Research Article

Formulation and evaluation of prolonged release transdermal drug delivery system of atenolol for the treatment of hypertension

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ABSTRACT

The objective of the present study was to formulate and evaluate controlled and prolonged release transdermal drug delivery system of atenolol for effective management of hypertension. The administration of atenolol via transdermal patch facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration. To fulfill above objective transdermal patches of atenolol were prepared by solvent evaporation method using combinations of Eudragit RL100, Ethyl cellulose and PVP in different proportions. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, water vapour transmission and tensile strength were evaluated. In-vitro Diffusion Study, skin irritation test and stability studies were also performed. In PVA and Eudragit RL 100 patches the water vapor transmission rate was found to be higher at 75% RH, RT conditions. Therefore at both % RH, RT conditions the PVA and Eudragit RL 100 patches provide the best resistance to water vapor.

Keywords: Atenolol, Eudragit RL100, Ethyl cellulose, PVP, Transdermal patch, In-vitro permeation study

INTRODUCTION

Transdermal drug delivery (TDDS) is defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. TDDS established itself as an integral part of novel drug delivery systems that breaks many barriers in drug delivery like need of assistance, intermediate dosing and uncomfortable administration [1]. Transdermal medication delivers a steady infusion of a drug over an ex-tended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided [2-4]. Transdermal delivery can also increase the therapeutic value of many drugs by avoiding specific problems associated with the drugs like gastrointestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects and short half-life necessitating frequent dosing etc [5]. Above all this drug input can be terminated at any point of time by removing transdermal patch. However, to deliver drugs through transdermal route, it must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very

difficult [6,7]. Hence relatively potent drugs are only suitable candidates for TDDS.

Atenolol is a β1-receptor selective antagonist and is mainly used in treating hypertension, angina, heart failure, and myocardial infarction; chemically, it is 4-(2-hydroxyl-3-isopropyl aminopropoxy) phenylacetamide. The physicochemical properties of atenolol, i.e., slight water solubility, low molecular weight (266.336), and its suitable elimination half-life (6–7 h), make it a suitable candidate for administration by TDDS [8,9].

The polymeric film containing Eudragit RL 100, Ethyl cellulose, PVP and drug (Table. 1.) were selected for transdermal administration based on evaluation studies [10,11]. The polymeric films were prepared by mercury substrate method employing PEG-400 as plasticizer. Two different penetration enhancers Urea and Dimethyl sulphoxide (DMSO) were employed in the study. The dried polymeric film was evaluated using different parameters including thickness uniformity, drug content of the film, in vitro drug release from films and in vitro skin permeation of drug [12].

MATERIALS AND METHODS

Materials

Atenolol was obtained as a gift sample from Fourt's India, Chennai. Eudragit RL100 and Eudragit RS (S. D. Fine Chem. Ltd., Mumbai), Ethyl cellulose, PVP K-30 (S. D. Fine Chem. Ltd., Mumbai), Urea and Dimethyl sulphoxide (DMSO) (S. D. Fine Chem. Ltd., Mumbai) were procured for above study. All other chemicals used were of analytical grade.

Preparation of Atenolol - Containing Transdermal Patches

The transdermal patch was prepared by solvent evaporation technique on mercury substrate. Polymer solution was prepared in ethanol (10 ml) and to it atenolol was added. The plasticizer and permeation enhancer were added during patch casting. The solution was poured on glass rings placed on mercury surface and allowed to dry in air for 24 h. Circular patches of 2 cm diameter (3.14 cm^2) were cut from semi dried patches and placed in vacuum desiccators [7].

Evaluation of patch

* Measurement of thickness and weight variation

Thickness was measured using micrometer screw gauge (Mitutoyo, Japan). Each patch was measured for thickness at six different points to ascertain thickness uniformity in patch [13,14]. Weight variation was determined by weighing three patches individually, from each batch and the average weight was calculated [5](Table 2).

