



Development and evaluation of Transdermal drug delivery system of Atenolol

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ABSTRACT

Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects such as diarrhea, ischemic colitis and mesenteric arterial thrombosis or reduction in drug concentration at the receptor site. Transdermal drug delivery (TDD) method has been selected as it provides controlled release of the drug, and produces a steady blood-level profile, leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. In the present work efforts have been made to prepare transdermal drug delivery system of Atenolol using various blends of polymers such as Eudragit RS 100, Hydroxy Propyl methyl cellulose and Poly vinyl pyrrolidone using propylene glycol as a permeation enhancer. The prepared patches were evaluated for various physicochemical properties and *in-vitro* drug release studies. The release were fitted to statistical treatment such as Zero order kinetics, Higuchi's and Peppas's plot. The optimized formulation from the *in-vitro* drug release study is used to carry out *in-vitro* skin permeation study using porcine ear skin, snake shed skin and rat skin. The *in-vivo* evaluation of formulation F 7 (2% Eudragit RS 100, 1%HPMC) show better correlation with the *in-vitro* drug release which confirms the achievement of targets of the present study such as controlled prolonged zero order release, reduced frequency of administration, greater therapeutic effect, overcome the side effects, simplify the treatment regimen and thus may improve patient compliance.

Keywords: Atenolol; Eudragit RS 100; Transdermal Patch; Zero order kinetic

INTRODUCTION

Atenolol is a β -blocker without membrane stabilizing or intrinsic sympathomimetic activity, which has been used for the treatment of hypertension (Hoffman BB, 2001). The drug is also frequently indicated in the prophylactic treatment of migraine. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects such as diarrhea, ischemic colitis and mesenteric arterial thrombosis (Cho CW & Shin SC, 2004) or reduction in drug concentration at the receptor site (Sastry SV *et al.*, 1997).

To overcome these adverse effects in the GI tract while sustaining the therapeutic efficacy of atenolol, an alternative drug delivery method might be useful (Young-Chang Ah *et al.*, 2009). Transdermal drug delivery (TDD) method has been selected as it provides controlled release of the drug, and produces a steady blood-level profile (Modamio P *et al.*, 2000), leading to reduced systemic side effects and, sometimes, im-

proved efficacy over other dosage forms (Ranade VV, 1991). In addition, it confers several advantages over more traditional administration and leads to improved patient compliance. Consequently, the transdermal therapeutic system is of particular clinical significance for the prevention and long-term treatment of chronic diseases like hypertension (Changshun Rena *et al.*, 2009).

The aim of the present study was to investigate atenolol transport from a transdermal patch system and to determine whether therapeutically relevant delivery rates could be achieved under these conditions. After an initial investigation of formulation parameters their effect on atenolol transport across porcine ear skin, rat skin and snake shed skin was also investigated by *in-vitro* method. The sustained activity was due to the controlled release of drug into the systemic circulation following transdermal administration.

EXPERIMENTAL WORK

Materials and Methods

Atenolol was gift from Sun Pharmaceutical Industries Ltd. (India). Hydroxy Propyl methyl cellulose (HPMC K4M), Poly vinyl pyrrolidone (PVP K30), Eudragit RS 100 was purchased from Loba Chemie Ltd. (India). All other chemicals used for this study were of analytical grade.

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Preformulation Studies

Drug partition coefficient

The partition co-efficient of the drugs was determined using n-octanol: Phosphate buffer (pH 7.4) system. The n-octanol- Phosphate buffer partition coefficient serves as a parameter of lipophilicity. n- Octanol and Phosphate buffer were presaturated with each other for at least 24 h before the experiment. An accurately weighed quantity of each drug was dissolved in 10 ml of the n-octanol phase and shaken at 37°C for 24 h against 10 ml buffer in a sealed container. The separated n-octanol phase was assayed by UV spectroscopy to determine its residual concentration and hence the amount partitioned into the buffer (Marin *et al.*, 1998, McDaid *et al.*, 1996). The partition coefficient was expressed as the concentration of drug in the n-octanol phase (% w/v) divided by the concentration in the aqueous phase.

