Size-fitting of Intravaginal Rings for Macaques and in vitro Release Kinetics of Zinc Finger Inhibitors


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Introduction

The HIV pandemic can arguably be best viewed and eventually stopped by an effective vaccine. Although great strides have been made towards that end, an effective vaccine is militarily still many years away, providing a compelling argument for the exploration of other avenues of HIV prevention. Currently, there is a handful of effective microbicides that are designed to prevent HIV transmission by targeting specific viral proteins and hindering viral replication. Many of these compounds can potentially inhibit replication of HIV at the site of exposure and, therefore, especially important in female users who engage in heterosexual relationships.

The Estring is a transdermal drug delivery device that is designed to work as a barrier to transmission. The drug delivery device consists of a flexible silicone elastomer ring inserted into the vagina. The ring is designed to release an active agent over a period of time. The active agent is a blend of estradiol and progesterone. The Estring is inserted into the vagina and remains in place for 28 days. The active agent is released from the ring and is absorbed into the bloodstream. The amount of active agent that is released from the ring is determined by the design of the ring and the properties of the silicone elastomer.

Estring is an example of a transdermal drug delivery device that is designed to work as a barrier to transmission. The drug delivery device consists of a flexible silicone elastomer ring inserted into the vagina. The ring is designed to release an active agent over a period of time. The active agent is a blend of estradiol and progesterone. The Estring is inserted into the vagina and remains in place for 28 days. The active agent is released from the ring and is absorbed into the bloodstream. The amount of active agent that is released from the ring is determined by the design of the ring and the properties of the silicone elastomer.

In several independent studies, the utility and acceptance of intravaginal rings as a delivery device for hormones and other medications has been demonstrated. These studies have shown that intravaginal rings are effective and acceptable as a form of contraception. In addition, the use of intravaginal rings as a delivery device for other medications, such as HIV inhibitors, has been explored. The use of intravaginal rings as a delivery device for HIV inhibitors has several advantages. First, the intravaginal ring is a convenient and discreet method of delivery. Second, the intravaginal ring can be easily inserted and removed by the user. Third, the intravaginal ring can deliver a sustained and consistent dose of the active agent. Fourth, the intravaginal ring can be used by individuals who are unable to take oral medications or who have difficulty swallowing tablets.

In vitro Release Kinetics of Zinc Finger Inhibitors

The in vitro release kinetics of zinc finger inhibitors (ZFI) in the nucleocapsid protein (NCp7) of HIV-1 are potent inhibitors of HIV and SIV. These inhibit virus replication in cell cultures and in animal models of HIV infection. The in vitro release kinetics of ZFI inhibitors in the NCp7 of HIV-1 are important for the development of new anti-HIV therapies.

Macaques were monitored for 8 weeks for mucosal disruption by colposcopy and proinflammatory cytokine markers in cervical vaginal lavages (CVL) using Luminex bead-based technology. Three different ZFIs (compounds 52, 89 and 122, each derived from an N-substituted amine) were tested in 5-mm and 25-mm rings for their cumulative release and daily output over 28 days, subjected to linear regression analysis.

Results

Qualitative evaluation at the time of ring insertion suggested that the 25 mm ring provided optimal fit in both macaque species. All rings remained in place for the study duration (3 weeks). The amount of ZFI released was measured and the results of statistical analysis were evaluated. No significant differences in cumulative NCp7 inhibition were observed during the 28-week period following ring insertion. A Pigtailed and Chinese Rhesus macaque showed a 4.8% difference in the amount of ZFI released and no significant correlation was observed. In this case, a ZFI concentration of 50-100 µM was selected for use in macaque studies.

<table>
<thead>
<tr>
<th>ZFI</th>
<th>Compound</th>
<th>MW (g/mol)</th>
<th>log P</th>
<th>DSC Melting point (°C)</th>
<th>HPLC retention time (min)</th>
<th>Cumulative % release after 14 days</th>
<th>Release rate* (mg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZFI 52</td>
<td>89</td>
<td>164.8</td>
<td>1.31</td>
<td>184.9</td>
<td>0.15</td>
<td>0.132</td>
<td>9.25</td>
</tr>
<tr>
<td>ZFI 89</td>
<td>52</td>
<td>164.8</td>
<td>1.31</td>
<td>184.9</td>
<td>0.15</td>
<td>0.132</td>
<td>9.25</td>
</tr>
<tr>
<td>ZFI 122</td>
<td>122</td>
<td>164.8</td>
<td>1.31</td>
<td>184.9</td>
<td>0.15</td>
<td>0.132</td>
<td>9.25</td>
</tr>
</tbody>
</table>

In conclusion, the intravaginal ring is a promising delivery device for HIV inhibitors. The use of intravaginal rings as a delivery device for HIV inhibitors has several advantages. First, the intravaginal ring is a convenient and discreet method of delivery. Second, the intravaginal ring can be easily inserted and removed by the user. Third, the intravaginal ring can deliver a sustained and consistent dose of the active agent. Fourth, the intravaginal ring can be used by individuals who are unable to take oral medications or who have difficulty swallowing tablets.

Future work

Further studies are needed to evaluate the long-term safety and efficacy of intravaginal rings as a delivery device for HIV inhibitors. This includes evaluating the long-term impact of intravaginal rings on mucosal integrity and the potential for long-term suppression of HIV infection.

Acknowledgments

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References


