Transdermal delivery of pravastatin sodium in transdermal patches using solid microneedles

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ABSTRACT SUMMARY

The skin is a nearly impermeable membrane that prevents passage of various substances through it (like drugs), for this reason is searched for ways to improve its permeability in a reversible manner by using a chemical or physical enhancer. Microneedles are a physical enhancer, which create micro- abrasions on the skin by making it more permeable. The present study focuses on in vitro pravastatin sodium penetration through human skin formulated in three different transdermal patches of chitosan by using a solid microneedle arrays of two different length (0.25mm and 2.25mm).1

Finding that exists statistical difference only in the lag time (T_L) when using microneedles of 0.25 mm or 2.25 mm. We also found that the type of formulation affects permeability constant (Kp), Flux (F) and T_L parameters.

INTRODUCTION

Nowadays ischemic heart disease is the leading cause of death in adults worldwide, both in countries with high, medium and low income. Therefore, we have tried to design new therapeutic strategies to treat them, usually the treatment for hyperlipidemia is for oral route (tablets) and this may have some disadvantages such as: food interactions, side effects (due to dose), fluctuations in the plasma concentrations of drugs, etc., among the most important compared to transdermal route, which avoids the hepatic first pass effect, allows a steady release over a given period, if the patient has an adverse reaction is easy to remove the transdermal device.

This project aims to develop and characterize physicochemically and by in vitro permeation studies pravastatin sodium transdermal patches using solid microneedles as physical penetration enhancer. Our design represents an interesting alternative for the treatment of such diseases due to its easy application and patient comfort.

EXPERIMENTAL METHODS

The Pravastatin sodium (hypolipidemic drug) transdermal patches were prepared by modification of the casting method in plate of Escobar-Chavez et al; 2011. We analyzed three formulations with different proportions of poloxamer 407 (PF-127) (without PF-127 (TP wo), 1% of PF-127 (TP 1%) and 3% of PF-127 (TP 3%). Previously the transdermal patches were characterized by bioadhesión, post-wetting bioadhesion, tensile strength, dissolution studies, chemical assay and DSC. In vitro permeation studies were performed using Franz diffusion cells. We used human skin obtained from abdominal lpectomy. The receptor medium was HEPES buffer of pH = 7.4. The receptor solution was maintained under continuous agitation using magnetic stir at 50 rpm, the temperature was maintained at 37 °C. Sampling was performed at different time intervals for 36 hours and content of pravastatin was determined by UV-Vis spectrophotometry at 238nm.2

Percutaneous penetration studies play an essential role in optimizing the formulation and design of transdermal delivery systems. These studies allow the assessment of both kinetic transdermal drug uptake and diffusion through the skin.2

RESULTS AND DISCUSSION

The results of bioadhesión studies showed values in the range of 46.22-60.14 g.f displaying good bioadhesive properties for the three TP. The TP 3% results with the best post-wetting bioadhesión (42.01 g.f). The patch with more tensile strength was TP 1%. Dissolution studies of the transdermal patches were fitted to a zero-order kinetic. The best release of pravastatin sodium was obtained for TP 1% and a delayed release was showed for TP 3% (Figure 1). Chemical assay was acceptable in all patches (17.05±1.88 mg). Finally, the DSC studies of the formulations with PF-127 (TP 1% and TP 3%) proved to be more stable due to the fact that higher temperature was required to decompose them compared to TP wo (without PF-127) (Figure 2).
Figure 1. Pravastatin release profiles by varying the percentage of poloxamer 407.

Figure 2. Thermograms of transdermal patches and excipients evaluated by differential scanning calorimetry.

In the case of percutaneous absorption studies, we analyzed with a multifactorial ANOVA test (p ≤ 0.05), to find out which parameters (Kp, F or TL) are affected when using microneedles (0.25 or 2.25 mm) or TP (TP wo, TP 1%, TP 3%). The parameter TL was affected when using microneedles of different length (Table 1 and Figure 3), and the type of formulation affected Kp, F and TL parameters.

Table 1. Permeations parameters obtained for each formulation (TP wo, TP 1% and TP 3%) using microneedles of 2.25mm and 0.25mm of length.

<table>
<thead>
<tr>
<th>Patch</th>
<th>Microneedles length (mm)</th>
<th>Flux (mg/cm²/hr)</th>
<th>Kp (cm²/hr)</th>
<th>TL (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP wo</td>
<td>2.25</td>
<td>0.0398</td>
<td>0.0060</td>
<td>14.6718</td>
</tr>
<tr>
<td>TP wo</td>
<td>0.25</td>
<td>0.0967</td>
<td>0.0148</td>
<td>20.8420</td>
</tr>
<tr>
<td>TP 1%</td>
<td>2.25</td>
<td>0.1193</td>
<td>0.0182</td>
<td>12.7394</td>
</tr>
<tr>
<td>TP 1%</td>
<td>0.25</td>
<td>0.0967</td>
<td>0.0147</td>
<td>18.6764</td>
</tr>
<tr>
<td>TP 3%</td>
<td>2.25</td>
<td>0.0548</td>
<td>0.0083</td>
<td>21.6794</td>
</tr>
</tbody>
</table>

CONCLUSION

The length of microneedles (0.25 and 2.25 mm) on the penetration of pravastatin sodium only affects TL parameter. However, the type of formulation (without PF-127, 1% y 3% of PF-127) affects Kp, F and TL.

It was determined that the size of the generated transdermal patch system would be dependent on the length of the microneedles (2.25mm and 0.25mm) as follows: to 4.3 PT 10.5 cm², for the PT 1% from 3.5 to 4.3 cm² and the PT 3% from 7.6 to 13.5 cm² to achieve a therapeutic equivalent dose of a tablet of 10 mg. Besides giving the possibility to maintain a constant release and avoiding the disadvantages of oral administration. The increase in permeation of pravastatin sodium was of 29% comparing TP 1% vs TP 3%.

REFERENCES


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PAPIME 200414 and PAPIIT TA 200312.