Drug–excipient interaction study

The pure drug, Atenolol and a mixture of it with the polymers, HPMC, PVP and CP were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying pressure in a hydraulic press (Jagmohan *et al.*, 2003). The pellets were scanned over a wave number range of 4000-400 cm^{-1} in Shimadzu Japan, FTIR instrument.

Table 1: Composition of transdermal patches using Atenolol

Formulation Code	Eudragit RS100	HPMC	PVP
F 1	1.0	1.5	0.5
F 2	1.0	0.5	1.5
F 3	1.0	1.0	1.0
F 4	1.0	2.0	-
F 5	1.0	-	2.0
F 6	2.0	0.5	0.5
F 7	2.0	1.0	-
F 8	2.0	-	1.0
F 9	1.5	1.5	-
F 10	1.5	-	1.5
F 11	-	1.5	1.5

Drug loaded in each film: Atenolol: 25mg; Plasticizers: Propylene Glycol (30% w/w of polymer), backing membrane: Aluminium foil.

Fabrication of transdermal patches

Transdermal patches composed of different polymers containing Atenolol were prepared by Solvent Casting technique as illustrated in Table 1. Firstly, drug was dissolved in ethanol. Base materials were added into the solution and swelled in ambient temperature. Permeation enhancers and plasticizer were added to the solution, and then agitated in a sonicator. This was casted on a glass surface containing ring, it was covered by funnel to control evaporation of solvent and allowed to dry at room temperature over night. The

films were separated and the backing membrane used was aluminium foil and the formulations were stored in desiccator. After being dried, the single-layer patch was obtained (Anitha P *et al.*, 2011).

Physico chemical evaluation of the prepared films

Thickness and weight variation

The thickness of the patch at three different points was determined using thickness gauge and the patches were then weighed individually using digital balance to determine the weight of each patch taken out from the casted film. The patches were subjected to weight variation by individually weighing ten randomly selected patches. Such determinations were carried out for each formulation (Mundada *et al.*, 2009).

Folding endurance test

Folding endurance test was carried out by folding the patch at the same point a number of times till it broke (Ubaidulla *et al.*, 2007). The test was carried out to check the efficiency of the plasticizer and the strength of the film prepared using varying ratios of the polymers. The test was carried out in triplicate.

Percentage Moisture Loss

Accurately weighed films of each formulation were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days (Kusum Devi *et al.*, 2003). The test was carried out in triplicate. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight.

Percentage moisture uptake

Accurately weighed films of each formulation were kept in a desiccator which is maintained at 79.5% relative humidity (saturated solution of aluminium chloride) at room temperature and weighed after 3 days (Biswajit Mukherjee *et al.*, 2005). The test was carried out in triplicate. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Water absorption capacity

Three film units of each formulation were kept in an atmosphere of relative humidity RH = 82% for one week and the difference in weight of the film was taken as the water absorption capacity for that film (Udupa *et al.*, 1992).

Water vapor transmission rate

For water vapor transmission studies glass vials of equal diameter were used as transmission cell (Kulkurni Raghavendra *et al.*, 2000). These transmission cells were washed thoroughly and dried in an oven. About 1 gm of anhydrous calcium chloride was taken in the cell and the polymer film was fixed over the brim with the help of the solvent. The cell were accurately weighed

Table 2: Physico-chemical evaluation of transdermal films

F Code	Thickness (mm) ± SD	Weight Uniformity ± SD	Folding Endurance ± SD	Drug Content (%)
F 1	0.35± 0.001	290.7±0.21	281 ±1.0	98.21
F 2	0.38± 0.004	272.3±0.31	270± 2.0	99.31
F 3	0.33± 0.002	302.4±0.21	273 ±2.0	98.62
F 4	0.39± 0.004	286.2±0.32	272 ±2.0	99.36
F 5	0.37± 0.001	281.3±0.58	286 ±2.0	98.64
F 6	0.39± 0.004	321.2±0.42	280±1.0	98.48
F 7	0.31±0.002	299.4±0.21	290 ±1.0	99.65
F 8	0.40± 0.004	276.2±0.32	264± 2.0	98.31
F 9	0.37± 0.001	291.3±0.58	273 ±2.0	98.52
F 10	0.38± 0.004	301.2±0.42	282 ±2.0	99.33
F 11	0.34±0.002	292.4±0.21	290 ±2.0	98.65

