Transdermal delivery of fluoxetine

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ABSTRACT SUMMARY

Feasibility of the transdermal delivery of fluoxetine was studied in vitro using hairless mouse and rat skin. The optimized formulations obtained from the in vitro study were then evaluated in rats for an in vivo pharmacokinetic study. The results of the in vitro/in vivo studies demonstrate that transdermal delivery of fluoxetine is feasible.

INTRODUCTION

Fluoxetine (FX) is a selective serotonin reuptake inhibitor (SSRI) marketed under the trade name Prozac. It is used in depression, bipolar disorder, obsessive compulsive disorder, bulimia nervosa, panic disorder. FX is also used in obesity as an off-label drug. FX is known to cause dose-related serotonergic side effects. Thus, careful monitoring is required, since FX is usually used for long-term treatment.

Transdermal drug delivery system offers many advantages over the oral system. For example, it can avoid first-pass effect of the liver and gastrointestinal (GI) irritation. Improved bioavailability, patient compliance, uniform plasma level and reduced side effects have been reported as significant clinical benefits of transdermal drug delivery system. Thus, transdermal delivery of FX could be an effective strategy for avoiding GI irritation and for reducing side effect caused by the fluctuation of plasma concentration. Moreover, transdermal delivery of FX also can improve the patient compliance in long-term treatment.

Therefore, the aim of this study was to investigate the feasibility of the transdermal delivery of FX. Effects of various permeation enhancers on the skin permeation of FX were investigated using hairless mouse and rat skin. Based on the results of the in vitro permeation studies, in vivo pharmacokinetic study of FX was conducted in rats to demonstrate the feasibility of transdermal delivery of FX.

EXPERIMENTAL METHODS

In vitro skin permeation study across hairless mouse skin or rat skin was conducted with Keshary-Chien diffusion cells at 37°C. The donor cells, which contained various concentrations of FXH (salt form) or FXB (base form) in propylene glycol (PG) with or without permeation enhancers, were occluded with parafilm. The receptor cells were filled with 6% (w/v) PBS solution of Brij98. The diffusion cell was maintained at 37°C using a water bath and the solution in the receptor chambers was stirred continuously at 600 rpm. At predetermined time intervals, 0.5 mL of the solution in the receptor cell was withdrawn, and replaced immediately with an equal volume of fresh receptor media.

In vivo pharmacokinetic studies were performed in rats after transdermal delivery of FX. Abdominal hair of rats was removed with an electric clipper, and depilatory cream was applied to the skin. The femoral artery (for blood sampling) and vein (for intravenous injection) were cannulated with a PE-50 polyethylene tube. FXB in PG with permeation enhancers were applied to the abdomen of the rats. For transdermal application to the rats, a specially designed device was mounted on the abdomen and fixed with surgical glue, as reported in the literature which made it possible to apply FXB in PG solution without loss of liquid. Blood samples were collected from the femoral artery cannula at predetermined time intervals.

A liquid chromatography–mass spectrometry (LC–MS) method was used to
determine the concentration of FX in the in vitro/in vivo samples.

RESULTS AND DISCUSSION

The in vitro permeation profiles of FXH and FXB through hairless mouse skin are shown in Figure 1. Flux of FXB was approximately 8.83-fold increase compared to that obtained with saturated solution of FXH. Thus, FXB was selected for further permeation studies.

![Figure 1. The in vitro permeation profiles of FXH and FXB through hairless mouse skin. Donor solution (PG) contained 0.5% (w/v) FXB (●) or saturated FXH (○). Each value represents the mean ± S.D. (n≥3).](image)

To evaluate the effect of permeation enhancers on the skin permeation of FX, various permeation enhancers were incorporated in PG solutions at 1% (w/v). Permeation parameters of FX across hairless mouse are shown in Table 1. The results indicate that only three permeation enhancers (IPM, limonene and oleic acid) significantly (p<0.05) increased the flux of FX. Therefore, these permeation enhancers were selected for further studies.

Table 1. Effect of different permeation enhancer on the permeation parameters of FXB through the hairless mouse skin from propylene glycol containing 0.5% (w/v) FXB and 1% (w/v) enhancer

<table>
<thead>
<tr>
<th>Enhancer</th>
<th>Flux (μg/hr/cm²)</th>
<th>Permeation coefficient (cm²/hr) x 10⁻³</th>
<th>Lag time (h)</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3.09±0.48</td>
<td>0.62±0.10</td>
<td>4.82±0.43</td>
<td>1</td>
</tr>
<tr>
<td>IPM</td>
<td>27.41±4.50*</td>
<td>5.48±0.90</td>
<td>4.58±0.25</td>
<td>8.87</td>
</tr>
<tr>
<td>Limonene</td>
<td>10.52±1.80**</td>
<td>2.10±0.36</td>
<td>4.76±0.32</td>
<td>3.40</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>7.87±2.27*</td>
<td>1.57±0.45</td>
<td>6.54±0.20</td>
<td>2.55</td>
</tr>
</tbody>
</table>

All data represent the mean ± S.D. (n≥3). * p<0.05 versus control (none) group; ** p<0.01 versus control (none) group

Figure 2 shows a good linear relationship of the in vitro flux of FXB between hairless mouse and rat skin. Table 2 shows the effect of enhancers (% w/v) on the in vivo pharmacokinetic parameters of 0.5% (w/v) FXB in PG applied on the rat abdominal skin.

![Figure 2. Relationship of the in vitro flux of FXB between hairless mouse and rat skin.](image)

Table 2. Effect of permeation enhancers (% w/v) on in vivo pharmacokinetic parameters of 0.5% (w/v) FXB in PG through the SD rat skin

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>IPM 1% (w/v)</th>
<th>IPM 1% (w/v) + Limonene</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀ (ng/mL)</td>
<td>5.70±4.52</td>
<td>104.81±31.06</td>
<td>142.44±22.26</td>
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<tr>
<td>T_max (hr)</td>
<td>23.33±15.73</td>
<td>11.50±1.22</td>
<td>14.00±4.90</td>
</tr>
<tr>
<td>AUC₀→∞ (ng·hr/mL)</td>
<td>238.30±298.66</td>
<td>2719.91±87.70</td>
<td>2719.91±87.70</td>
</tr>
<tr>
<td>C₀ (ng/mL)</td>
<td>2.86±1.94</td>
<td>66.20±8.30</td>
<td>75.55±2.44</td>
</tr>
</tbody>
</table>

CONCLUSION

The in vitro permeation study using hairless mouse skin showed that the mixture of IPM and limonene is the most promising permeation enhancer for transdermal delivery of FX. The in vivo pharmacokinetic studies in rats showed a constant plasma level over an extended period of time. Thus, the transdermal delivery of FX seems to be feasible.

REFERENCES