FORMULATION AND EVALUATION OF ANTIPLATELET TRANSDERMAL PATCH OF CLOPIDOGREL BISULPHATE

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ABSTRACT

Transdermal drug delivery is an alternative route for systemic drug delivery which minimizes the absorption and increases the bioavailability. The purpose of this research work was to formulation and evaluation of transdermal drug delivery system of Clopidogrel bisulphate using various polymers such as HPMC, PVP and Ethyl cellulose by solvent evaporation technique for improvement of bioavailability of drug and reducing toxic effects. The developed transdermal patches increase the therapeutic efficacy and reduced toxic effect of Clopidogrel bisulphate. The prepared transdermal drug delivery system of Clopidogrel bisulphate using different polymers such as HPMC, EC and PVP had shown good promising results for all the evaluated parameters. Based on the In-vitro drug release, drug content and folding endurance results formulation F2 was concluded as an optimized formulation which shows its higher percentage of drug release.

KEYWORDS: TDDS, Solvent Evaporation Technique, Polymers.

INTRODUCTION

Recently, the transdermal drug delivery system (TDDS) has become one of the most innovative topics for research facilitating administration of the drugs through transdermal route. Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For the effective TDDS the drug must be able to penetrate the skin membrane. They are self contained, discrete dosage forms when applied to the intact skin, delivers the drug through the skin at a controlled rate to the systemic circulation. The goal of this dosage
design is to maximize the flux through the skin into the systemic circulation and to maintain the concentration of drug in the blood at therapeutic level by means of controlled permeation through the skin, therefore avoiding the first pass effect.

![Transdermal patch](image)

**Figure 1. Transdermal patch (A) On upper arm (B) On lower abdomen**

**Importance and uses**

- It is helpful in quit smoking, ease motion sickness to provide oral contraception or to infuse hormones into the blood stream to alleviate the symptoms of menopause.
- They are considered to be parenterals and are diffused through intact skin structures.

**Working of Transdermal Patch**

Patch adheres to the skin and delivers medication through the skin to the blood stream. Drug penetrates through the skin via pores and lipid membrane present in the skin. Drug should posses some physicochemical properties which are capable of facilitating the sorption of drug by the stratum corneum the penetration of drug through various skin tissues and also the uptake of the drug by the capillary network in the dermal papillary layer. A part from the drug quality the patches need to protect the drug reservoir for several days without any pilferage after it is adhered to skin.

**MATERIALS AND METHODS**

Drug sample was gifted by Ranbaxy, Ponta Shahib, HPMC and ethyl cellulose from Loba chemicals Mumbai and others ingredients were provided by S.D. fine chemical Mumbai.

**Preparation of Transdermal Patch**
Transdermal patches containing Clopidogrel bisulphate were prepared by solvent casting technique. Ethyl cellulose was dissolved in equal mixture of methanol and chloroform in 1:1 ratio. The drug was dissolved separately in the same solvent mixture and added with the polymer solution. The solution stirred under magnetic stirrer for half an hour. 0.5 ml of dibutyl phthalate was added as the plasticizer. The solution was mixed well and poured into plastic mould. The solvent was allowed to evaporate at a controlled rate by placing an inverted funnel over the plastic mould. The control of evaporation is necessary for uniform drying of patches. The drying was carried out at room temperature for 24 hrs. After 24 hrs the dried patches were removed from plastic mould and stored in desiccators until used.

RESULT AND DISCUSSION

Table 1. Composition of formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation Bases (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Clopidogrel bisulphate</td>
<td>37</td>
</tr>
<tr>
<td>HPMC</td>
<td>100</td>
</tr>
<tr>
<td>EC</td>
<td>100</td>
</tr>
<tr>
<td>Chloroform(ml)</td>
<td>2.5</td>
</tr>
<tr>
<td>Methanol(ml)</td>
<td>2.5</td>
</tr>
<tr>
<td>PVP</td>
<td>100</td>
</tr>
<tr>
<td>Dibutyl phthalate</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Preparation of Transdermal Patch

Description of Patch

(A) Colour: Creamish white           (B) Shape: Rounded

![Optimized Antiplatelet patch of Clopidogrel with backing layer](image)

Figure 2. Optimized Antiplatelet patch of Clopidogrel with backing layer

Thickness of the patch
The thickness of the patches varied from 0.149±0.009 to 0.246±0.002mm. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible result. The result of thickness is shown Figure 3.

![Figure 3. Thickness study of the formulated batches](image)

**Drug content uniformity**

The drug content uniformity of the prepared formulations had shown that the process used to prepare the transdermal patch in this study was capable of giving patch with uniform drug content. The result of drug content indicates that drug was uniformly dispersed in formulations as shown.

