Formulation and Evaluation of Transdermal Patches of Atenolol

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Abstract: *Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. It provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first pass metabolism. Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Skin penetration enhancers are used for bioavailability and increase the range of drugs to be administrated topically or transdermal routes. This study was done to develop matrix type transdermal patches containing Atenolol with different ratios of HPMC (Hydroxyl propyl methyl cellulose) & EC (Ethyl cellulose) by solvent casting method. Atenolol is a receptor blocking agent. It does not have membrane β-1 selective (cardio-selective) β adrenergic stabilizing and intrinsic sympathomimetic (partial agonist)activities. It is effective at reducing blood pressure but it does not reduce the morbidity or mortality rate. Hydroxypropylmethylcellulose (HPMC) is used in the development of hydrophilic matrices. It provides the release of a drug in a proper way, which increases the duration of release of a drug to prolong its therapeutic effect. 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. In-vitro studies were performed using Franz diffusion cell.*

Key Words: *Transdermal drug delivery systems (TDDS), Atenolol, HPMC, In-vitro permeation study.*

1. INTRODUCTION:

Transdermal drug delivery system(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. It provides a controlled rate release of medicaments, it avoids hepatic metabolism, ease of termination and long duration of action. It is used in the treatment of skin disease. The systemic drug administration through skin maintains drug level in blood and improves the bioavailability of hepatic first pass metabolism and increase patient compliance. Skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the blood stream. Skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the blood stream. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and directly into the blood stream. Transdermal patches are used in many therapeutic areas like pain management, smoking cessation and treatment of heart disease, hormone replacement and management of motion sickness. Atenolol is a receptor blocking agent. It does not have membrane β-1 selective (cardioselective) β adrenergic stabilizing and intrinsic sympathomimetic (partial agonist) activities. The elimination half-life of atenolol is 6 to 7 hours and there is no alteration of kinetic profile of drug by chronic administration. Atenolol reduces renal vascular resistance in hypertensive. No effect on creatinine clearance, glomerular filtration rate or renal blood flow. Atenolol does not pass the blood brain barrier. Atenolol is used in many conditions such as hypertension, angina, acute myocardial infarction, supera ventricular tachycardia, ventricular trachycardia and in withdrawal symptoms of alcohol. Antihypertensive therapy with atenolol provides weaker protective action against cardiovascular complications such as myocardial infraction and stoke. Hydroxy propyl methyl cellulose (HPMC) in the development of hydrophilic matrices. It is a semisynthetic, inert, viscoelastic polymer, excipients and controlled- delivery component in oral medicaments. It is a methyl and hydroxyl propyl mixed ether of cellulose. It provides the release of a drug in a controlled manner, which increases the duration of release of a drug toprolong its therapeutic effect. This application may be used in many fields including: tile adhesives, pharmaceuticals, paint and coatings, food, cosmetic, detergents and cleaners, eye drops, contact lens.

2. MATERIALS AND METHODS:

Atenolol (Gift sample from molecular lab Ahmadabad), Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC)(Gift sample from molecular lab Ahmadabad), Propylene glycol, Span 80, Ethanol, Cyclohexane, Methylene chloride, Ethyl acetate, Ether, Franz Diffusion Cell (Ponmani& Co, Coimbatore), Magnetic Stirrer (Remi equipment Ltd., Vasai), pH Meter (Hanna instruments, Italy) UV/VIS Spectrophotometer (Shimadzu, Indore), FTIR (Brukar optics. Germany)

3. Preparation of standard Calibration curve of Atenolol:

Atenolol was estimated by measuring the absorbance at 275nm.Calibration curve was prepared by taking absorbances of five serial dilutions of stoke solution. The graph was plotted between absorbance and concentration of drug.

Preparation of transdermal patches of Atenolol:

Matrix patches were casted on a glass dish by solvent casting method. First two patches were prepared by using HPMC alone with drug and polymer ratio 1:2, 1:3 using Water and methanol ratio 1: 9 and one more formulation prepared 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:(4:8), 1: (1:9) using methanol as a solvent with using permeation enhancer Span 80 (1%) and Propylene glycol (3%) used as a plasticizer. One patch was prepared using EC alone as a polymer with drug polymer ratio 1: 4 and Span 80(1%) and Propylene glycol (3%).

Table No: 1Fabrication of Transdermal patches of Atenolol

Ingredient	F1	F2	F3	F4	F5	F6
Atenolol(Drug)	100mg	100mg	100mg	100mg	100mg	100mg
HPMC	200mg	300mg	400mg	400mg	100mg	---
EC	---	---	---	800mg	900mg	400mg
Span 80	---	---	1%	1%	1%	1%
Propylene Glycol	---	---	3%	3%	3%	3%

4. Evaluation of Transdermal Patches:

1. Physico-Chemical Evaluation

Thickness of the patch:

Thicknesses of the films were measured by using VarnierCaliper.