Table 3: Physico-chemical evaluation of transdermal films

F. Code	Percentage Moisture Loss ± SD	Percentage Moisture Uptake ± SD	Water Absorption Capacity ± SD	Water Vapour Transmission Rate (mg/cm ² /hr) ± SD
F 1	7.14±0.014	5.2±0.012	3.2± 0.015	7.231 x10 ⁻⁶
F 2	6.12±0.015	5.21±0.01	4.21±0.02	5.321 x10 ⁻⁶
F 3	8.21±0.01	8.26±0.014	6.92±0.12	6.166 x10 ⁻⁶
F 4	7.21±0.015	8.43±0.01	5.24±0.01	7.287 x10 ⁻⁶
F 5	5.26±0.012	7.32±0.012	7.5±0.015	7.468 x10 ⁻⁶
F 6	4.92±0.021	8.34±0.021	8.21±0.02	6.214 x10 ⁻⁵
F 7	5.62±0.014	7.38±0.02	7.24±0.02	7.86 x10 ⁻⁶
F 8	5.12±0.021	7.43±0.01	10.24±0.01	8.28 x10 ⁻⁶
F 9	9.26±0.032	6.32±0.01	8.5±0.015	6.68 x10 ⁻⁶
F 10	10.20±0.015	9.34±0.02	8.21±0.02	8.214 x10 ⁻⁵
F 11	12.26±0.014	11.38±0.021	13.24±0.04	9.641 x10 ⁻⁶

and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6 and 7th day. Water vapor transmission rate usually expressed as the number of grams of moisture gain/hours/ sq.cm.

$$WVT = WL/S$$

Where, W is water vapor transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm².

Drug content

Films of specified area were cut and the pieces were taken into a 100 ml volumetric flask containing phosphate buffer (pH 7.4), and the flask was sonicated for 8 h (Mazzo *et al.*, 1994). A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-µm filter and the drug content was analyzed at 229 nm by UV spectrophotometer.

In vitro drug release studies

The *in-vitro* release studies were carried out by using Keshary chain apparatus. The receptor compartment was maintained at 37±1°C by means of a water bath, circulator, and a jacket surrounding the cell. The cells

were filled with freshly prepared phosphate buffer pH 7.4. The solution in the receptor compartment was continuously stirred at 60 rpm by means of Teflon coated magnetic stirrer, in order to avoid diffusion layer effects. The Commercial Semi-permeable membrane were mounted between the donor and receptor compartment and secured in place by means of a clamp. The patch was placed on one side of the semi-permeable membrane (Ji-Hui Zhao *et al.*, 2007, Yanli Gao *et al.*, 2000). Aliquots of 1ml were removed from the receptor compartment by means of a syringe and replaced immediately with the same volume of buffer solution kept at 37± 1°C. Test samples were taken from the medium at predetermined time intervals over a period of 24 hours and the samples were analyzed for Atenolol content by UV spectrophotometer at 229 nm (Vlassios Andronis *et al.*, 1995). The diffusion kinetics of the Atenolol was analyzed by graphical method for zero order, Higuchi and Peppas's exponential equation.

In vitro Transdermal permeation

The hairs of the male Wistar albino rat were cleared by using scissors. After cleaning the skin with Phosphate buffer pH 7.4, animal was sacrificed by excessive ether inhalation. An incision was made on the flank of the animal and the skin was separated. The prepared skin

was washed with Phosphate buffer pH 7.4 and used (Yanli Gao *et al.*, 2009).

Snakeskin, (Hatanaka T *et al.*, 2006) offers considerable advantages over human material, as it is relatively abundant. In shed snake, the permeability co-efficient of lipophilic drugs was in the same range as those through the human skin. Shed skin of "NAJA NAJA" was collected and soaked in pH 7.4 Phosphate buffer for half an hour and then used. The shed skin was mounted in such a way that the ventral surface side of the skin was kept intimate contact with the formulation and keeping the dorsal region of skin being contact with the release surface of the donor compartment.

