Design and Development of Transdermal Drug Delivery for Anti-Hypertensive Drug Using Different Polymeric System

Hemul V. Patel1*, Jaimin D. Bhatt1 and Naynika K. Patel2

1Department of Pharmaceutical Chemistry, Ashok & Rita Patel Institute of Integrated study and Research in Biotechnology and Allied Sciences (ARIBAS), New Vallabhbhi Vidyannagar - 388121, Gujarat, India.

2Department of Biosciences, Sardar Patel University, Vallabhbhi Vidyannagar - 388120, Gujarat, India.

ABSTRACT
Atenolol is a selective β1 receptor antagonist, a drug belonging to the group of beta blockers (sometimes written β-blockers), a class of drugs used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Atenolol with different polymeric systems by the solvent evaporation technique using 20% w/w of di butyl phthalate to the polymer weight, as plasticizer which can deliver the drug up to 24 hours in a controlled manner. The matrix-type transdermal patches were prepared using different polymers like Cellulose Acetate Butyrate (CAB), Cellulose Acetate Phthalate (CAP), Poly Methyl Methacrylate (PMMA) and their combinations. Dichloromethane as a solvent system was selected for the preparation of patch of Atenolol and di butyl Phthalate (DBP) as plasticizer. The diffusion study was carried out using K-C type diffusion cell for 30 hours which showed drug release up to 25 hours in a sustained and controlled manner.

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

INTRODUCTION
Transdermal delivery of drugs is a novel drug delivery system and this system breaks many barriers in drug therapy like need of assistance, intermediate dosing and uncomfortable administration. The transdermal route of administration is recognized as one of the potential route for local and systemic delivery of drugs, it also provides a controlled release of medicament into patients. Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance. Atenolol is a β-blocker without membrane stabilizing or intrinsic sympathomimetic activity, which has been used for the treatment of hypertension. 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 or reduction in drug concentration at the receptor site. To overcome these adverse effects in the GI tract while sustaining the therapeutic efficacy of atenolol, an alternative drug delivery method might be useful. 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 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. 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 shedded 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

Materials and Methods

Atenolol was gift from Zydus Cadila Pvt Ltd. (India). Cellulose Acetate Phthalate (CAP), dibutyl Phthalate (DBP), Cellulose Acetate Butyrate (CAB), Poly Methyl Methacrylate (PMMA) were purchased from Hi media Chemicals Ltd. (India). All other chemicals used for this study were of analytical grade. Double-distilled water was used throughout the study.

Drug–excipient interaction study

The pure drug, Atenolol and a mixture of it with the polymers, CAP, CAB and PMMA were mixed separately with IR grade KBr in the ratio of 100:1 and correspond-ing pellets were prepared by applying pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000-400 cm⁻¹ in Shimadzu Japan, FTIR instrument. The spectra obtained for Atenolol, polymers, and physical mixtures of atenolol with polymers were compared.

Formulation of Drug Free Patches

Polymers of single or in combination are accurately weighed and dissolve in respective solvent and then casted on a glass surface containing ring. The films were allowed to dry overnight at room temperature. Then the films were separated and noticed for film formations.

Formulation of Drug Incorporated Transdermal Patches

Accurately weighed quantities of polymer individually and /or in combination were dissolved in required quantity of solvents namely dichloromethane in which drug and polymer have been dissolved. The solution was mixed with magnetic stirrer to get homogeneous consistency. 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 aluminum foil and the formulations were stored in desiccators. The composition of patches prepared using atenolol is given in Table 1.

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.

Folding Endurance

It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance.

Percentage Moisture Loss

Accurately weighed films of each formulation were kept in desiccators and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days. 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.

Percent Moisture Absorption

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the following manner. The films were placed in desiccators containing saturated solution of aluminum chloride, keeping the humidity inside the desiccators at 79.5% RH. After 3 days the films were taken and weighed the percentage moisture absorption of three films was found.

Percentage Moisture Loss

This test was also carried to check the integrity of films at dry condition. Three films of 5 square centimeter area was cut out and weighed accurately and kept in a desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture losses of three films were found out.

Thickness

Thicknesses of the films were measured at six different points using a screw gauge and
average thicknesses of three films were found out.

**Drug content**
A film of 1 square centimeter area was cut and dissolved in phosphate buffer pH 7.4. After adding suitable reagent and dilution, optical density was found out at 229.2nm. Average drug content of three transdermal films were determined.

**Folding Endurance**
It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance.

**Weight Uniformity**
Each film was weighed individually and average weight of three films was found.

**In vitro drug release studies**
The *in-vitro* release studies were carried out by using Keshary- chein 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. 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. The diffusion kinetics of the atenolol was analyzed by graphical method for zero order.

