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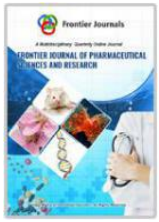

## Original Research Paper

# FORMULATION AND EVALUATION OF ATENOLOL TRANSDERMAL PATCHES

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ARTICLE INFO

ARTICLE HISTORY

Received 28 Oct 2018
Received in revised form 20 Nov 2018
Accepted 25 Nov 2018
Available online 28 Nov 2018

**Key words:**

Atenolol, HPMC, Eudragit, Ethylcellulose, solvent casting technique.

ABSTRACT

The objective of present study was to develop matrix type transdermal therapeutic systems of Atenolol using various polymers such as Sodium alginate, HPMC, Ethylcellulose and Eudragit polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interactions. The in-vitro release study revealed that F-1 formulation showed maximum release in 8 hrs. Formulation F-1 was subjected for accelerated stability studies. The F1 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FT-IR Spectroscopy. Thus conclusion can be made that stable transdermal patches of Atenolol has been developed. F1 formulation showed highest cumulative percentage drug release of 96.63 % which was obtained during in-vitro drug release studies after 8 hrs. The release of Atenolol appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. In the prent study based upon the in-vitro dissolution data the F-1 formulation was concluded to be an optimized formulation.

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## 1. INTRODUCTION :

Transdermal delivery represents an attractive alternative to oral delivery of drugs. These therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation.[1,2] Thus it is anticipated that transdermal drug delivery system (TDDS) can be designed to deliver drug at appropriate rates to maintain suitable plasma drug levels for the therapeutic efficacy by using skin as the port of entry of drugs.[3] TDDS basically consists of adhesive drug-containing devices of defined surface area that delivers a predetermined amount of drug to the intact skin at a programmed rate, which is able to penetrate through different layers of skin to reach the systemic circulation.[4,5] Currently, the transdermal route, along with oral treatment, ranks as the most successful innovative research area in drug delivery. Baking layer,

drug containing layer, rate controlling membrane, adhesive and release liner are the components of TDDS though all layers may not be available in all types of TDDS as there are several types of transdermal patches. There are single layer drug in adhesive, multilayer drug in adhesive, vapour patch, reservoir system and matrix system. Similarly natural polymers, synthetic polymers, synthetic elastomers and biopolymers have been used in TDDS. [6] Atenolol (Tenormin) is ß-1 cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension as oral dosage form, in strengths of 25mg, 50mg and 100mg. The drug is insoluble in water and has half-life of six to eight hours with oral bioavailability of 50% due to smaller dose of drug.[7,8]

## 2. MATERIAL AND METHODS

### MATERIAL

Atenolol was collected as a gift sample from Reddy's laboratories, Hyderabad and was purchased from AR chemicals, Hyderabad, India.

### METHODODOLOGY[9,10,11]

**Compatibility studies of drug and polymers:**

In the preparation of film formation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre-formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Atenolol and the selected polymers. The pure drug and drug with excipients were scanned separately. Potassium bromide was mixed with drug and/or polymer and the spectra were taken. FT-IR spectrum of Atenolol was compared with the FT-IR spectra of Atenolol with polymer. Disappearance of Atenolol peaks or shifting of peak in any of the spectra was studied.

**Formulation design:**[12,13,14]

**Preparation of Transdermal patches:**

Transdermal patches containing Atenolol were prepared by the Solvent casting evaporation technique. The drug Atenolol was dissolved in methanol. Polymers such as HPMC, Ethylcellulose, Sodium alginate and Eudragid ERS100 were taken in a boiling tube, to this add Atenolol drug which was previously dissolved in methanol. About 30 ml of solvent mixture of dichloromethane: methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps. The boiling tube was set aside for 4 hrs. to allow the polymer to swell. PEG was taken as a plasticizer, and added to the mixture and mixed well. It was set aside for 2 hrs. to exclude any entrapped air and was then transferred into a previously cleaned petri plate (40 $cm^2$), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

**Table-1 Formulation Design of Atenolol Transdermal Patches**

| S. No | Formulation code | Ingredients (gms) | | | |
|---|---|---|---|---|---|
| | | Drug (mg) | HPMC | Ethyl cellulose | Eudragit |
| 1 | F-1 | 100 | 1000 | 900 | |
| 2 | F-2 | 100 | - | 1000 | |
| 3 | F-3 | 100 | 500 | 500 | 1000 |
| 4 | F-4 | 100 | 500 | - | 500 |

**Fig-1 Atenolol transdermal patch**

### 3. Evaluation of Transdermal formulation: [15,16]

**Physico- chemical evaluation:**

**Physical appearance:**

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

**Folding endurance:**

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

**Thickness of the film:**

The thickness of each film was measured by using screw gauge. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

**Weight uniformity:**

The prepared patches are to be dried at 60 $^0$C for 4hrs. before testing. A specified area of 4.52 cm$^2$ of patch is to be cut in different parts of the patch and weighed on a digital balance. The average weight and standard deviation values were calculated from the individual weights.

**Drug content :**

The formulated transdermal films were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug.

**Procedure:**

The transdermal films (4.52 cm$^2$) were added to conical flask containing 100 ml. of phosphate buffer pH 7.4. This was then stirred using a stirrer with a magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analysed spectrophotometrically for drug content at 270 nm. Similarly a blank was prepared from transdermal films without drug.

