Fabrication and evaluation of transdermal matrix patches of Metoprolol Tartrate

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ABSTRACT

Transdermal drug delivery systems are devices containing drug of defined surface area and overcomes the disadvantages associated with oral products like first pass hepatic metabolism, reduced bioavailability, dose dumping and dosing inflexibility. These devices allow for pharmaceuticals to be delivered across the skin barrier. The aim of this study is to fabricate and evaluate different polymeric matrix films of HPMC and PVP combination containing Metoprolol tartrate with the objective to avoid first-pass metabolism, improve the therapeutic efficacy, improve the bioavailability and to improve the patient compliance. The patches were prepared by solvent casting method using polymers (HPMC K 100M & PVP) of single or in combination and were dissolved in suitable solvents. The glass surface containing ‘O’ ring is used for casting the film and the prepared transdermal patches were stored in a desiccator until evaluation. The patches were evaluated for thickness, folding endurance test, percentage of moisture content, content uniformity, in vitro drug release studies. The thickness of the patches varied from 0.21 to 0.28 mm, folding endurance of the films varied from 150 to 191 no of folds. The formulation F-I (HPMC 2%) and F-II (PVP 2%) has shown release 96.66 % and 92.25% at 12th hour, F-III (1% HPMC and1% PVP) and F-IV (0.5%HPMC and 0.5% PVP) has shown the drug release of 98.331% and 94.55% at 12th hour respectively and F-V formulated with PVP 0.5 % and HPMC 1.5% has shown release 99.21% at 12th hour. Hence, based on the drug release and physico chemical evaluation, the Formulation F-V is considered as an optimized formulation which shows higher percentage of drug release with diffusion mediated mechanism and also satisfies the objective of the present study.

Keywords HPMC; Metoprolol Tartrate; PVP; solvent casting method; transdermal patch.

INTRODUCTION

Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin (Prausnitz et al., 2004). The success of Transdermal Therapeutic System has created much interest in the pharmaceutical industry and has activated research activities related to it. In the present decade, a good number of drugs have been reported for their Transdermal applications like scopolamine, nitro-glycerin, nicotine, estrogens, testosterone, fentanyl, buprenorphine, lignocaine, clonidine, oxybutynin and diclofenac (Brown M.B et al., 2006).

Metoprolol Tartrate is a (RS)-1-[(Isopropyl amino)-3-[4-(2-methoxyethyl) phenoxy] propane-2-ol. The anti-hypertensive compound approved for chemical use. Oral Metoprolol Tartrate has a short elimination half-life (2-3hrs), low bioavailability (35%) under goes high first pass metabolism and frequent high doses (100mg two divided doses for 24hrs) are required to maintain the therapeutic level as a result, dose development toxic side effects are frequently observed (Chong S et al.,1989). The molecular weight and the melting point of Metoprolol Tartrate is 684.82 and 45c, hence it is suitable for TDDS. Metoprolol Tartrate is highly hydrophilic, a character that adversely effects it’s permeability through the stratum corneum. The use of vehicles of improved transdermal permeation of Metoprolol Tartrate has been investigated by several groups single vehicles were not successful in increasing transdermal permeation of Metoprolol Tartrate, but the use of vehicle combinations appear to promising.

To avoid serious toxic effects resulting from oral administration, the use of transdermal approach for metoprolol Tartrate delivery has been proposed (Meenakshi Bharkatiya et al., 2010)

MATERIALS & METHODS

Metoprolol Tartrate and PVP were procured from Dr. Reddy’s laboratories ltd. HPMC collected from Aurobindo Pharma, Hyderabad as a gift sample.
FABRICATION OF TRANSDERMAL PATCHES

Fabrication of Drug Free Patches

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

Fabrication of drug incorporated Transdermal Patches

Accurately weighed quantities of polymer individually were dissolved in required quantity of solvents namely Ethanol, water and Propylene glycol in which drug polymer has been dissolved. The solution was mixed occasionally to get semisolid consistency. This was casted on a glass surface containing ‘O’ ring, it was covered by funnel to control the evaporation of solvent & allowed to dry at room temperature over night. The films were separated and backing membrane used was aluminium foil. The formulations were stored in desiccators. The formulation has been shown in Table 1

Table 1: Formulation of metoprolol transdermal patches

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>HPMC</th>
<th>PVP</th>
<th>Plasticizer and permeation enhancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-I</td>
<td>2</td>
<td>-</td>
<td>30% v/v of glycerine</td>
</tr>
<tr>
<td>F-II</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>F-III</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>F-IV</td>
<td>0.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>F-V</td>
<td>1.5</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

EVALUATION OF TRANSDERMAL PATCHES OF METOPROLOL TATRATE

Physico chemical evaluation of patches

Patch thickness

Patch thickness was measured using a screw gauge at three different places and the mean value was calculated (Mishra A.N. et al., 1997).

Folding endurance test

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value. (Murthy N et al., 1995).

Percentage of moisture content

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight (Prausnitz MR et al., 1997, Murthy N et al., 1995).

