bangles. The bottom of the bangle was wrapped with aluminum foil then solution followed by drying at room temperature for 24hrs. Drug matrix was prepared by dissolving requisite amount of drug (Atenolol) and EC in Water, methanol.(1:1) ratios To this solution Propylene glycol (30%w/w of polymer composition) was added which is shown in (Table-4). The formulations are subjected to evaluation for different parameters which are enlisted in the (Table-4.) and (Table-4.). The prepared transdermal therapeutic systems were thin, flexible and smooth. The solvent Casting method used for the preparation of patches was found satisfactory.

Physicochemical Evaluation

The thickness of the patches varied from 0.34 ± 0.02 to 0.38 ± 0.004mm. The values obtained for all the formulations are given in the table. The low SD values in the Patches thickness measurements ensured uniformity of thickness in each formulation (Table-4). Theweight variation was to be in the range of 0.218 ± 0.005 to 0.234 ± 0.01mg. The values for all the formulations are tabulated in the table. The weights of all transdermal systems were found to be uniform with their low SD values (Table-4).

The drug content uniformity was determined for all transdermal systems. The results of this study revealed that, the drug content was uniform in all systems with relatively low SD values i.e. 91.51 ± 2.17 to 94.71 ± 1.42 (Table-4).

The folding endurance of patch is frequently used to estimate the ability of patch to withstand repeated bending, folding and creasing and may encountered as a measure of the quality of the patch. The folding endurance was found to be in the range of 130± 24.33 to 135.7 ±12.04 number of folds. The values for all eleven formulations are given in the table. This data revealed that the patches had good mechanical strength along with flexibility (Table-4). Tensile strength of the patch was determined to measure the ability of patch to with stand rupture. The tensile strength was found to be in the range of 2.40 ± 0.70 to 4.45 ± 2.18 Kg/mm^2. The formulation F6 showed the best tensile strength. The values for all the patch are tabulated in the table (Table-4). The % elongation was found to be in the range of 23.80 ± 2.12 to 28.04±4.71%. The results obtained for all the formulations are tabulated in the (Table 5).

The percentage moisture content study was carried out to check the integrity of the transdermal patches at dry condition. The moisture content was found to be in the range of 1.85 ± 0.35 to 3.23 ± 2.78. The values for all the patches are tabulated in the respective table. The percentage moisture uptake test was carried out to check physical stability or integrity of the patch at humid condition. Moisture uptake was found in the range of 3.6 ± 3.70 to 4.87 ± 3.13 (Table 3.5). Swelling index was found in the range of from 22.82 ± 1.25 to 25.75 ± 0.72 (Table-5).

***In vitro* Drug Permeation Kinetics**

The results obtaining in In-vitro release studies were plotted in different model of data treatment as follow

The penetration of drug from the Patches is dependent on the type of polymer as well used concentration. *In-vitro* permeation studies were carried out by using franz diffusion cell through cellophane membrane in Phosphate Buffer pH 7.4. In drug Permeation study the formulation F6 contain eugenol is used as natural penetration enhancer it shows maximum drug permeation 96.45% of at the end of 24hrs. Due to which reported that penetration enhancers had functional groups with hydrogen- bonding ability effectively improving the drug transport through skin and also improvement in the partitioning of the drug to stratum corneum. The drug permeation data was plotted for Zero order, First order, Higuchi model and Korsmeyer-Peppas model to evaluate the permeation pattern of the dosage form. From these plots, kinetic values of the drug permeation were determined. In Zero order plot the r^2 value was obtained 0.988 to 0.990, 1storder it was 0.805 to 0.949 for Higuchi model it was 0.988 to 0.997 and for Korsmeyer-Peppas it was 0.902 to 0.926 describing the permeation rate independent of concentration of drug. Hence, formulation prepared containing PVPK30, EC and HPMC fit into zero order and Higuchi model behavior. The process of drug permeation in most controlled permeation devices including transdermal patches is governed by diffusion and the polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three–dimensional network of polymers chain. The *In-vitro* permeation profile could be best expressed by Higuchi's equation for the permeation of drug from the matrix.from a homogeneous- polymer matrix type delivery system that depends mostly on diffusion characteristics. To know the mechanism of drug permeation release kinetics from these formulations, the data were treated according to; Korsmeyer-Peppas model (log cumulative percentage of drug permeated vs.log time) equations (Figure .15) All formulations F1 to F6 showed high linearity with slope (n) values ranging from 0.93 to 1.13 this (n) value indicating that the drug permeation is controlled by more than one mechanism, The exponent (n) values was obtained for optimized formulation F6 by fitting data into Korsmeyer-Peppas equation i.e. 1.013 indicating diffusion of drug from the formulation followed Non-Fickian case II.

Stability Studies

Stability is the essential factor for quality, efficacy and safety of drug product. The drug product with insufficient stability

can result in change of their physical as well as chemical characteristics. The selected formulations namely, F6 were subjected for stability studies and observed for changes in color, appearance, flexibility and drug content at a temperature of 40^0C and 75% RH, at an interval of one month. There were no physical changes in appearance, flexibility and color and physicochemical evaluation parameter was slightly changed (Table-5). The percentage of degradation with respect to drug content was observed 1-2.

6. CONCLUSION

Recently the transdermal patches has been increasingly used for administration of drug mainly because of advantages like the drug with narrow therapeutic window, or drug with short half-life which causes non-compliance due to frequent dosing and easy removal of patch from the site.

In the present study, attempt was made to formulate and evaluate TDDS for Atenolol by solvent casting method. Low molecular weight, good permeability and shorter half-life of Atenolol made it a suitable drug candidate for the development of transdermal delivery system.

The scheme of work has been divided into various parts. The collection of theoretical and technical data by extensive literature survey, review of literature, drug and polymer profile is presented. This was followed by procurement of material and standardization of all materials used in the formulation of transdermal patches.

In the pre-formulation studies λmax, IR, solubility, partition coefficient and melting point of drug was determined to assess its application for transdermal delivery.

The transdermal patches were prepared by using combination of different polymers along with plasticizer and penetration enhancers. The three different penetration enhancers used.

The prepared transdermal patches were evaluated for evaluation parameters to check the integrity of formulation such as thickness uniformity, weight uniformity, drug content uniformity, folding endurance, tensile strength, percentage elongation, flatness, moisture content, moisture uptake, swelling index, In-vitro drug diffusion through cellophane membrane.

The results obtained have been discussed in the Results of FT-IR revealed that there was no chemical interaction between the drug and the polymer used. The prepared transdermal patches were, thin, smooth and flexible, uniformity in drug content, physicochemical properties were observed with their low SD values. Among the formulations F_6 was found to be best with respect to drug release rate i.e. 96.45% at the end of 24 hr. All the formulations follow nearly zero order and Higuchi matrix kinetic by Non-Fickian case II mechanism of drug release. From the above result formulation F6 was found to be best formulation for transdermal delivery of Atenolol that complied with all the parameters. However Ex-vivo experiments need to be carried out to know the permeation pattern and bioavailability of drug from the transdermal patches and thus enabling to establish *In-vitro-In-vivo* correlation.

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