Percentage ofMoisture content:

The prepared films were weighed individually and put in a desiccator containing calcium chloride at room temperature for 24 h. The films were weighed again after a specified interval until they showed a constant weight. The percent moisture content was calculated using following formula:

%Moisture content =
(Initial weight -Final weight) X 100 / Final weight

Percentage of Moisture uptake

Weighed films were put in a desiccator at room temperature for 24 h. These were then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake was calculated as given below.

% Moisture uptake =
(Final weight - Initial weight) X 100 / Initial weight

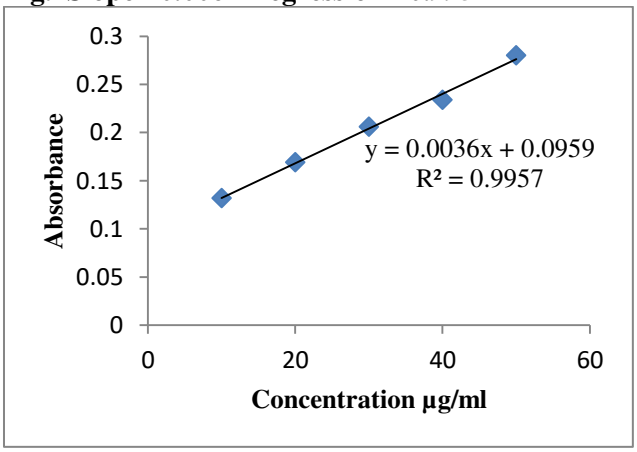
Drug Content uniformity test:

Patch was 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 was determined using spectrophotometer at 275 nm. Content of drug was found between 85 % to 115 % of the specified value.

Table No: 2 Standard curve of Atenolol

S. No.	Concentration (µg/ml)	Absorbance
1.	10	0.132
2.	20	0.169
3.	30	0.206
4.	40	0.234
5.	50	0.280

Fig.1Slope= 0.0061 Regression= 0.995



The preliminary study conducted on compatibility between Atenolol with HPMC and EC revealed that no interaction between the drug and polymer was observed in FTIR spectra. HPMC polymer was selected for preparation of Patches. It is used as rate controlling polymer for sustained release and also it acts as stabilizing agent.

Compatibility Study: The drug was identified and compatibility was confirmed by FTIR spectra shown in Figure no: 2, 3, and 4.

Fig.2IR spectrum of Atenolol

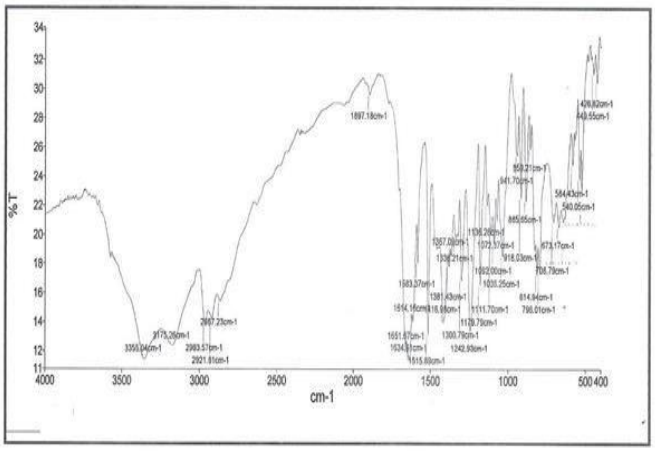


Fig 3.IR Spectrum of Atenolol + HPMC

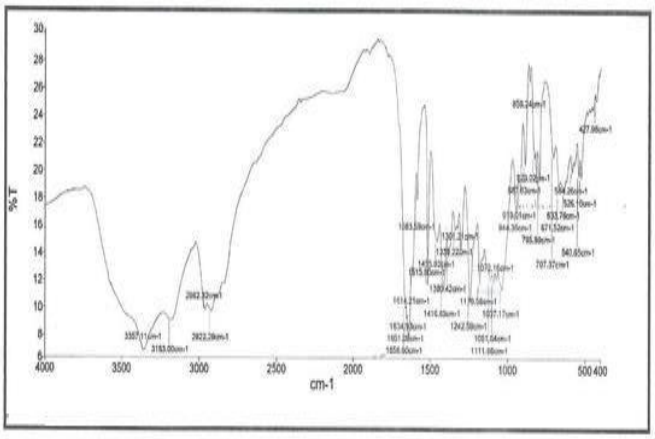
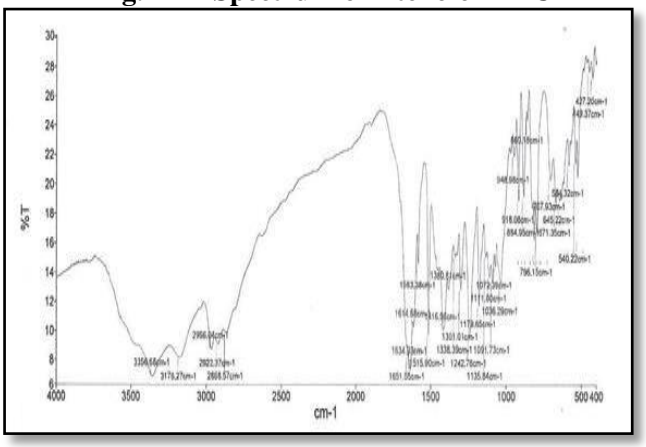