**Moisture absorption studies:**

The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50 % RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

**Moisture loss studies:**

Three films were weighed individually and kept in desiccators containing calcium chloride at 37 $^0$C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch.

**Stability studies:**

Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 $^0$C and 75 ± 5 % RH for 3 months as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

***In-vitro* release study:**

The drug release was determined using Franz diffusion cell apparatus thermo stated at 37 ± 0.5 $^0$C and stirred at a rate of 200 rpm. Sink conditions were maintained throughout the study. The vessel containing 10 ml. of phosphate buffer pH 7.4. Aliquots of 1ml of samples were withdrawn at different time intervals and then analyzed using a UV Spectrophotometer at 270 nm against blank.
Percentage of drug release was determined using the following formula :

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

**Stability studies:**

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.
The prepared Atenolol transdermal patches were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40 ± 2 ° C and refrigerated at 2-8 °C for a period of 30 days.

**4. RESULTS & DISCUSSION**

**Evaluation of Transdermal Formulation**

**Physical appearance:**

The prepared patches were found to be uniform, smooth, flexible and homogenous.

**Folding endurance:**

The folding endurance numbers of all the Atenolol patches are 180 – 292. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that it has high mechanical property. The folding endurance number was increased with increasing the HPMC content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

**Thickness of the film:**

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness.

**Weight uniformity:**

The weights are in the range of 230-286. The F-2 formulation patches showed maximum weight.

**Drug content:**

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90 – 101%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Atenolol transdermal patch

**In vitro release study:**

Phosphate buffer pH 7.4 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. The drug release profiles of Atenolol patches containing different ratios of polymers Sodium alginate, HPMC, Ethylcellulose and Eudragit. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and conte

**Stability studies**

Optimized formulation F-1 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40 $^{0}$C) maintained during the studies.

**Table-2: Physicochemical evaluation of Atenolol patches**

| Code | Weight (mg) | Thickness (mm) | Folding endurance | Drug content | Moisture loss |
|---|---|---|---|---|---|
| F-1 | 236.9 | 0.90 | 189 | 98.45 | 8.90 |
| F-2 | 242.4 | 0.96 | 191 | 93.54 | 9.20 |
| F-3 | 254.2 | 0.91 | 192 | 91.26 | 10.25 |
| F-4 | 263.5 | 0.95 | 188 | 95.59 | 11.20 |

**Table-3: *In-vitro* Drug release profiles of Atenolol Transdermal Patches (F-1 to F-4)**

| Time (Hrs.) | F-1 | F-2 | F-3 | F-4 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 25.57 | 26.10 | 27.10 | 24.50 |
| 2 | 34.21 | 36.10 | 35.20 | 35.84 |
| 3 | 45.85 | 37.52 | 42.55 | 44.65 |
| 4 | 51.16 | 49.28 | 53.26 | 52.20 |
| 5 | 62.60 | 58.63 | 63.15 | 61.55 |
| 6 | 73.25 | 67.46 | 71.19 | 70.10 |
| 7 | 81.45 | 78.60 | 80.53 | 82.76 |
| 8 | 96.63 | 89.35 | 92.10 | 90.92 |

**Table-4: Stability studies of optimized formulations at 40 ± 2 $^0$C and 75 ± 5% RH fo**

| Time in days | Drug content (%) | Folding endurance | Physical appearance | % Cumulative drug release |
|---|---|---|---|---|
| 0 | 98.45 | 181 | No change in color | 98.45 |
| 90 | 98.48 | 183 | Slight yellowish color | 98.48 |

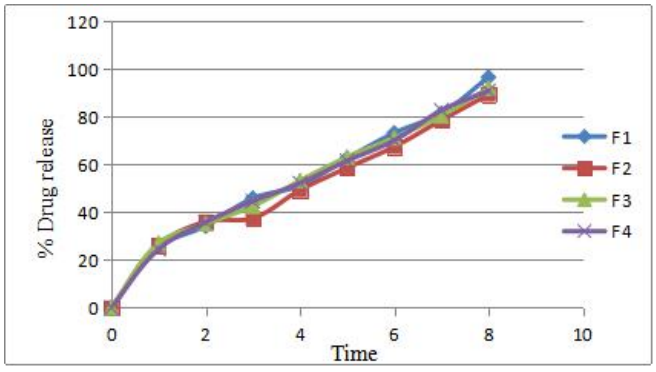


**Fig-2: Drug release rate of Atenolol formulations (F-1 to F-4**

**5.CONCLUSION**

The following conclusions could be drawn from the results: Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F-1 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable Transdermal patches of Atenolol has been developed. F-1 formulations showed highest cumulative percentage drug release of 96.63 %, which was obtained during In-vitro drug release studies after 8 hrs. The release of Atenolol appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Hence, in the present study, based upon the In- vitro dissolution data the F-1 formulation was concluded to be an optimized formulation.

Percentage drug release of 96.63 %, which was obtained during In-vitro drug release studies after 8 hrs. The release of Atenolol appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Hence, in the present study, based upon the In- vitro dissolution data the F-1 formulation was concluded to be an optimized formulation.

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