* Tensile strength

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength [15]. The tensile strength of the patches was determined by using a tensile strength instrument as described by Agarwal GP, et al (Fig. 1.). Average reading of three patches was taken as the tensile strength. The transdermal patch was fixed to the assembly, the weights required to break the patch was noted, and simultaneously elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the patch using the following formula

T. S. = break force/ a.b (1+ΔL/L)

Where a, b and L are width, thickness and length of the patch respectively.

ΔL is the elongation of patch at break point.

Break force = Weight required to break the patch (Kg) [16].

* Folding Endurance

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness [17]. This was determined by repeatedly folding one patch at

the same place till it break (Table 2). The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance [18].

* Water vapour transmission

The water vapour transmission is defined as the quantity of moisture transmitted through unit area of a patch in unit time. The water vapour transmission data through transdermal patches are important in knowing the permeation characteristics [19]. Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to constant weight in an oven. About 1 gm of fused calcium chloride as a desiccant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape. These pre-weighed vials were stored in a humidity chamber at RH of 80% with the temperature set to 30ºC for a period of 24 hours (Table 2). The weight gain was determined every hour up to a period of 24 hours [20].

The water vapour transmission was calculated using the equation

Rate = WL/S

Where W is gm of water permeated / 24 hr. L is thickness of the patch S is exposed surface area of the patch [21].

* Drug Content Uniformity

In order to ascertain the uniform distribution of the drug in the patches, the content uniformity test was carried out utilizing the pharmaceutical standard by means of a UV/Visible spectrophotometer. The transdermal patch of specified area (3.14 cm²) was dissolved in 100 ml pH 7.4 phosphate buffer. This was then shaken in a mechanical shaker for 2 h to get a homogeneous solution and filtered (Table 2). A blank was performed using a drug free patch treated similarly. The drug content in each formulation was determined by measuring the absorbance at 274 nm after suitable dilution using a UV/visible spectrophotometer [22].

* *In-vitro* Diffusion Study:

The in-vitro diffusion study is carried out using Franz Diffusion Cell (Ponmani & Co, Coimbatore) [23,24]. 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 PBS pH 7.4. The receptor compartment is surrounded by water jacket to maintain the temperature at $37 \pm 0.5°C$. 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 were withdrawn and replaced by equal volumes of fresh receptor fluid on each occasion. The sample withdrawn was analyzed spectrophotometrically at 274 nm (Table 3, Figure 2).

* Skin irritation test

The skin irritation test was performed on a healthy rabbit weighing between 2 to 3 kg. Drug loaded polymeric film of 3.14 cm² was placed on the left dorsal surface of the rabbit. The patch was removed after 24 h with the help of alcohol swab. The skin was examined for erythema and oedema [25].

Stability studies:

All the films were exposed to three selected temperatures of 4°C, 27°C and 40°C. Transdermal films were kept in the oven for period of 45 days. The films were analyzed for the drug content on 0, 15, 30 and 45 day of storage. The averages of triplicate readings were taken (Table 4).

RESULTS AND DISCUSSION

The main goal of the present investigation efforts was to develop and evaluate new

patches comprising of Atenolol containing Eudragit RL 100, Ethyl Cellulose and PVP in various combinations. The physicomechanical evaluation (Table 2) indicates that the weight variation of these formulated patches varied between 153.1±1.25 (F 3) and 173.9±2.54 (F10). The thickness of these patches varied between 0.239±0.0032 and 0.352±0.0023mm, the thinnest being formulation F9 and the thickest being formulation F4. Folding endurance was measured manually. The highest folding endurance was observed in the case of F7 and the lowest in the case of F1. The range of folding endurance study ensured flexibility of these formulated patches. The drug content (%) in all formulations varied between the range 96.87% and 98.87. This indicates that the drug dispersed uniformly throughout the polymeric film.