Fig. 4 IR Spectrum of Atenolol + EC



5. Evaluation of Transdermal Patches :

Thickness of the patch: Results are shown in table 3

S. no./ Code	F1(mm)	F2(mm)	F3(mm)	F4(mm)	F5(mm)	F6(mm)
1.	0.155	0.176	0.186	0.272	0.237	0.197
2.	0.157	0.172	0.178	0.269	0.231	0.193
3.	0.151	0.168	0.183	0.271	0.235	0.190
4.	0.154	0.174	0.181	0.264	0.241	0.199
5.	0.155	0.164	0.189	0.274	0.238	0.194
Mean	0.154	0.170	0.183	0.270	0.236	0.194

Moisture content:

Amount of water in each patch was determined and found within criteria. Higher moisture content causes the degradation of patch.

Table 4. Moisture content

S. no.	Code	% Moisture Content
1.	**F1**	1.20
2.	**F2**	1.45
3.	**F3**	1.50
4.	**F4**	1.38
5.	**F5**	1.17
6.	**F6**	1.27

Moisture uptake:

Table: 5 Moisture Uptake Determinations

S. no.	Code	% Moisture Uptake
1.	**F1**	2.21
2.	**F2**	2.34
3.	**F3**	2.99
4.	**F4**	1.47
5.	**F5**	2.22
6.	**F6**	2.01

Folding Endurance:

Table: 6 Folding Endurance Study

S. no.	Code	Folding Endurance
1.	**F1**	25
2.	**F2**	28
3.	**F3**	35
4.	**F4**	51
5.	**F5**	42
6.	**F6**	47

***In vitro* Diffusion studies**

Table: 7 Diffusion Studies of Patches

S. No.	Time(hr)	% Cumulative Drug Release					
		F1	F2	F3	F4	F5	F6
1.	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.	1.00	4.03	17.11	9.00	19.00	12.02	17.12
3.	2.00	6.06	21.33	12.01	23.23	21.32	21.52
4.	4.00	10.09	27.57	14.11	28.98	27.65	26.46
5.	6.00	15.18	33.92	17.46	34.00	32.61	30.77
6.	8.00	18.37	39.38	21.56	40.42	36.98	35.23

Table: 8 *In- Vitro* Permeation Profile of Atenolol from Formulation F4

S. No.	Time(hr)	√T	LogT	% Cumulative Drug Release	% Cumulative Drug Remain	Log % Cumulative Drug Release	Log % Cumulative Drug Remain
1.	0.00	0.00	-	0.00	100.00	0.00	2.00
2.	1.00	1.00	0.00	19.00	81.00	1.28	1.91
3.	2.00	1.41	0.30	23.23	76.77	1.37	1.89
4.	4.00	2.00	0.60	28.98	71.02	1.46	1.85
5.	6.00	2.45	0.78	34.00	66.00	1.53	1.82
6.	8.00	2.83	0.90	40.42	59.58	1.61	1.78

