Release Kinetics for a Cilostazol Eluting Stent Using RES TECHNOLOGY™

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Develop a Dual Drug Stent:

- Cilostazol Release in Luminal Direction
- Sirolimus Release in Abluminal Direction

Anti-platelet Action – Increase Thromboresistance
Anti-proliferative – Synergize with Sirolimus
Filled Dual Drug Stent

Different Drugs Can Be Deposited in a Specified Pattern

Cilostazol
Sirolimus
Cilostazol: Background

• Cilostazol is a platelet inhibitor with vasodilator\textsuperscript{1,2} properties

• Animal studies have indicated that cilostazol inhibits smooth muscle cell (SMC) growth and inflammation, and accelerates endothelialization\textsuperscript{3}

• Clinical studies have shown that cilostazol not only reduces stent thrombosis (ST), but also decreases restenosis and target lesion revascularization (TLR)\textsuperscript{4,5}
Modulation of Cilostazol RK

• Reservoir Inlay Design
  – Single Direction Release
  – Bidirectional Release

• Drug / Polymer Weight Ratio (D/P)
  – D/P = 25/75 → 70/30

• PLGA Polymer: Lactide / Glycolide Ratio
  – PLGA 75/25: More Hydrophobic, Slower Degradation
  – PLGA 50/50: More Hydrophilic, Faster degradation
Bidirectional v. Single Direction Release

Drug Matrix D/P = 50/50 - PLGA 75/25 - *In Vitro*

Reservoir Inlay Design Can Control Release Direction
First Order Kinetic Release Plots

Bidirectional Rate ~2.5X Single Direction Rate

First Order Release Kinetics for ~50-60 Days
Higuchi Plot: Bidirectional v. Single Direction

Diffusion Controlled Release to ~80% of Dose
Effect of D/P on Single Direction Release

PLGA 75/25 - In Vitro

D/P Ratio Affects Drug Release Duration & Profile
Effect of D/P on Single Direction Release
PLGA 50/50 - *In Vitro*

Polymer Properties Can Change Profile Shape
Cilostazol *In Vitro* Release Kinetics

<table>
<thead>
<tr>
<th>Polymer</th>
<th>D/P</th>
<th>Initial First Order Rate Constant $k_1(3D)$ (d$^{-1}$)</th>
<th>Extent of Release Profile That Exhibits 1$^{st}$ Order Kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA 75/25</td>
<td>55/45</td>
<td>0.12</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>70/30</td>
<td>0.39</td>
<td>90%</td>
</tr>
<tr>
<td>PLGA 50/50</td>
<td>55/45</td>
<td>0.04</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>70/30</td>
<td>0.14</td>
<td>20%</td>
</tr>
</tbody>
</table>

1$^{st}$ Order Release Rate: PLGA 75/25 > PLGA 50/50
Effect of L/G Ratio on Release Profile

D/P = 55/45 - *In Vitro*

At D/P 55/45, Choice of PLGA L/G Has Marked Effect
Effect of L/G Ratio on Release Profile
D/P = 70/30 - In Vitro

At D/P 70/30, Less Effect of Polymer L/G Ratio
Porcine Safety Study

*In Vivo v. In Vitro* Release

**Luminal Direction Release**

In Vitro Release

In Vivo Release

**Good In Vivo – In Vitro Correlation**
Porcine Safety Study: Histology
Day 30

Cilostazol / Sirolimus

BMS
**In Vitro Blood Flow Loop Model**

(3 and 7-day Pre-Incubation)

**Pre-Incubation for 3 days**

- **Polymer Only Control**
- **Cilostazol**

**Pre-Incubation for 7 days**

- **Polymer Only Control**
- **Cilostazol**

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**3-day Incubation Thrombosis (Radiation/time normalized to Polymer only)**

- Control: 100
- Cilo: 22

**P < 0.001**

*N = 6*

**7-day Incubation Thrombosis (Radiation/time normalized to Polymer only)**

- Control: 100
- Cilo: 42

**P = 0.008**

*N = 6*
Conclusions

• Wide range of *in vitro* cilostazol release profiles can be achieved.
  • First order
  • Biphasic
  • Linear ("Zero Order")
• Direction of cilostazol release is controllable (bidirectional v. unidirectional).
• Adjusting drug / polymer ratio allows refinement of release profile and drug dose.
• PLGA lactide / glycolide ratio has marked effect on RK profile.
• Cilostazol eluted in dual drug design was safe in porcine model.
• Eluted cilostazol improved thromboresistance in an *in vitro* model.
References