The water vapour transmission data through transdermal patches are important in knowing the permeation characteristics that was performed in a humidity chamber at RH of 80% with the temperature set to 30ºC for a period of 24 hours. The maximum water vapour transmission was found with F1 while least was observed with formulation F12.

The in vitro drug release pattern of atenolol from formulated transdermal patches is shown in Figure 2. All of these patches slowly released the drug, incorporated and sustained over a period of 10 h. The drug release from patches varied with respect to the polymer composition and nature. An increase in drug release from the patches was found with increasing concentration of polymers that are more hydrophilic in nature. Among all formulations, the maximum in vitro drug release (56.49mg) over a period of 10 h was observed in the case of formulation no. F2, while the minimum in vitro drug release (32.46mg) over a period of 10 h was found in the case of formulation F6. The in vitro drug release was more sustained for the atenolol patches which were composed with high proportion of Eudragit RL 100. The *in vitro* permeation data shows that the release of atenolol with polymer of eudragit and PVP is more sustain compare to EC and PVP. The increase in proportion of PVP shows more diffusion of drug. Skin irritation test on rabbit showed no sign of skin reaction and erythema hence the fabricated transdermal patch was suitable for further studies.

SUMMARY AND CONCLUSION

Transdermal drug delivery systems are polymeric patches containing dissolved or dispersed drugs that deliver therapeutic agents at a constant rate to the human body. Matrix type transdermal patches containing atenolol were prepared by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, tensile strength, folding endurance, drug content, water vapour transmission and skin irritation studies.

The permeability of Atenolol was increased with increase in PVP content. The burst effect due to the incorporation of PVP was because of the rapid dissolution of the surface hydrophilic drug which results in the formation of pores and thus leads to the decrease of mean diffusion path length of the drug molecules to permeate into dissolution medium and higher permeation rates. Based on the above observations, it can be reasonably concluded that Eudragit RL100-PVP polymers are better suited than EC-PVP polymers for the development of transdermal patches of Atenolol.

Table 1. Composition of Transdermal Patches of Atenolol

Formulation Code	% ERL 100	% EC	% PVP	Atenolol	%PEG400	%Urea	%DMSO
F1	10	-	-	70mg	-	-	1
F2	9	-	1	70mg	1	1	2
F3	8	-	2	70mg	2	2	4
F4	7	-	3	70mg	3	3	6
F5	6	-	4	70mg	4	4	8
F6	5	-	5	70mg	5	5	10
F7	-	5	5	70mg	5	5	10
F8	-	6	4	70mg	4	4	8
F9	-	7	3	70mg	3	3	6
F10	-	8	2	70mg	2	2	4
F11	-	9	1	70mg	1	1	2
F12	-	10	-	70mg	-	1	1

Table 2. Characterization of transdermal patches

Code	Wt. variation (mg)	Thickness (mm)	Tensile strength (kg/m^2)	Folding Endurance	Water vapour transmission (gm/cm^2.24h)	Drug Content (%)
F1	160.8±1.24	0.312±0.0024	0.412±0.0062	258±4.23	4.12 X10^{-4}	95.54
F2	160.2±1.76	0.303±0.0024	0.473±0.0036	272 ± 4.34	4.81 X10^{-4}	98.87
F3	153.1±1.25	0.318±0.0021	0.463±0.0045	265 ± 3.11	4.93 X10^{-4}	97.92
F4	176.3±2.34	0.352±0.0023	0.449±0.0057	259 ± 5.23	5.19 X10^{-4}	97.11
F5	157.0 ±1.84	0.334±0.0031	0.435±0.0069	248 ± 3.88	5.56 X10^{-4}	98.92
F6	168.9±1.92	0.331±0.0042	0.426±0.0071	246 ± 4.61	5.93 X10^{-4}	98.40
F7	165.3±2.41	0.236±0.0027	0.421±0.0028	315 ± 4.12	5.99 X10^{-4}	96.87
F8	168.7±2.13	0.242±0.0036	0.409±0.0035	309 ±3.86	6.25 X10^{-4}	97.32
F9	158.4±1.35	0.239±0.0032	0.394±0.0046	298 ±5.02	6.36 X10^{-4}	98.67
F10	173.9±2.54	0.241± 0.0041	0.386±0.0055	294 ±5.11	6.53 X10^{-4}	98.77
F11	166.2±1.82	0.248±0.0058	0.377±0.0072	289 ±4.51	6.88X10^{-4}	98.55
F12	171.6±1.42	0.292±0.0012	0.312±0.0036	285±3.78	6.92 X10^{-4}	97.54