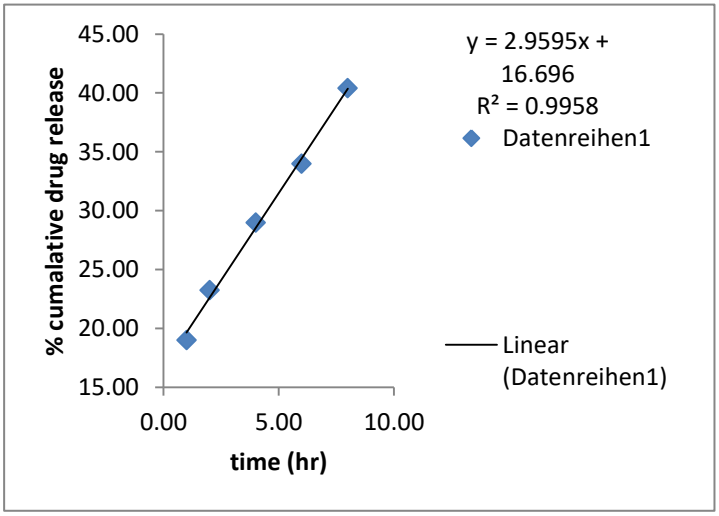


Fig.5: Zero Order Release Plot of Atenolol patch Formulation F4

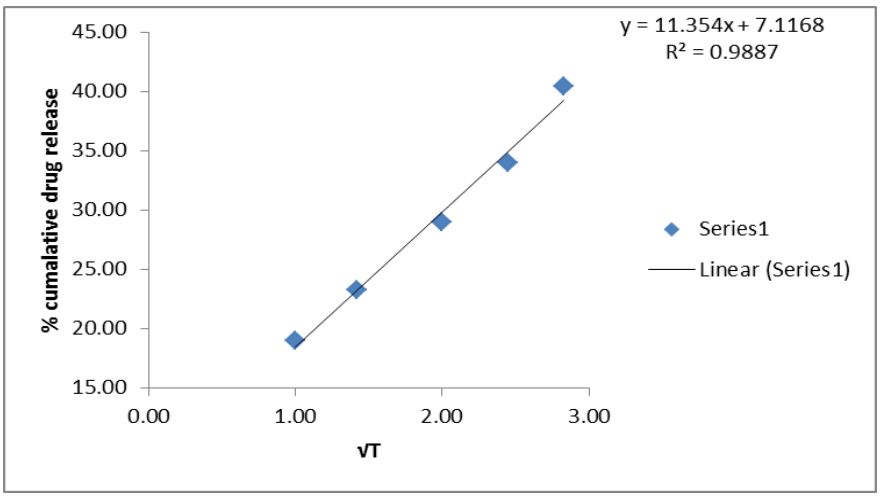


Fig. 6: Higuchi Plot of Atenolol patch Formulation F4

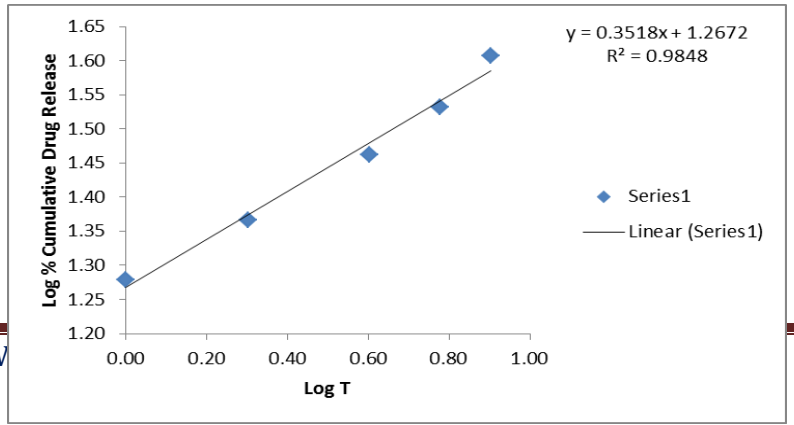


Fig. 7: KorsmeyerPeppa's Plot of Atenolol patch Formulation F4

6. CONCLUSION:

The transdermal patches were prepared using solvent casting method by using combination of HPMC and Ethyl cellulose in various ratio using propylene glycol and span 80 as a plasticizer and permeation enhancer. 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. Atenolol is anti-hypertensive drug and transdermal patch are efficiently used in the management of hypertension for prolong period of time. From the experimental results of the formulation F-1, F-2, F-3, F-4, F-5 and F-6 the thickness were found to be 0.154mm, 0.170mm, 0.183mm, 0.270mm 0.236 and 0.194mm respectively. Uniformity of weight was found to be 304,401.2, 502.4, 1302.6, 1102.4 and 503.2mg respectively. Folding endurance was found to be 25, 28, 35, 51, 42 and 47 respectively. Moisture absorbed was 2.21%, 2.34%,2.99%, 1.47%, 2.22%, and 2.01% respectively. Moisture Content was found to be 1.20%. 1.45%, 1.50%, 1.38%, 1.17% and 1.27% respectively. Drug content was found to be 78.56%, 87.63%, 92.39%, 98.52%, 96.33% and 94.58% respectively. In vitro Diffusion of the drug were 18.37%, 39.38%, 21.56%, 40.42%, 36.98% and 35.23% respectively. From the experimental results it can be concluded that the formulation F4 showed optimum drug diffusion 40.42% thickness 0.270mm, Moisture absorbed 2.99%, Moisture content 1.38%, Folding endurance 51 and Drug Content 98.52%.

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