Albino porcine ear, (Jagadish Singh *et al.*, 1999) was obtained from a local slaughter house. The epidermis was prepared by a heat separation technique. The whole skin was soaked in water at 60°C for 45 seconds, followed by careful removal of the epidermis. The epidermis was washed with pH 7.4 Phosphate buffer and used.

The transdermal permeation was performed in Chein Diffusion cell. The cells were filled with freshly prepared phosphate buffer pH 7.4. While placing the patch, the donor compartment contains patch on stratum corneum side of skin and dermis side was facing receptor compartment (Ke *et al.*, 2005). Receptor compartment contains phosphate buffer pH 7.4 and samples were withdrawn at regular time intervals and replaced the same with receptor fluid. The samples were analyzed at 229 nm against blank by UV spectrophotometer (Srinivas Mutalik *et al.*, 2006).

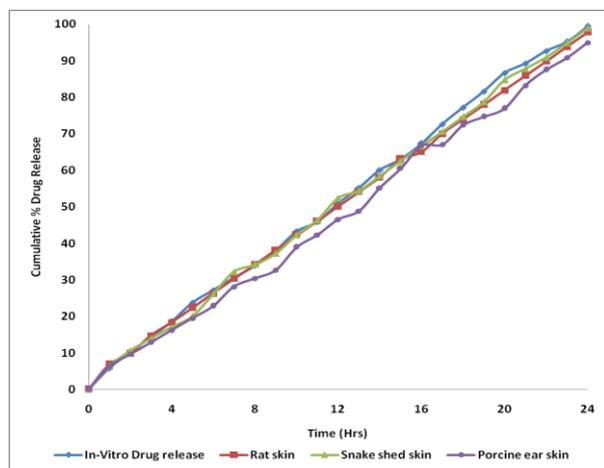


Figure 1: Comparative In-vitro drug diffusion through artificial semipermeable membrane and various biological skin

In vivo studies

Primary Skin Irritation Test

The dorsal part of rabbit was carefully shaved, and patch was applied on the shaved skin for 7 days. After the patch was removed, conditions of the dorsal skin were observed and are evaluated most often by mod-

ification described by Draize (Draize JH, 1944) and his colleagues in 1944, which is based on scoring method. Scores as assigned from 0 to 4 based on the severity of erythema or oedema formation. The safety of the patch decreases with increase in scoring.

Selection of animals

Rabbit's (*Cyrtolagus cuniculus*) of male sex 10-12 weeks old weighing 1-2 kg were selected. They were kept with husk bedding and were fed with standard rodent pellet diet and water. Light & dark cycles with 12 hours light and 12 hours dark were maintained. The temperature and relative humidity conditions were $28 \pm 2^\circ\text{C}$ and $60 \pm 15\%$ respectively. The protocols for all animal studies were approved by Institutional Ethical Committee (1220/a/08/CPCSEA).

Method

A set of healthy rabbits were selected. They were checked to ensure that they were free from disease. The dorsal surface of the selected rabbits was cleaned and hair was removed. The dose of Atenolol was calculated according to the body weight i.e., 3.2 mg respectively (Anitha P *et al.*, 2011; Jayaprakash *et al.*, 2010). The patch F 9 (HPMC 1.5%, Eudragit RS 100 1.5%) was placed on the dorsal surface. At specific time interval the patch was removed from the rabbit carefully and analyzed for remaining drug content. Initial drug content was determined before placing the film. The remaining drug content was subtracted from the initial drug content of the film. The value obtained denotes the amount of drug in diffused from the patch into the body (Chakkapan *et al.*, 1994).