Percentage of moisture uptake

A weighed film kept in a desiccator at room temperature for 24 hours was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Content uniformity

The medicated patch was allowed to dissolve in 100 ml isotonic phosphate buffer, pH 7.4. The amount of Metoprolol in the patch was measured spectrophotometrically at λmax of 223 nm (Hadgraft et al., 2005, Shashikant D et al., 2009)

In-Vitro Drug Release Studies

Freshly treated commercial semi permeable membrane24 was employed in this study. The membranes used were transparent and regenerated cellulose type, which were permeable to low molecular weight substances. The semi permeable membrane was tied to the open end cylinder which acted as donor compartment. The entire surface of the membrane was in contact with the receptor compartment containing 100 ml of pH 7.4 buffer. The content of the receptor compartment was agitated by a magnetic stirrer at 45 rpm. A transdermal patch of 5 cm in diameter was placed over the membrane which in turn placed over the donor compartment. Samples of 1 ml were withdrawn from receptor compartment for every hour and replaced by equal volumes of fresh receptor medium. The concentration of Metoprolol permeated was determined spectrophotometrically at 223 nm after suitable dilution against blank of Phosphate buffer pH 7.4 by U.V spectrophotometer.

RESULTS AND DISCUSSION

In the present work efforts have been made to prepare transdermal drug delivery system of Metoprolol using different polymers such as hydroxypropyl methyl cellulose, Polvyvinyl pyrollidone and then the results were compared for all the formulations. The drug reservoir was prepared by using different proportion of above mentioned polymers and plasticizer used was glycerine. The selection of polymer combinations which produced clear, smooth, uniform, substantive, flexible and desired thickness film were selected for the fabrication of the transdermal drug delivery systems of Metoprolol. The prepared formulation were evaluated for different Physicochemical characteristics such as Thickness uniformity, Folding endurance, Content uniformity, Percent moisture content, Percentage moisture uptake, Flatness and Mass uniformity. The release characteristics of the formulation were studied in vitro conditions. Invitro dissolution studies were
carried out in phosphate buffer (pH 7.4) for 12 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 3 different modes of graphical treatment they are

1. Percentage Cumulative drug release Vs Time
2. Percentage Cumulative drug release Vs Square root of time
3. Log Cumulative Percentage drug release Vs Log Time

The slope value and the degree of linearity of the above graphical treatments were considered as important statistical parameters to interpret the in-vitro profile of all formulations. The physico-chemical evaluation of the formulations has shown different physical characteristics, which change according to the presence of polymer nature and the level of the polymer. The higher Percentage moisture uptake and Percentage moisture content was found in the formulation FV.
(1.5%HPMC And 0.5% PVP) as and respectively which also revealed its high hydrophilicity. The formulations F-II(2% PVP) has shown the lowest value of Percentage moisture content and Percentage Moisture Uptake was 11.57 and 10.143 respectively which may be due to the hydrophobic nature of the polymer used in it. The thickness of the patches varied from 0.21 to 0.28 mm. The folding endurance of the films varied from 150 to 191 no of folds.

**Invitro Drug Release Studies**

The formulation F-I formulated with HPMC 2% has shown release 96.66 % at 12th hour. The in-vitro drug release plot has shown that the drug release followed zero order kinetics, which was envinced from the regression value. The Higuchi’s plot has shown the regression value of 0.971522, which indicated that diffusion mechanism influencing the drug release. In order to confirm this fact, Peppa’s plot was drawn which has shown slope value of 0.657, which confirms that the diffusion mechanism involved in the drug release was of non – fickian diffusion type. The formulation F-II formulated with PVP 2 % has shown release 92.25% at 12th hour. The in-vitro drug release plot has shown that the drug release followed zero order kinetics, which was envinced from the regression value. The Higuchi’s plot has shown the regression value of 0.973407, which indicated that diffusion mechanism influencing the drug release. In order to confirm this fact, Peppa’s plot was drawn which has shown slope value of 0.876, which confirms that the diffusion mechanism involved in the drug release was of non-fickian diffusion type. The formulation F-III (1% HPMC and1% PVP) and F-IV (0.5%HPMC and 0.5% PVP) has shown the drug release of 98.331% and 94.55%at 12th hour respectively. The drug release was diffusion mediated and from the Peppa’s plot, it is confirmed that it is of non-fickian type. The decrease in drug release of F-IVandF-III compared to F-I and F-II is due to the nature of the polymer. PVP has poor release characters when compared to the hydrophilic HPMC polymer based formulation. The formulation F-V formulated with PVP 0.5 % and HPMC 1.5% has shown release 99.21 % at 12th hour. The in-vitro drug release plot has shown that the drug release followed zero order kinetics, which was envinced from the regression value. The Higuchi’s plot has shown the regression value of 0.973861, which indicated that diffusion mechanism influencing the drug release. In order to confirm this fact, Peppa’s plot was drawn which has shown slope value of 0.676, which confirms that the diffusion mechanism involved in the drug release was of non – fickian diffusion type. The in-vitro release plots of all other formulations were suggestive of zero order release and are diffusion mediated which was envinced form the regression value Higuchi’s plot. All the formulations undergo non-fickian type of release which is confirmed form the slope values obtained from the Peppa’s plot. Based on the drug release the Formula- tion F-V is considered as an optimized formulation which shows higher percentage of drug release with diffusion mediated mechanism.

**CONCLUSION**

The prepared transdermal delivery system of Metoprolol Tartrate using HPMC and PVP had shown good promising results for all the evaluated parameters. Based on in-vitro maximum drug release, formulation F-V is concluded as an optimized formulation. From the results the formulation F V has shown optimum release in concentration independent manner. Higuchi’s plot for the formulation revealed that the predominant mechanism of drug release is diffusion.

**REFERENCES**