![Figure 4. Percentage drug content of formulation batch](image)

**In Vitro Drug Diffusion Studies**
Maximum percentage of drug release (i.e. 90.6%) was observed with formulation F2 and the minimum (i.e. 78.24%) was found with formulation F5 as shown in Table 2. The addition of hydrophilic components such as PVP in to the formulation tends to enhance its release-rate constants. This outcome can be attributed to the leaching of the soluble component which leads to the formation of pores and thus a decrease in the mean diffusion path length of drug molecules to release into the dissolution medium. The result is higher dissolution rates. Substances such as PVP act as antinucleating agents that retard the crystallization of a drug. Thus they play a significant role in improving the solubility of a drug in the matrix by sustaining the drug in an amorphous form so that it undergoes rapid solubilization by penetration of the dissolution medium.

Table 2. Percentage cumulative release of formulations

<table>
<thead>
<tr>
<th>Time(min)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>6.83±1.12</td>
<td>7.03±1.64</td>
<td>6.51±1.06</td>
<td>5.43±1.30</td>
<td>5.02±1.56</td>
<td>7.01±1.22</td>
</tr>
<tr>
<td>30</td>
<td>12.15±1.05</td>
<td>19.46±1.74</td>
<td>12.01±1.10</td>
<td>10.05±1.62</td>
<td>10.7±1.35</td>
<td>18.92±1.19</td>
</tr>
<tr>
<td>60</td>
<td>25.26±1.07</td>
<td>29.59±1.14</td>
<td>20.92±1.56</td>
<td>19.86±1.11</td>
<td>18.56±1.45</td>
<td>29.56±1.67</td>
</tr>
<tr>
<td>120</td>
<td>34.37±1.34</td>
<td>36.45±1.20</td>
<td>29.96±1.34</td>
<td>28.50±1.29</td>
<td>31.8±1.16</td>
<td>40.72±1.34</td>
</tr>
<tr>
<td>180</td>
<td>48.44±1.12</td>
<td>42.84±1.34</td>
<td>39.08±1.17</td>
<td>41.19±1.37</td>
<td>39.26±1.09</td>
<td>52.07±1.03</td>
</tr>
<tr>
<td>240</td>
<td>54.24±1.45</td>
<td>51.11±1.23</td>
<td>48.72±1.47</td>
<td>48.59±1.24</td>
<td>50.71±1.35</td>
<td>59.82±1.39</td>
</tr>
<tr>
<td>300</td>
<td>63.36±1.75</td>
<td>62.01±1.53</td>
<td>60.01±1.74</td>
<td>62.71±1.32</td>
<td>59.44±1.40</td>
<td>65.01±1.17</td>
</tr>
<tr>
<td>360</td>
<td>76.70±1.18</td>
<td>79.75±1.09</td>
<td>72.65±1.38</td>
<td>69.66±1.60</td>
<td>68.32±1.34</td>
<td>70.32±1.04</td>
</tr>
<tr>
<td>420</td>
<td>79.80±1.11</td>
<td>86.70±1.21</td>
<td>78.5±1.69</td>
<td>74.96±1.56</td>
<td>72.01±1.56</td>
<td>78.32±1.61</td>
</tr>
<tr>
<td>1440</td>
<td>85.35±1.23</td>
<td>90.6±1.42</td>
<td>83.92±1.19</td>
<td>80.68±1.18</td>
<td>78.24±1.78</td>
<td>81.61±1.38</td>
</tr>
</tbody>
</table>

Values represent, Mean ± SD, where n=3

Figure 5. Percentage cumulative release of formulation batches
In vitro drug release studies were carried out for the different formulations using diffusion cell. The medicated patches showed drug release study in percentage cumulative release. The relationship can be established as $F_2 > F_1 > F_3 > F_6 > F_4 > F_5$ thus by varying amount of polymer in patch, percent release can be varied. Drug-polymer affinity can be major factor that control release of drug from formulation. It is clear that in $F_2$ drug releases was maximum and minimum in $F_5$. So $F_2$ formulation was found to be most optimized formulation.

**SUMMARY AND CONCLUSION**

The present study deals with the investigation carried out on developing a transdermal drug delivery system releasing Clopidogrel bisulphate in skin for antiplatelet action. The prepared transdermal drug delivery system of Clopidogrel bisulphate using different polymers such as HPMC, EC and PVP had shown good promising results for all the evaluated parameters. Based on the In-vitro drug release, drug content and folding endurance results formulation $F_2$ was concluded as an optimized formulation, which shows its higher percentage of drug release.

**REFERENCE**