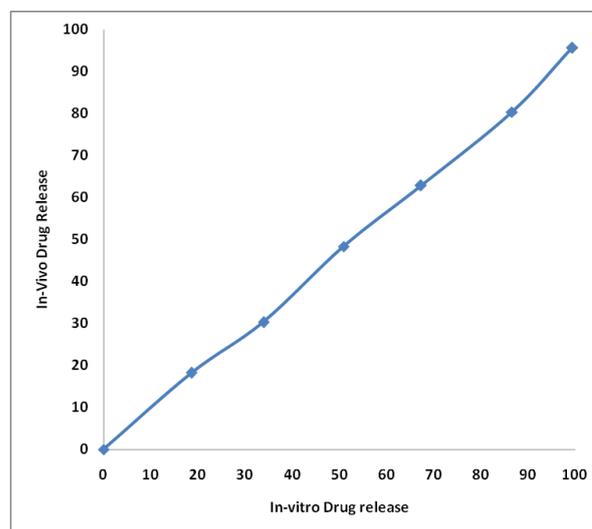


Figure 2: In vitro In-vivo Correlation of F 7

RESULTS AND DISCUSSION

In the present work efforts have been made to prepare transdermal drug delivery system of Atenolol using various blends of polymers such as Eudragit RS 100, Hydroxy Propyl methyl cellulose and Poly vinyl pyrrolidone. Permeation enhancer used was Propylene glycol.

The observed partition coefficients of Atenolol using n-octanol/Phosphate buffer pH 7.4 found to give log K values 2.21. The physicochemical compatibility of the drugs and the polymer was established through FTIR studies which show no interactions. Physico-chemical evaluation data of table 2 and 3 indicates that thickness of the patches varied from 0.31 ± 0.002 to 0.40 ± 0.004 . Folding endurance values of matrix films was found within 264-290 numbers of folds, indicating good strength and elasticity. The drug content analysis and the weight uniformity of the prepared formulation have shown that the process adopted for casting the films in this investigation is capable of giving films with uniform drug content and with minimum intra batch variability. The percentage Moisture uptake in the formulation F 11 (1.5% HPMC, 1.5% PVP) has shown the highest value of moisture absorption 11.38 ± 0.021 which may be due to higher polydispersity index and solubility parameter of HPMC, PVP. The formulation F 11 (1.5% HPMC, 1.5% PVP) shows higher value of Moisture loss 12.26 ± 0.014 which may be due to presence of higher concentration of hydrophilic polymers and formulation F 6 (2% Eudragit RS 100, 0.5% HPMC, 0.5% PVP) shows low value of 4.92 ± 0.021 .

The high water absorption capacity was found in F 11 (1.5% HPMC, 1.5% PVP) as 13.24 ± 0.04 . The formulation F 11 (1.5% HPMC, 1.5% PVP) has shown maximum water vapor transmission of 9.641×10^{-6} among all the patches which may be due to presence of higher concentration of hydrophilic polymers and F 2 has less water vapor transmission of 5.321×10^{-6} . The *in-vitro* release plots of all other formulations were suggestive of zero order release and are diffusion mediated which was confirmed from the regression value of Higuchi's plot. All the formulations undergo non-fickian type of release which is confirmed from the slope values obtained from the Peppas's plot. The cumulative percentage of drug released in 24 h was found to be the highest for Formulation F 7 (2% Eudragit RS 100, 1%HPMC) which has shown the drug release of 99.40%. The *in-vitro* drug release plot indicates that the drug release followed zero order kinetics, which was evinced from the regression value of the above mentioned plot. The Higuchi's plot has shown the regression value of 0.969. In order to confirm this fact, Peppas's plot was drawn which has shown slope value of 0.821. Hence formulation F 7 was selected as the optimized formulation by virtue of its drug release kinetics. *In-vitro* transdermal permeation study was carried out in rat skin, Snake shed skin and porcine ear skin the formulation F 7 (2% Eudragit RS 100, 1%HPMC) showed drug diffusion for 24 hours up to the extent of 97.76%, 98.91% and 94.91% respectively. The comparative *in-vitro* drug diffusion data has been illustrated in Figure 1. The variation among the used biological membrane could be attributed to the fat content and thickness of the membrane used. The result obtained from the primary skin irritation studies revealed that neither the adhe-

sive nor the drug Atenolol caused any noticeable irritation on the rabbit skin throughout the study. *In-vivo* study was carried out in rabbit, at the end of 24th hour the *in-vivo* drug release showed 95.62 %. The results which are illustrated in Figure 2 indicated that the *in-vitro* and *in-vivo* correlation was very good which reveals the reproducibility of drug release even in biological environment.

CONCLUSION

In conclusion formulation F 7 (2% Eudragit RS 100, 1%HPMC) has achieved the targets of present study such as controlled release, prolonged zero order release, reduced frequency of administration, greater therapeutic effect, overcome the side effects, simplify the treatment regimen and thus may improve patient compliance.

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