Table 3. In-Vitro diffusion studies of various Atenolol transdermal patches

S. No.	Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
						DRUG RELEASE					
1	0	0	0	0	0	0	0	0	0	0	0
2	0.5	4.58	5.55	6.78	7.98	8.14	2.45	3.98	4.90	5.12	6.45
3	1	6.26	7.56	8.22	9.55	10.45	4.03	5.25	8.14	9.11	11.41
4	2	12.22	14.26	16.25	16.34	17.41	6.06	7.22	10.22	10.97	12.08
5	3	17.56	19.45	21.40	22.14	24.51	10.09	12.25	14.65	15.26	16.25
6	4	22.26	25.16	27.48	29.42	31.26	15.18	17.26	19.24	21.26	24.26
7	5	28.26	30.20	32.55	33.27	35.85	18.37	19.56	22.59	23.45	28.47
8	6	34.56	36.08	39.21	41.12	43.56	22.60	23.78	25.04	26.24	31.24
9	7	40.22	43.57	46.79	48.06	50.21	26.90	28.04	30.22	31.26	34.22
10	8	45.65	49.25	51.24	53.11	55.22	29.28	30.87	31.26	32.44	35.58
11	9	48.95	52.26	55.21	56.54	58.42	31.72	33.26	33.99	35.26	37.89
12	10	52.39	56.49	48.98	51.68	53.49	32.56	34.58	35.09	36.89	39.21

Table 4. Stability studies data for F5

Days	% Drug Remained		
	4°C	**27°C**	**40°C**
0	98.92	98.92	98.92
15	98.20	97.88	96.58
30	97.82	97.16	95.12
45	97.66	96.42	94.56

Figure 1: The tensiometer used to measure the tensile strength
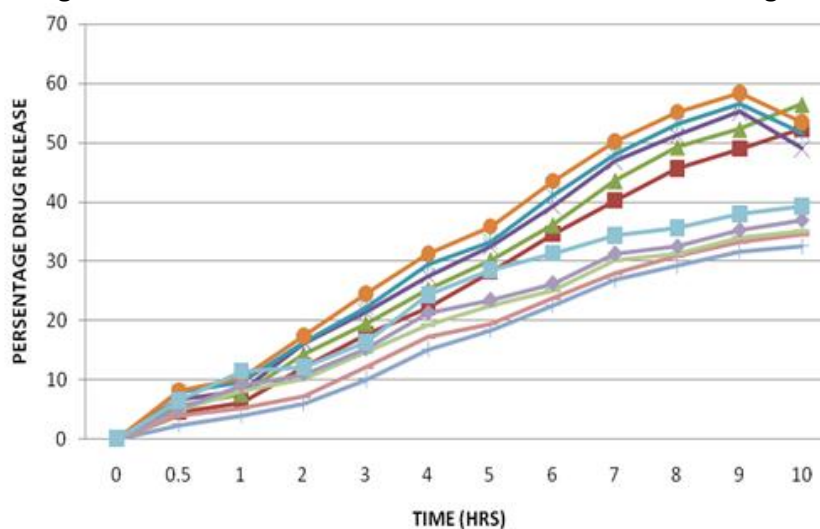
Figure 2: In-Vitro diffusion studies of various Atenolol transdermal patches

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