**RESULTS AND DISCUSSION**
In the present work efforts have been made to prepare transdermal patches of atenolol by using different polymers individually and /or in combination such as cellulose acetate butyrate, cellulose Acetate phthalate and poly Methyl Methacrylate. The plasticizer used was di butyl phthalate. The physicochemical compatibility of the drugs and the polymer was established through FTIR studies which show no interactions. From the IR spectra (figure 1-3) it is observed that there were no changes in the main peaks in IR spectra of pure drug, drug and polymer, which shows there were no physical interactions due to some bands formation between drug, solvent and polymer. Since there are no interactions between drug, solvent and polymer the patches were evaluated for *In-Vitro* skin permeability studies. FTIR spectra analysis of Atenolol showed that the principle peaks are observed at wave number 3357.79, 2964.94, 1638.30, 1515.81, 1242.91 cm⁻¹ in (fig-1) confirming the purity of the drug. In the FTIR spectra of the physical mixture of the drug and polymer (fig-3) major peaks of Atenolol were observed at wave numbers 3357.79, 2964.94, 1638.30, 1515.81, 1242.91 cm⁻¹ however some additional peaks were observed due to additives in the formulation. Thus there was no probable interaction observed between drug and polymeric system. The prepared formulations were subjected to various physicochemical characteristics such as percent moisture absorption, percent moisture loss, drug content, thickness, folding endurance and weight uniformity. The results are shown in Table 2 The release characteristic of the formulation was studied by in-vitro dissolution test. The formulation F5 (CAB: PMMA (1:1)) has shown lowest percent moisture absorption and percent moisture loss than other formulations. This might be because of the low water permeability of cellulose acetate butyrate polymer. It is also observed that F1 (CAB) has shown highest percent moisture absorption and percent moisture loss which might be due to high permeability of Cellulose acetate butyrate to water. The thickness of the films varied from 0.21 to 0.23mm. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible results. This fact is further confirmed by drug content and weight uniformity studied. In order to evaluate the flexibility the film were subjected to folding endurance studies. The values in the range of 340to 367 were observed in all batches. This revealed that the prepared films were having capability to withstand the mechanical pressure along with good flexibility.

**In-vitro Dissolution Studies**
*In-vitro* dissolution studies were carried out in phosphate buffer pH 7.4 for 30 hours. In order to find out the order of release and the mechanism, which was predominately influences, the drug release from the
membrane, the in-vitro dissolution data was subjected to graphical treatment that is:
Percentage drug release Vs Time. The slope value and the degree of linearity of the above
graphical treatment were considered as important statistical parameters to interpret the
in-vitro profile of all formulations. From the
graph of in – vitro drug release it is clearly
observed that all the six formulations (F1–F6)
showed the release of drug up to the period of
25 hours (fig:4-9) in a controlled manner. This
indicates that the Cellulose based polymers
either alone or in combination can be used to
deliver the drug in a controlled manner for
desired period of time.

CONCLUSION
Atenolol is a multiple-action cardiovascular
drug that is currently approved in many
countries for the treatment of hypertension.
Administration of these agents via dermal
route can bypass various disadvantages
caused when administered orally and may
maintain relatively consistent plasma levels for
long-term therapy. The present study is an
attempt to develop transdermal drug delivery
system for Atenolol Patches containing 30 %
Atenolol with different polyer and Dibutyl
Phthalate (DBP) as plasticizers has shown
better permeability coefficient.
Hence, Atenolol transdermal Patches
formulated using Plasticizer showed better flux
enhancement. Transdermal patches consisting
of the Cellulose Acetate Butyrate (CAB)
Cellulose Acetate Phthalate (CAP), Poly
Methyl Methacrylate (PMMA) drug reservoir
with plasticizer demonstrated sustained and
controlled release of the drug during in vitro
permeation studies. As an extension of this
work pharmacokinetic studies, in-vivo studies
on higher animals and controlled clinical
studies on human beings can be carried out in
future.

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necessary laboratory and Analysis facilities.

| Table 1: Composition of Transdermal Patches of Atenolol |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Formulation Code** | **Polymer** | **Plasticizer** | **Drug 30% wt of polymer** | **Solvent** |
| F1 | CAB | DBP | Atenolol | DCM |
| F2 | CAP | DBP | Atenolol | DCM |
| F3 | PMM | DBP | Atenolol | DCM |
| F4 | CAB:CAP | DBP | Atenolol | DCM |
| F5 | CAB:PMMA | DBP | Atenolol | DCM |
| F6 | CAP:PMMA | DBP | Atenolol | DCM |

| Table 2: Physicochemical Evaluation data of Atenolol Transdermal Patches |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Formulation code** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| % Moisture Absorption +SD | 8.64+0.047 | 6.44+0.023 | 7.027+0.039 | 5.35+0.032 | 4.26+0.015 | 7.08+0.024 |
| % Moisture Loss, +SD | 10.17+0.04 | 8.15+0.12 | 9.76+0.26 | 7.34+0.34 | 5.13+0.07 | 9.65+0.19 |
| Thickness (mm) +SD | 0.23+0.02 | 0.22+0.01 | 0.21+0.02 | 0.22+0.02 | 0.23+0.04 | 0.22+0.02 |
| Weight Variation (mg) | 302.4±0.21 | 289.4±0.14 | 293.4±0.07 | 299.4±0.11 | 321.4±0.30 | 308.4±0.19 |
| Folding Endurance +SD | 340±0.6 | 345±0.4 | 357±0.7 | 360±0.2 | 364±0.4 | 363±0.3 |
| % Drug Content +SD | 96.6±0.3 | 97.0±0.4 | 96.4±0.3 | 98.5±0.3 | 95.8±0.3 | 99.1±0.4 |
Fig. 1: IR Spectrum of drug

Fig. 2: IR Spectrum of CAP

Fig. 3: IR Spectrum of drug loaded patch
Fig. 4: Plot for the In vitro diffusion study of CAB (F1)

Fig. 5: Plot for the In vitro diffusion study of CAP (F2)

Fig. 6: Plot for the In vitro diffusion study of PMMA (F3)

Fig. 7: Plot for the In vitro diffusion study of CAB:CAP (F4)
REFERENCES


