Formulation and evaluation of Bisoprolol fumarate transdermal patches

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ABSTRACT

The aim of the present work is to investigate the formulation of bisoprolol fumarate transdermal patches for controlled release medication in order to treat the blood pressure and cardiac diseases. Studies disclosed that Bisoprolol is more effective than Propanolol, Atenolol and Metoprolol. In the present study we have developed the bisoprolol transdermal patches by using Poly vinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) using glycerin as plasticizer. After optimizing the polymer ratio the best patches were selected based on the physical evaluation. Then physical evaluation and in vitro studies were performed by using Franz diffusion cell employing porcine ear skin as the membrane. From the above results F2 formulation was found to have good controlled release over the formulation F1. Further in order to find the effect of plasticizer in the drug release for the F2 formulation, glycerin was replaced with Tri ethyl citrate (TEC). Thus the prepared film shows good release of about 98.3% with TEC as plasticizer.

Key words: Bisoprolol, PVP, Glycerol and TEC

INTRODUCTION

Transdermal application is an attractive method of drug administration, providing several advantages: for example, avoidance of a potential hepatic first-pass effect, and the feasibility of constant drug delivery over a period up to one week. In addition, the dosage form of transdermal patches is user-friendly, convenient, painless, and offers multi-day dosing, it is generally accepted that it is associated with improved patient compliance.  

High blood pressure (BP) is a high risk factor for cardiovascular disease (CVD). The age related rise in SBP is major cause for an increase in both incidence and prevalence of hypertension with increasing age. Many elderly people have difficulty taking medicines because of their reduced swallowing capability. Bisoprolol is a cardio selective beta blocker, devoid of intrinsic sympathomimetic and membrane-stabilizing properties. Bisoprolol fumarate (BF) is effective in reducing blood pressure (BP) with beneficial cardiac effects in patients with hypertension.

So the present aim of our work is to formulate and optimize a stable and controlled release transdermal formulation by using various polymers in order to avoid the first-pass effect, to obtain great therapeutic efficacy and also to increase patient compliance especially in geriatric patients.

MATERIALS AND METHODS

Materials

Bisoprolol Fumarate (BF) was obtained from Unichem Laboratories Ltd., Raigad, India. Polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), Tri ethyl citrate (TEC), Azone and Glycerol were incurred from Sigma Aldrich. All the above materials used were of analytical grade. All the substances were used as received without any further processing.

**Preparation of Patches**

The matrix-type transdermal patches of bisoprolol were prepared by using different ratios of PVA; PVP polymers as in table 1. First PVA was dissolved in the hot water at about 70-80ºC with stirring then slowly the PVP was mixed with stirring thoroughly to obtain uniform solution. Glycerol was used as a plasticizer and then drug was dissolved in the above polymeric solution with stirring after cooling it to the room temperature. The polymeric solution of drug was poured onto the glass moulds and dried at room temperature in dust free environment. The patches were stored in air tight container at ambient conditions for further evaluation. Then the final best formulation was chosen with reference to in vitro drug diffusion studies and to this formulation Glycerin was replaced with TEC as plasticizer to know the effect of plasticizer in drug release.

**Evaluation of prepared patches**

**Folding Endurance**

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film can be folded at the same place without breaking was the folding endurance value.

**Tensile Strength**

The force at tearing and elongation was measured during tensile test by a universal testing apparatus. The test sample was clamped between the tensioning tools. The drawing rate was 50 mm/min and no preload was used. Tensile stress at break (MPa) was calculated.

**Thickness Test**

Precise film thickness measurements were carried out using NIKON DigiMicro encoders/gauges (Nanowave Inc. MA 01590 USA, MF501 - 50mm travel range along with TC-101). Each Patch was measured at five positions (four corners and central) and the mean thickness was calculated.

**In vitro Skin Permeation Studies**

A cell fabricated on the lines of Franz diffusion cell with a diffusional area of 2 cm² was used. The porcine ear skin was collected from local slaughter house. The hair and fat were removed after treating the skin. The stratum corneum side of the skin was kept in intimate contact with the release surface of patch under test placed between the two halves of the diffusion cell. The receiver phase was Phosphate buffer of pH 7.4 stirred at 500 rpm on magnetic stirrer. The whole assembly was kept at 37 ±0.5ºC. The amount of drug permeated was determined by removing an aliquot 1ml samples at appropriate time intervals up to 24 h. volume was replenished with an equal quantity of pre-warmed receiver solution.

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The absorbances were read at 227 nm spectrophotometrically.

Skin Irritation Test
Skin irritation test was carried in order to find any allergic reactions caused by the application of transdermal patches\(^1\). This work has been carried out at Sree Vidyanikethan College of Pharmacy, Tirupathi with the ethical committee approval. Six rabbits of either sex weighing 2.0 to 3.5 kg were used. Hair present on the abdominal portion was shaved and removed. Shaved portions were cleaned with 70% alcohol and allowed to dry. Transdermal patches were applied on to the shaved portion of skin of each rabbit and left in contact for 24 hours. The portion of the skin was observed after removing the patches, for any visual changes such as erythema (reddening of the skin), inflammation and contact dermatitis.

RESULTS AND DISCUSSION
Bisoprolol fumarate transdermal patches were prepared using PVP and PVA in different concentrations as shown in table 1. The physical appearance of the patches were acceptable, but as PVP concentration if further increased apart from the above concentrations mentioned the patches were showing stickiness. So there by the tensile strength of the formulation may get decreased. Higher concentration of PVA was preferred for good texture of patches. The consistency and texture were satisfactory to the above concentrations mentioned from table 1. For the above formulations Glycerin was used as a plasticizer, the good nature and the better flexibility of the film depends on the concentration of glycerin used upto some extent, so even after if the concentration of plasticizer increased the film shows difficulty in drying and leads to more tackiness. As a part of our study we have used TEC as a plasticizer replacing glycerin to the formulation which shows good release through *in vitro* diffusion.

After the final optimization of the formulations two best formulations F1 and F2 respectively, were selected based on the physical appearance of the films and *in vitro* studies were performed, which infers F2 has good controlled release over F1 formulation. There by to know the effect of plasticizer glycerin was replaced with TEC. But the concentration of the TEC used was very much less compared to that of glycerin. Even at low concentration it gave good characteristics to the films. So from the table 2 it depicts that F3 films shows less thickness compared to that of F1 and F2 films, as F3 contains TEC at lower concentrations which might have shown this slight impact on the thickness of the films and that might be one of the reason for its lower tensile strength and as well as folding endurance when compared with that of other two formulations. But all these parameters do not make any remarkable notice, as it shows narrow differences. As the concentration of PVP was increased (or PVA concentration decreased), the tensile strength was decreased (F2). It was understandable, because PVP is water soluble and hygroscopic.

In *in vitro* diffusion studies were carried out for the above three formulations using Franz diffusion cell using porcine ear skin as the diffusional membrane. From the Figure 1 it depicts that the % cumulative drug release from the from the F1 formulation was about 93.16% around 12 hours, but the formulation F2 shows 95.82% around 24 hours. This infers as the concentration PVP is increased the release behavior and pattern can be controlled. As F1 contains low concentration of PVP the drug release from the polymer matrix is much faster compared to that of formulation F2.

Azone is known to be safe and has been used to increase the skin permeation of a large number of drugs. Azone is nonirritant to human skin, even in undiluted form reversible in its action and very poorly absorbed through human skin. Azone is also included in the Chinese Pharmacopoeia (2005) and is an ideal permeation enhancer for clinical use. Such enhancing activity of azone is due to the direct effects on the barrier properties of the skin. It is reported that azone affects the lipid structures of the stratum corneum and reduces transition temperatures within lipid bilayers to induce formation of a liquid phase with *melting transitions in lipid bilayer*, that’s why it also helped to penetrate the bisoprolol through the skin by the above mentioned mechanism and further bisoprolol alone shows good lipophilic characteristics.

In order to know the effect of the plasticizer, TEC was replaced with the Glycerin in the formulation F3. So the drug releases were compared for F2 and F3 formulations. From figure 2 it infers that at 24th hour the % cumulative drug release was found to be 95.82% and 98.31% respectively. This shows that there was not that much difference in the drug release, but there was an interesting finding from these results, which was almost 98% of drug release, was found in the formulation F3 as only 95% with F2 and around 93% in F1. This shows that total drug release from the matrix might be achieved when TEC was used as plasticizer, but as it is well known that glycerin has some amount of binding property which might allows the drug to release slowly. So for the drug it might found difficult to come out of the matrix from F1 and F2 formulations.

The skin irritation tests were performed for the above three formulations. The about test revealed that there is no reddening of the skin without any inflammation was observed after a day, at the site where the transdermal patch was applied. Apart from this, the rabbits did not show any symptoms of itching. During the

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Table 1: Composition of the optimized film solutions

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1(%w/w)</th>
<th>F2(%w/w)</th>
<th>F3(%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVP</td>
<td>29.66</td>
<td>55.1</td>
<td>58.2</td>
</tr>
<tr>
<td>PVA</td>
<td>55.1</td>
<td>29.66</td>
<td>31.38</td>
</tr>
<tr>
<td>Glycerol</td>
<td>6.35</td>
<td>6.35</td>
<td>0.8968</td>
</tr>
<tr>
<td>Azone</td>
<td>8.5</td>
<td>8.5</td>
<td>8.968</td>
</tr>
<tr>
<td>Drug</td>
<td>0.43</td>
<td>0.43</td>
<td>0.4484</td>
</tr>
</tbody>
</table>

Table 2: Physico-chemical properties of the prepared thin film formulations

<table>
<thead>
<tr>
<th>Properties</th>
<th>n</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film thickness (µm)</td>
<td>5</td>
<td>185±0.7</td>
<td>191±1.5</td>
<td>143±0.3</td>
</tr>
<tr>
<td>Tensile strength (MPa)</td>
<td>5</td>
<td>7.79±0.05</td>
<td>5.73±0.03</td>
<td>4.98±0.08</td>
</tr>
<tr>
<td>Content uniformity (%)</td>
<td>5</td>
<td>94.5±4.5</td>
<td>96.7±3.7</td>
<td>94.9±1.6</td>
</tr>
</tbody>
</table>

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Figure 1: Percentage Cumulative drug release for the formulations F1, F2 and F3

Figure 2: Comparison of % cumulative drug release when glycerin and TEC were used as plasticizers in the formulations F2 (Glycerin) and F3 (TEC)
period of study, no symptoms of allergy or dermatitis were observed.

CONCLUSION

From the above results it can be concluded that Azone can be used as good penetration enhancer for the bisoprolol. PVP can be used as a good controlled release polymer for transdermal delivery systems at higher concentrations, apart from these above findings TEC can be used as plasticizer at lower concentrations when compared to that of glycerol which further helps in total release of the drug from the matrix.

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REFERENCES


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